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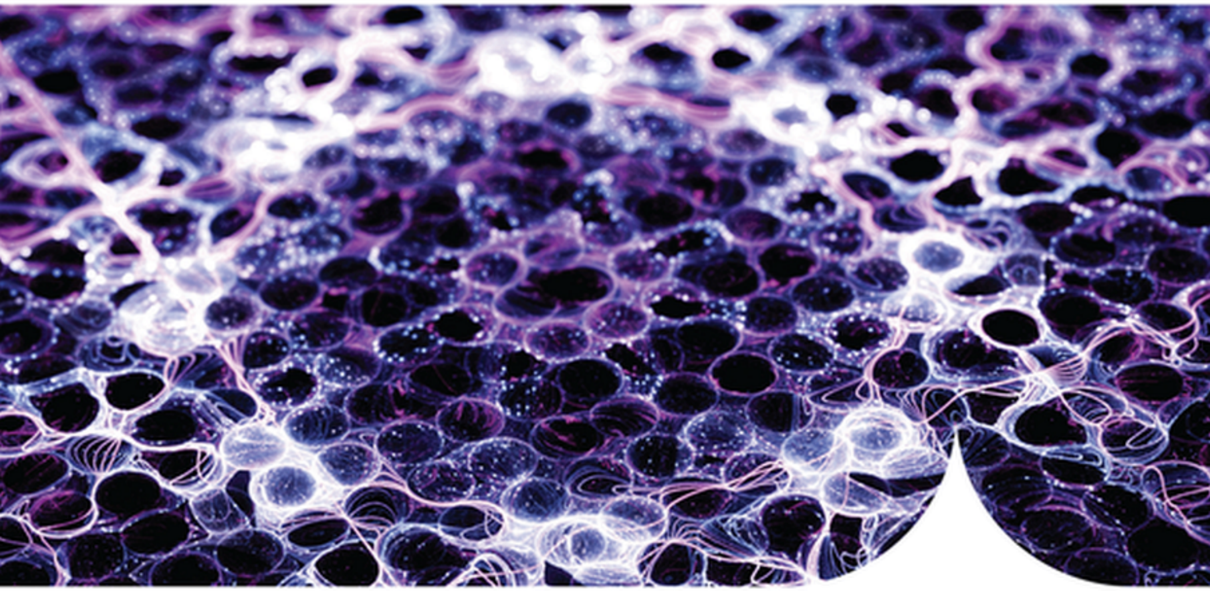

Nanotechnology Applications for Improvements in Energy Efficiency and Environmental Management

M.A. Shah, M.A. Bhat, and J. Paulo Davim

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Nanotechnology Applications for Improvements in Energy Efficiency and Environmental Management

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The important aspect of nanotechnology is the remarkable size dependant physico-chemical properties of nanomaterials that have led to the development of synthesis protocols for synthesizing nanomaterials over a range of sizes, shapes, and chemical compositions. This book chapter describes the various aspects of nanotechnology: its dimensions and manipulation of matter with primary focus on inorganic materials. Detailed account of various methods lying within top down and bottom up synthesis approaches has been discussed like Chemical Vapour Condensation (CVC), Arc discharge, Hydrogen plasma-metal reaction, and Laser pyrolysis in the vapour phase, Microemulsion, Hydrothermal, Sol-gel, Sonochemical taking place in the liquid phase and ball milling carried out in the solid phase. The book chapter also presents a brief account of the various characterization techniques used for the identification of the nanomaterials: X-ray diffraction, UV-Visible Spectroscopy and Electron microscopy viz Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Atomic Force Microscopy (AFM).

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Nanoindentation technique is used to assess the mechanical properties of materials at nano- level. A very small tip (usually diamond) produces indents at the surface of the material to be tested. A load versus deflection curve is generated and is used to study the elastic properties of materials. Generally, it is used for obtaining the hardness and Young's modulus of materials at nano-meter scale. Currently, the method to evaluate the mechanical properties by nanoindentation is restricted to homogeneous materials. Cement-based materials are heterogeneous in nature. Therefore, nanoindentation study of cement-based materials is critical and requires several important steps, which need to be performed accurately. This chapter provides a review on the theory of nanoindentation, instruments being used for nanoindentation, sample preparation techniques, indentation strategy and determination of nanomechanical properties and data analysis for cement-based materials.

Carbon-based nanotechnology has been rapidly developing, with a particular interest in the bio-application of carbon nanotubes (CNTs) as a scaffold in tissue engineering. It is essential that the materials used in scaffold fabrication are compatible with cells, as well as with the biological milieu. Many synthetic polymers have been used for tissue engineering so far; however, many lack the necessary mechanical strength and may not be easily functionalized, in contrast to CNTs, which have shown very attractive features as a scaffold for cell culture system. In spite of many attractive features, the toxicity of CNTs is a prime concern. The potential applications of CNTs seem countless, although few have reached a marketable status so far and there is need of more studies on CNTs biocompatibility issues. This chapter aims to revisit the basics of CNTs with their bio-applications including their use as a scaffold in cell culture systems.

The scope of the chapter is showing novel experimental findings on preparing anatase TiO2 nanoparticles, first anodizing titanium into an organic media for obtaining TiO2 nanotubes, and these used as a photo catalytic active electrode in treating water polluted with organic contaminants. The substrates were grit blasted in order to obtain mechanical fixation of the generated nanotubular TiO2 structure. This was successfully achieved without diminishment of the nanotubes order and with a self-leveling of the outer surface. A new phenomenon is investigated consisting in the process of oxidation of the nanotubes in water after anodizing. Along this process, methyl orange added to the aqueous solution was discolored as part of the redox reaction involved. The final state of the modified layer was composed of conglomerates of crystalline TiO2 nanoparticles, around 4 nm in size, consisting of anatase. This was obtained under room conditions.

The nanotechnology has emerged important field of modern scientific research due to its diverse range of applications in the area of electronics, material sciences, biomedical engineering, and medicines at nano levels such as health care, cosmetics, food and feed, environmental health, optics, biomedical sciences, chemical industries, drug-gene delivery, energy science, optoelectronics, catalysis, reprography, single electron transistors, light emitters, nonlinear optical devices, and photoelectrochemical applications and other applications. Due to these immense applications of nanotechnology in biomedical science it has became possible to design the pharmaceuticals in such a way which could directly treat diseased cells like cancer, microscopic repairs in hard-to-operate-on areas of the body. The nanomachines have been designed to clean up toxins or oil spills, recycle all garbage, and eliminate landfills etc. The chapter summarizes the present and future applications of nanotechnology for human welfare but needs further applications in catalysis, optical devices, sensor technology, cancer treatment, or drug delivery systems.

The chapter emphasizes nanotechnology, which is an emerging field that covers a wide range of technologies that are presently under development in nanoscale. Nanotechnology offers the potential of novel nanomaterials for treatment of surface water, ground water, and waste water contaminated by toxic metal ions, organic and inorganic solutes, and microorganisms. The advantages of the use of nanomaterials, which are related to their properties that are completely different from the bulk materials, make them extremely attractive and give them enormous potential. Among the areas that are influenced by nanotechnology, environmental remediation is highlighted in this chapter. This chapter emphasizes several nanomaterials (Zero valent iron, titanium dioxide, nanoclays, nanotubes, dendrimers, ferritin, metalloporphyrinogens, and SAAMS) and their application in water treatment, purification, and disinfection. The use of nanoparticles in environmental remediation, which inevitably leads to the release of nanoparticles into the environment and subsequent ecosystems, is also explained.

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This chapter examines the importance of nanotechnology in cancer prevention, cure and diagnosis. This chapter deals with the applications of nanomedicine in cancer and various strategies to target cancer cells by using nanotechnology such as gold nanoparticles, liposomes, nanodots, nanorods etc. Nanotechnology is an interdisciplinary area with potential applications in fighting many diseases including cancer. Conventional drugs have poor cell specificity, solubility and high toxicity. The continued development of cancer nanotechnology holds the promise for personalized oncology. For accurate and self-confirming cancer diagnosis, it is essential to combine dual-mode and multi-mode imaging functionalities within one nanoparticle system. Nanoparticles improve the solubility of poorly water-soluble drugs and prolong the half-life of drugs. Disadvantages of nanotechnology include the potential for mass poisoning. Understanding how nano-materials affect live cell functions, controlling such effects, and using them for disease therapeutics, are now the principal aims and most challenging aspects of nanobiotechnology and nanomedicine.

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This chapter addresses the potential application of nanotechnology in various areas of the food industry. Nanotechnology is having an impact on several aspects of the food industry, from product development to packaging processes. Nanotechnology is capable of solving the very complex set of engineering and scientific challenges in the food processing industries. This chapter focuses on exploring the role of nanotechnology in enhancing food stability at the various stages of processing. Research has highlighted the prospective role of nanotechnology use in the food sector, including nanoencapsulation, nanopackaging, nanoemulsions, nanonutraceuticals, and nanoadditives. Industries are developing nanomaterials that will make a difference not only in the taste of food but also in food safety and the health benefits that food delivers. While proposed applications of nanotechnologies are wide and varied, developments are met with some caution as progress may be stifled by lack of governance and potential risks.

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The tremendous success in developing new nanomaterials and fostering technological innovation arises from its focus on interdisciplinary research and collaboration between physical and medical scientists. The concept of nano-medicine is one of the most important and exciting ideas ever generated by the applications of nanoscience. One of the most challenging tasks in the pharmaceutical industry is the formulation of poorly soluble drugs. The implication of conventional techniques for improving the solubility has gained limited success. Nanoparticles facilitate formulation with improved solubility and efficacy mainly through nanosuspension approach. Techniques such as media milling, high-pressure homogenization and use of microemulsion have been used for production of nanosuspensions for a novel delivery system. Moreover, they are manoeuvred to patient-acceptable dosage forms like tablets, capsules and lyophilized powder products. Nanosuspension technology has also been studied for active and passive targeted drug delivery systems which the chapter highlights on various formulation perspectives and applications as a biomedicine delivery system.

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S. A. Akhoon, National Institute of Technology, Srinagar, India
S. Rubab, National Institute of Technology, Srinagar, India
M. A. Shah, National Institute of Technology, Srinagar, India

The problem of dwindling energy can be attributed to the rapidly increasing worldwide energy demand, leading to an urgent need for alternative energy-harvesting technologies to sustain the economic growth by maintaining our appetite for energy. Among them, solar-energy-harvesting is most promising and the huge demand for clean, cost-effective and cost-efficient energy can be met by solar energy. The large scale solar energy utilization has not become practical because of the high cost and inadequate efficiencies of the current solar-energy-conversions. Nanotechnology offers tools to develop cost-effective and cost-efficient based technologies for solar-energy conversions. Nanostructures such as nanowires, nanopillars, nanodomes, nanorods, quatumdots, nanoparticles, etc facilitate photon absorption, electron transport and electron collection properties of the solar-energy-conversion devices. It lifts up a hope of smooth present and sustainable future. This review specifically summarizes the contribution of the nanotechnology to photovoltaics, dye-sensitive solar cells, quantum-dot-sensitized solar cells and solar hydrogen production devices.

The convergence of nanotechnology with microbiology is a nifty interdisciplinary research area that could amplify the limits of technology, enhance global health through formation of different drugs which can be effective against different infectious diseases, for treatment of drinking water to kill the pathogens and make it safe for public use. Bacteria, fungi, actinomycetes and plants have been successfully used for the formation of nanoparticles of silver, gold, zinc, etc. As the microorganisms especially bacteria are becoming resistant to the commonly used antibiotics an alternative antimicrobial agent which can be effective against the antibiotic resistant bacteria is needed. In the present chapter we have highlighted the relationship between these two mighty disciplines. The chapter deals with many aspects like antimicrobial activity of nanoparticles, formation of nanoparticles using microorganisms etc. The green synthesis of nanoparticles is an emerging as a new field of science hence it has been discussed in detail.

Preface

The world is a dangerous place to live; not because of the people who are evil but because of the people who don't do anything about it. - Albert Einstein

The culmination of a long line of Greek philosophers, including Democritus, Lucretius formulated the first detailed atomistic description of nature in the first century BC. This was not yet nanoscience; it was simply science. However, it was not until the beginning of the 19th century, some 20 centuries later, that the atomic theory would be scientifically established by the chemists Dalton, Lavoiser, Gay-Lussac, and others. The science of the microscopic would then work its way up through the ranks during the 19th and especially the 20th centuries.

Physics and Chemistry as we know them are largely built upon our knowledge of matter on the atomic scale. Continuing this same trend from the beginning of the 1980s, it would seem that several new chapters have been added to the history of science, associated with the prefix nano. The notions of Nanosciences and nanotechnology pop up in every sector of modern knowledge.

Young scientists today are likely to be attracted by the depth and novelty of this new technology, setting off on a voyage of discovery in an unknown world, where the ways have not yet been signposted. One of the aims of this book is precisely to provide a tool that can be used to train not only students but also teachers and research scientists. It has been written by research workers and university teachers who are experts in their own fields and fully up to date with the latest developments. It has been put together in such a way as to produce a uniform and complete entity that can be approached directly via any of the chapters.

OVERVIEW OF THE BOOK

Chapter 1: Nanomaterials, Novel Preparation Routes, and Characterizations

This chapter describes the various aspects of nanotechnology: its dimensions and manipulation of matter with primary focus on inorganic materials. Detailed accounts of various methods lying within top-down and bottom-up synthesis approaches are discussed, like Chemical Vapour Condensation (CVC), arc discharge, hydrogen plasma-metal reaction, and laser pyrolysis in the vapour phase, microemulsion, hydrothermal, sol-gel, sonochemical taking place in the liquid phase, and ball milling carried out in the solid phase. The chapter also presents a brief account of the various characterization techniques used for the identification of the nanomaterials: x-ray diffraction, UV-visible spectroscopy, and electron microscopy (e.g. Transmission Electron Microscopy [TEM], Scanning Electron Microscopy [SEM], Atomic Force Microscopy [AFM]).

Chapter 2: Nano-Mechanical Characterization of Cement-Based Materials

Nanoindentation technique is used to assess the mechanical properties of materials at nano-level. A very small tip (usually diamond) produces indents at the surface of the material to be tested. A load vs. deflection curve is generated and is used to study the elastic properties of materials. Generally, it is used for obtaining the hardness and Young's modulus of materials at nano-meter scale. Currently, the method to evaluate the mechanical properties by nanoindentation is restricted to homogeneous materials. Cement-based materials are heterogeneous in nature. Therefore, nanoindentation study of cement-based materials is critical and requires several important steps, which need to be performed accurately. This chapter provides a review of the theory of nanoindentation, instruments being used for nanoindentation, sample preparation techniques, indentation strategy, and determination of nanomechanical properties and data analysis for cement-based materials.

Chapter 3: Carbon Nanotubes: Basics, Biocompatibility, and Bio-Applications Including Their Use as a Scaffold in Cell Culture Systems

Carbon-based nanotechnology has been rapidly developing with particular interest in bio applications of Carbon Nanotubes (CNTs) as a scaffold tissue-engineering replacement in biomaterial construct or scaffold. Carbon nanotubes are essential and compatible scaffold fabrication materials with cells as well as with surrounding tissue. In addition, synthetic polymers, which lack mechanical strength, can be functionalized easily in contrast to CNTs. In spite of many attractive features, the toxicity of CNTs is a prime concern. CNTs' toxicity in both *in vivo* and *in vitro* studies has been attributed to various factors, and there is a need of more studies on CNTs' toxicity and biocompatibility issues. The potential applications of carbon nanotubes seem countless, although few have reached a marketable status so far. This chapter aims to revisit the basics of CNTs with their bio-applications including their use as a scaffold in cell culture systems.

Chapter 4: Novel Synthesis of 4nm Anatase Nanoparticles at Room Temperature Obtained from TiO_2 Nanotube Structures by Anodizing Ti

The scope of the chapter is showing novel experimental findings on preparing anatase TiO_2 nanoparticles, first anodizing titanium into an organic media for obtaining TiO_2 nanotubes, and these used as a photo catalytic active electrode in treating water polluted with organic contaminants. The substrates were grit blasted in order to obtain mechanical fixation of the generated nanotubular TiO_2 structure. This was successfully achieved without diminishment of the nanotubes order and with a self-leveling of the outer surface. A new phenomenon is investigated consisting in the process of oxidation of the nanotubes in water after anodizing. Along this process, methyl orange added to the aqueous solution was discolored as part of the redox reaction involved. The final state of the modified layer was composed of conglomerates of crystalline TiO_2 nanoparticles, around 4 nm in size, consisting of anatase. This was obtained under room conditions. Moreover, another new phenomenon occurred when detached fragments from the modified layer were electrophoretically deposited. They were ordered and grow as deposits. In addition, they maintain their nanotubular shape conferring a homogeneous size in the porous structure.

Nanotechnologies as key and cross-sectional technologies exhibit the unique potential for decisive technological breakthroughs in the energy sector, thus making substantial contributions to sustainable energy supply. The range of possible nanoapplications in the energy sector comprises gradual short and medium-term improvements for a more efficient use of conventional and renewable energy sources as well as completely new long-term approaches for energy recovery and utilization.

Chapter 5: Nanotechnology, Metal Nanoparticles, and Biomedical Applications of Nanotechnology

The chapter is examines the role nanotechnology and its biomedical applications. Nanotechnology has emerged as an important field of modern scientific research due to its diverse range of applications in the area of electronics, material sciences, biomedical engineering, and medicines at nano levels such as healthcare, cosmetics, food and feed, environmental health, optics, biomedical sciences, chemical industries, drug-gene delivery, energy science, optoelectronics, catalysis, reprography, single electron transistors, light emitters, nonlinear optical devices, and photoelectrochemical applications and other applications. Due to these immense applications of nanotechnology in biomedical science, it has became possible to design the pharmaceuticals in such a way that they could directly treat diseased cells like cancer and make microscopic repairs in hard-to-operate-on areas of the body. The nanomachines have been designed to clean up toxins or oil spills, recycle all garbage, eliminate landfills, etc. The chapter summarizes the present and future applications of nanotechnology for human welfare but needs further study in catalysis, optical devices, sensor technology, cancer treatment, and drug delivery systems.

Chapter 6: Nanotechnology for Environmental Control and Remediation

The chapter emphasizes nanotechnology, which is an emerging field that covers a wide range of technologies that are presently under development in nanoscale. Nanotechnology offers the potential of novel nanomaterials for treatment of surface water, ground water, and waste water contaminated by toxic metal ions, organic and inorganic solutes, and microorganisms. The advantages of the use of nanomaterials, which are related to their properties that are completely different from the bulk materials, make them extremely attractive and give them enormous potential. Among the areas that are influenced by nanotechnology, environmental remediation is highlighted in this chapter. This chapter emphasizes several nanomaterials (Zero valent iron, titanium dioxide, nanoclays, nanotubes, dendrimers, ferritin, metalloporphyrinogens, and SAAMS) and their application in water treatment, purification, and disinfection. The use of nanoparticles in environmental remediation, which inevitably leads to the release of nanoparticles into the environment and subsequent ecosystems, is also explained.

Chapter 7: Applications of Nanotechnology in Cancer

This chapter examines the importance of nanotechnology in cancer prevention, cure, and diagnosis. This chapter deals with the applications of nanomedicine in cancer and various strategies to target cancer cells by using nanotechnology such as gold nanoparticles, liposomes, nanodots, nanorods, etc. Nanotechnology is an interdisciplinary area with potential applications in fighting many diseases including cancer. Conventional drugs have poor cell specificity, solubility, and high toxicity. The continued development of cancer nanotechnology holds the promise for personalized oncology. For accurate and self-confirming cancer diagnosis, it is essential to combine dual-mode and multi-mode imaging functionalities within one nanoparticle system. Nanoparticles improve the solubility of poorly water-soluble drugs and prolong the half-life of drugs. Disadvantages of nanotechnology include the potential for mass poisoning. Understanding how nano-materials affect live cell functions, controlling such effects, and using them for disease therapeutics are now the principal aims and most challenging aspects of nanobiotechnology and nanomedicine.

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Chapter 9: Nanosuspensions in Nanobiomedicine

The concept of nanobiomedicine is one of the most important and exciting ideas ever generated by the applications of nanoscience. Although there have been extensive interdisciplinary activities, major collaborative efforts are needed to jointly address some of the most challenging issues in life and medical sciences. One of the most challenging tasks for formulators in the pharmaceutical industry is the formulation of poorly soluble drugs. Conventional techniques employed for improving solubility of these drugs have gained limited success. This holds true more often when dealing with drugs having poor aqueous as well as organic solubility. Nanoparticles facilitate formulation of hydrophobic drugs to improve solubility and efficacy mainly through nanosuspension approach. Nanosuspensions are submicron colloidal dispersions of pure drug particles, stabilized by surfactants. This nanobiomedicine delivery system is simple and advantageous compared to other strategies. Techniques such as media milling, high-pressure homogenization, and use of microemulsion as a template have been used for production of nanosuspensions. This green nanobiomedicine can be delivered by various routes, such as oral, parenteral, pulmonary, and ocular systems. It is also possible to convert nanosuspensions to patient-acceptable dosage forms like tablets, capsules, and lyophilized powder products. Nanosuspension technology has also been studied for active and passive targeted drug delivery systems. This chapter focuses on various manufacturing and formulation perspectives and applications of nano-suspensions as a drug delivery system.

Chapter 10: A Review of Various Nanostructures to Enhance the Efficiency of Solar-Photon-Conversions

The problem of dwindling energy can be attributed to the rapidly increasing worldwide energy demand compared with the supply and excessive greenhouse gas emissions resulting from ever-growing fuel consumption. It has led to an urgent need for alternative energy-harvesting technologies to sustain the economic growth by maintaining our appetite for energy through cost-effective and cost-efficient economies. Among them, solar-energy-harvesting is the most promising as solar energy is the most abundant, renewable, clean, and free source of energy available. Thus, the huge demand for clean, cost-effective, and cost-efficient energy can be met by solar-energy conversions. The large-scale solar energy utilization has not become fully possible because of the high cost and inadequate efficiencies of the current solar-energy-conversions.

Nanotechnology offers tools to develop cost-effective and cost-efficient based technologies for solar-energy conversions. It has the potential to increase the efficiency of current solar-energy-harvesting devices and also in the energy storage and use. Nanostructures such as nanowires, nanopillars, nanocones, nanodomes, nanotubes, nanorods, quatumdots, nanoparticles, etc. facilitate photon absorption, electron transport, and electron collection properties of the solar-energy-conversion devices and also lead to new generation devices for more efficient, cost-effective, and reliable solar energy conversion. This review specifically summarizes the contribution of the nanotechnology to photovoltaics, dye-sensitive solar cells, quantum-dot-sensitized solar cells, and solar hydrogen production devices.

Chapter 11: Convergence of Nanotechnology and Microbiology

The convergence of nanotechnology with microbiology is a nifty interdisciplinary research area that could amplify the limits of technology, enhance global health through formation of different drugs that can be effective against different infectious diseases, and for treatment of drinking water to kill the pathogens and make it safe for public use. Bacteria, fungi, and actinomycetes have been successfully used for the formation of nanoparticles of silver, gold, zinc, etc. The nature of cilia and flagella, which are molecular machines, nanotechnology can be extremely helpful in studying these structures in details. The formation of aerial hyphae by bacteria and fungi is directed by the order and controlled assembly of building blocks, and the formation of capsid in a virus is a process of molecular recognition and self assembly at the nano-scale. The size of nanoparticles is similar to that of most biological molecules and structures; therefore, nanoparticles can be useful for both in vivo and in vitro biomedical research and applications. As the microorganisms, especially bacteria, are becoming resistant to the commonly used antibiotics, an alternative antimicrobial agent that can be effective against the antibiotic resistant bacteria is needed. Much research is going on in the formation of nanoparticles from natural sources like plants to find effective and safe antimicrobial agents. Noble metal nanoparticles, particularly Silver Nanoparticles (SNPs), have shown a good antimicrobial activity against antibiotic-resistant bacteria. In the present chapter, we have highlighted the relationship between these two mighty disciplines. The chapter deals with many aspects like antimicrobial activity of nanoparticles, formation of nanoparticles using microorganisms, etc. The green synthesis of nanoparticles is an emerging new field of science; hence, it has been discussed in detail. As the use of nanoparticles is expected to increase in the coming years, there are concerns about the safety and effect of these NPs on human health and on environment. Hence, it is necessary to be aware of the precautionary measures while dealing with the nanoparticles.

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Chapter 1

Nanomaterials, Novel Preparation Routes, and Characterizations

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ABSTRACT

The important aspect of nanotechnology is the remarkable size dependant physico-chemical properties of nanomaterials that have led to the development of synthesis protocols for synthesizing nanomaterials over a range of sizes, shapes, and chemical compositions. This chapter describes the various aspects of nanotechnology: its dimensions and manipulation of matter with primary focus on inorganic materials. Detailed accounts of various methods lying within top-down and bottom-up synthesis approaches are discussed, like Chemical Vapour Condensation (CVC), arc discharge, hydrogen plasma-metal reaction, and laser pyrolysis in the vapour phase, microemulsion, hydrothermal, sol-gel, sonochemical taking place in the liquid phase, and ball milling carried out in the solid phase. The chapter also presents a brief account of the various characterization techniques used for the identification of the nanomaterials: X-ray diffraction, UV-visible spectroscopy, and electron microscopy (e.g. Transmission Electron Microscopy [TEM], Scanning Electron Microscopy [SEM], Atomic Force Microscopy [AFM]).

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INTRODUCTION

"Nanotechnology" broadly defined as the creation of objects and surfaces whose unique functions are the direct result of the nanoscale dimensions and / or organization. These unique properties may be mechanical, electrical, or photochemical and are not seen in the bulk materials. The prefix comes from the ancient Greek word *νᾶνος* through the Latin *nanus* meaning literally *dwarf* and, by extension, *very small*. Within the convention of International System of Units (SI) it is used to indicate the reduction factor of 10^{-9} times. Nanotechnology manipulates matter at the scale of one billionth of a meter. It is more of an approach to engineering than a science, although it draws on the scientific knowledge of biology, physics, chemistry, and materials science and is expected to change these sciences dramatically.

"Nanoscale" generally refers to objects 1-100 nm in one or more dimensions. At its lower limit this definition intentionally excludes individual molecules which generally define the lower end of the nanotechnology, i.e. nano derived features are as much a function of larger bulk materials approaching a molecular scale as they are a selective change in molecules' properties as they aggregate (Ratner, 2003).

Nanocrystals/Nanoparticles are crystalline clusters of a few hundred to a few thousand atoms with sizes of a few nanometres. Although more complex than individual atoms, their properties are different from bulk crystals. Due to their small size, much of their chemical and physical properties are dominated by their surfaces and not by their bulk volume. Nanocrystals can be synthesized from metallic materials such as gold (Brust, 1995; Brown 1999; Ahmad, 2013), silver (Rivas, 2001; Wani, 2010; Wani, 2011; Wani, 2013) or cobalt (Ershov, 2000; Puntes, 2001), from semiconductor materials such as cadmium sulphide (Murray, 1993; Merkoci, 2006), cadmium selenide (Steigerwald, 1990; Colvin, 1992), cadmium telluride (Eychmuller,2000; Talapin, 2001), gallium arsenide (Olshavsky, 1990) or indium phosphide (Guzelian, 1996; Micic, 1997), and from insulators such as iron oxide (Rockenberger, 1999; Santra, 2001) or titanium oxide (Trentler, 1999) and many others.

Inorganic nanosystems are defined as the chemical objects whose composition is merely inorganic, which exhibit new phenomenon due to quantum size effects due to the occurrence of large amounts of surfaces and interfaces because of their reduced size in the nanometre scale (1-100 nm). Infact, isolated molecules exhibit properties that follow quantum mechanical rules, while the chemical and physical properties of bulk materials obey the laws of quantum mechanics. In the middle, nanosystems display electronic, photochemical, electrochemical, optical, magnetic, mechanical or catalytic properties that differ significantly not only from those of molecular units, but also from those of macroscopic systems.

HISTORICAL BACKGROUND

The concept of nanotechnology though considered to be a modern science has its history dating to as far back as the 9th century. Nanoparticles of gold and silver were used by the artisans of Mesopotamia to generate a glittering effect to pots. The first scientific description of the properties of nanoparticles was provided in 1857 by Michael Faraday in his famous paper "Experimental relations of gold (and other metals) to light" (Faraday, 1857). In 1959, Richard Feynman gave a talk describing molecular machines built with atomic precision. This was considered the first talk on nanotechnology. This was entitled "There's plenty of space at the bottom". The 1950's and the 1960's saw the world turning its focus towards the use of nanoparticles in the field of drug delivery. In Japan, Sugibayashi et al., (1977) bound 5-fluorouracil to the albumin nanoparticles, and found denaturation temperature dependent differences in drug release as well as in the body distribution in mice after intravenous tail vein injection. An increase in life span was observed after intraperitoneal injection of the nanoparticles into Ehrlich Ascites Carcinoma-bearing mice (Kreuter, 2007). The nano-revolution conceptually started in the early 1980's with the first paper on nanotechnology being published in 1981 by K. Eric Drexler of Space Systems Laboratory, Massachuetts Institute of Technology. This was entitled "An approach to the development of general capabilities for molecular manipulation". With gradual advancements such as the invention of techniques like TEM, AFM, DLS etc., nanotechnology today has reached a stage where it is considered as the future to all technologies.

Synthesis Aspects of Nanomaterials

Atoms and molecules are the essential building blocks of every object. The manner in which things are constructed with these basic units is vitally important to understand their properties and their reciprocal interactions. An efficient control of the synthetic pathways is essential during the preparation of nanobuilding blocks with different sizes and shapes that can lead to the creation of new devices and technologies with improved performances. To do this, two opposite, but complementary approaches are pursued. One is a top-down strategy of miniaturizing current components and materials, while the other is a bottom-up strategy of building ever-more-complex molecular structures atom by atom or molecule by molecule. These two different methods highlight the organization level of nanosystems as the crossing point hanging between the worlds of molecular objects and bulk materials. The integration of the two techniques is expected to provide, at least in principle, the widest combination of tools for nanofabrication.

Top-Down Approach

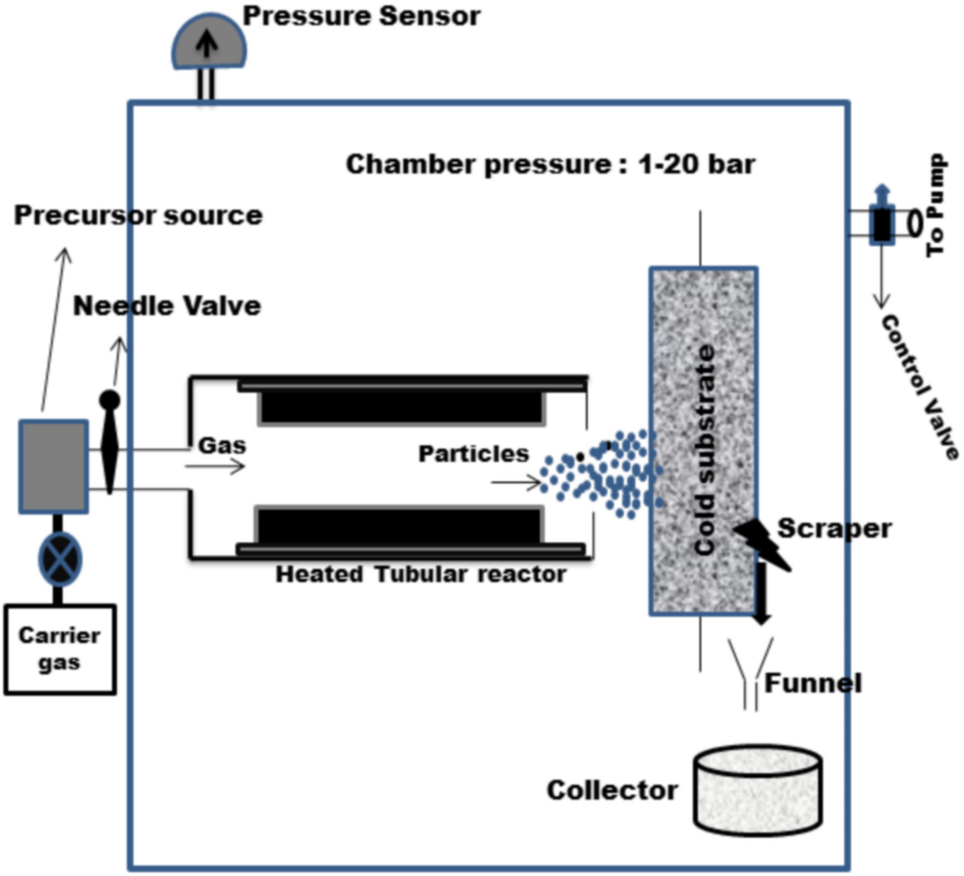
The top-down approach was advanced by Richard Feynman in his 1959 landmark lecture stating that "there is plenty of room at the bottom" (Glenn, 2006). This approach is ideal for obtaining structures with long-range order and for making connections with macroscopic world. It is based on miniaturizing techniques, such as machining, templating or lithographic techniques. Top-down methods usually start from patterns generated at larger scale (generally at microscale) and then they are reduced to nanoscale. A key advantage of the top-down approach is that the parts are both patterned and built in place, so that no further assembly steps are needed.

It is worth underlining that the development in the top-down methodology was mainly driven from the traditional disciplines of materials engineering and physics, whereas the role of inorganic chemists has been minor in the exploitation of these techniques. The top down approach is normally called physical methods and applied by physists. Several methods have been reported for the synthesis of nanomaterials by the top down approach as has been discussed below.

Chemical Vapour Condensation (CVC)

In this approach, vapour phase precursors are brought into a hot-wall reactor under conditions that favour nucleation of particles in the vapour phase. This method has tremendous flexibility in producing a wide range of materials and can take advantage of the huge database of precursor chemistries that have been developed for chemical vapour deposition (CVD) processes (Swihart, 2003). The precursors can be solid, liquid or gas at ambient conditions, but are delivered to the reactor as a vapour (from a bubbler or sublimation source, as necessary) (Swihart, 2003). This method has been developed for preparation of many kinds of nanoparticles with a narrow size distribution. Their unique properties and the improved performances are determined by their particle sizes, surface structures, and interparticle interactions. The schematic representation of a chemical vapour condensation set up is shown in Figure 1.This process proceeds essentially in two separate segments; a reaction chamber that is maintained at vacuum and a precursor delivery system operating at ambient pressure. The segments are connected via a needle valve, which continuously monitors and controls the flow rate of precursor/carrier gas stream from the gas delivery system into the reaction chamber. During the short residence time of precursor in the heated tube, individual molecules start to decompose and combine to form small clusters or nanoparticles. At the outlet of the furnace tube, rapid expansion of the two-phase gas stream consisting of gas plus nanoparticles serves to mitigate particle growth and agglomeration. Finally, the nanoparticles condense out on a rotating liquid nitrogen cooled substrate from which the particles can be scraped off and collected (Tavakoli, 2007). There are many good examples of the application of this method in the recent literature. Ostraat et al. have demonstrated a two-stage reactor for producing oxide-coated silicon nanoparticles that have been incorporated into high-density nonvolatile memory devices (Ostraat, 2001). Magnusson et al.produced tungsten nanoparticles by decomposition of tungsten hexacarbonyl (Magnusson, 2000) and Nasibulin et al.produced copper and copper oxide nanoparticles from copper acetylacetonate (Nasibulin, 2002). A real beauty of this approach is the formation of salt encapsulated particles by using sodium metal/metal halide chemistry (Ehrman, 1999). The salt-encapsulation can potentially be used to prevent agglomeration of the particles, and the salt can then be washed away in a post-processing step.

Figure 1. Schematic representation of a Chemical Vapour Condensation (CVC) setup



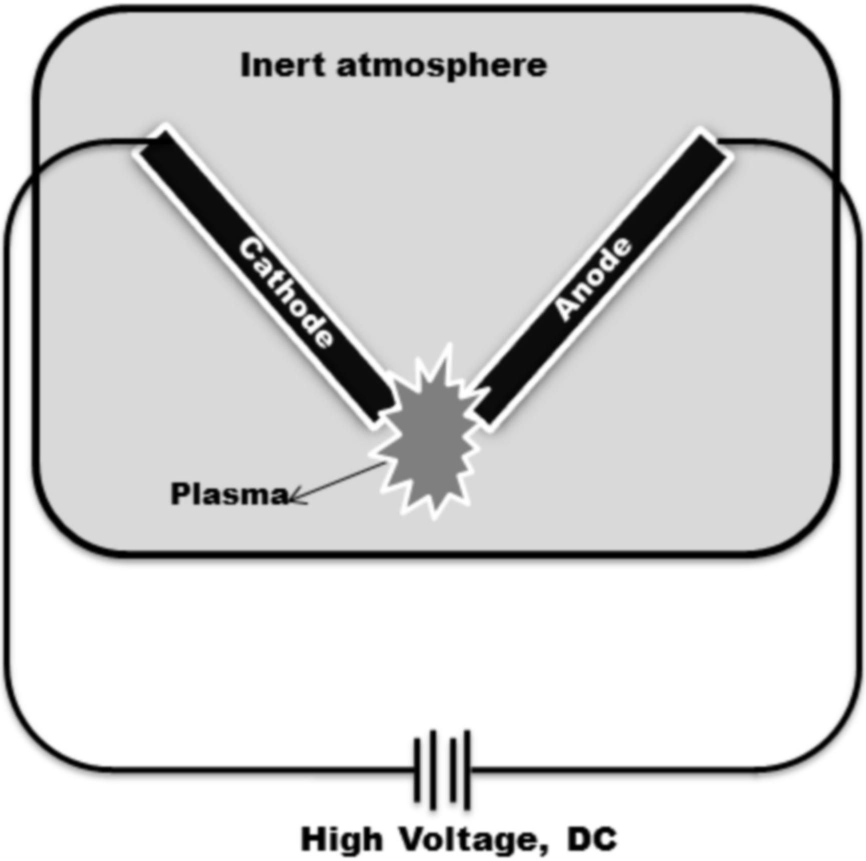
Arc Discharge

This method achieves the super saturation necessary to induce nucleation by vaporizing metals in the form of charge electrodes in presence of an inert background gas until the breakdown voltage is reached. At the breakdown voltage, the arc of spark formed across the electrodes then vaporizes a small amount of metal. This method produces very small amounts of nanoparticles, but does so reproducibly. Metal-oxides or other compounds can be produced by this method by employing oxygen or another reactive background gas. The background gas present can be continuously pulsed between the electrodes at the same time that the arc is initiated, as in the pulsed arc molecular beam deposition system. Dravid and co-workers (Dravid, 1995) modified the arc discharge method to successfully produce nanophase Ni encapsulated in graphite shells. Harris and Tsang (Harris, 1998) prepared carbon-encapsulated metal or metal carbides using the high-temperature (1800°C) treatment of microporous carbon materials impregnated with metal. Magnetic metal-filled carbon nanocapsules, ranging from 10 nm to 50 nm in diameter have been synthesized by using an arc discharge apparatus and purified by concentrated acid treatment (Chen, 2002). Purification methods used for removing various contaminants in arc-discharge products were reported (Chen, 2002; Ajayan, 1999). Figure 2 shows the schematic drawing of an arc reactor. Usually an anode is formed by a graphite rod in which a hole is drilled and filled with a mixture of appropriate catalysts such as Fe, Mo, metal composite and carbon source, i.e. graphite powder. The catalyst-filled anode is supported by a holder connected to a translation-motion feed through a cathode, a pure graphite rod fixed by a stationary holder(Wang, 2004). The arc reactor may be filled with an inert gas such as He, Ar, and water, or hydrogen.

Hydrogen Plasma

Another method proceeding in the vapour phase is hydrogen plasma commonly known as hydrogen plasma metal reaction (HPMR). This method was developed by Ohno and Uda(Ohno, 1984) and is used to produce nanoparticles by DC thermal plasma in a mixture of hydrogen and argon gas. In principle, it is similar to the arc discharge method, with some differences. It is an aerosol method and is a very promising way to produce inter metallic compound nanoparticles with the possibility to control the content of each element in the nanoparticles accurately. It is also a suitable method to prepare ultrafine particles (UFPs) industrially at low cost (Liu, 2003; Liu, 2003). Nanoparticles of several metals and alloys have been prepared by employing this versatile method (Liu, 2003; Shao, 2003). The mean particle size of the nanoparticles can be controlled by changing the content of hydrogen in the

Figure 2. Schematic diagram of Arc discharge set up



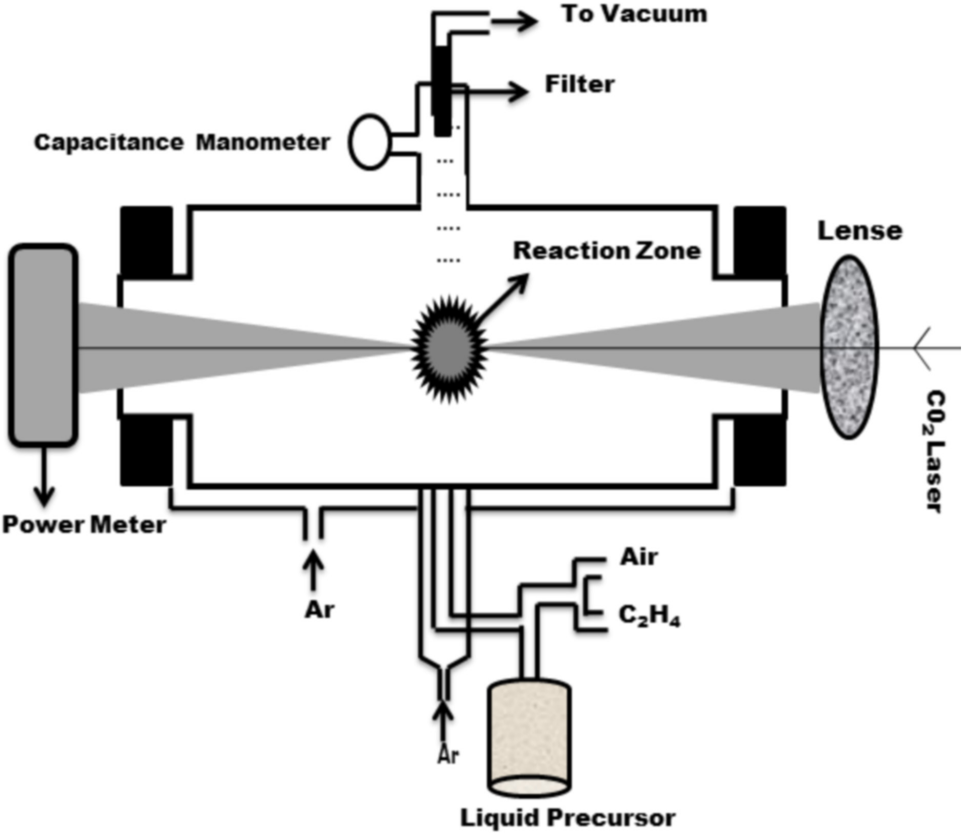
arcing atmosphere and arc current. The former is the main controlling factor of the process. In hydrogen plasma method, the evaporation rate of metal elements is an important factor affecting the rate of generation of metal nanoparticles (Shao, 2004).

Laser Pyrolysis

An alternate means of heating the precursors to induce reaction and homogeneous nucleation is absorption of laser energy. This method allows highly localized heating and rapid cooling, as compared to heating the gas in a furnace, since only the gas (or a portion of the gas) is heated, and its heat capacity is small. Heating is usually performed by an infrared (CO_2) laser, whose energy is either absorbed by one of the precursors or by an inert photosensitizer such as sulfur hexafluoride (Swihart, 2003). Laser-driven pyrolysis of organometallic precursors is a general synthetic tool allowing the synthesis of nanoscale particles ranging from 2 nm to 20 nm at rapid heating and cooling rates (≈100 000°C s^{-1}) (Grimes, 2000; David, 2004). Nanoparticles of many materials have been obtained using this method (Borsella, 2007; Kamlag, 2001; Ledoux, 2002; Ledoux, 2002).

A scheme of an apparatus used for laser synthesis of nanosized powder is depicted in Figure 3. CO2 laser radiation orthogonally intersects the reactant gas stream admitted to the center of the reaction cell through a nozzle. The reactant gas is confined to the flow axis by coaxial Argon, Ar stream. The nucleated particles formed during the reaction are carried by the gas stream towards the cell exit where they are collected in a trap, closed with a microporous filter in the direction of the rotary pump.

Figure 3. Schematic diagram of laser pyrolysis system



This technique is based on the resonant interaction between laser photons and at least one gaseous species, reactants or sensitizer. A sensitizer is an energy transfer agent that is excited by the absorption of the CO_2 laser radiation and transfers, by collision, the absorbed energy towards the reactants (Dumitrache, 2005).

High Energy Ball Milling

High energy ball milling is a convenient way to produce nanosized powders(Janot, 2002) and is the most common method reported in the literature for the synthesis of intermetallic nanoparticles (Pithawalla, 2000). This method is a mechanical process that requires high energy for the synthesis of various glassy, metastable, and amorphous materials(Roh, 2001)and has been widely used to produce amorphous alloys in various systems, such as metal-metal, transition metal-metalloid, and even metal-carbon systems(Murty, 1991). Before a mechanical milling is started, powder(s) is loaded together with several heavy balls (steel or tungsten carbide) in a container. By vigorously shaking or high-speed rotation, a high mechanical energy is applied on the powders because of collision with heavy balls. The milling process promotes the diffusion of particles. Hence, an alloying phase may be formed at low temperature (mechanochemical process) (Chin, 2005). Thermal energy generated during mechanical alloying or reactive milling (Murty, 1991) facilitates chemical reactions leading to the metallothermic reduction and/or resulting in the formation of compounds. Most of the oxides were reduced by the solid metallic reducing agents through an unstable combustion reaction, which is similar in nature to the thermally ignited self-propagating high-temperature synthesis (SHS) technique. The high defect densities as well as the nanocrystalline particles induced in the reactive milling enhance diffusion rates through the product phases. The reaction proceeds in a controlled manner without the occurrence of spontaneous combustion provided that diluents are added to the powder mixture to prevent powder agglomeration. The role of diluents is to reduce local temperatures and inhibit the particle welding process.

In spite of simplicity and efficiency of ball milling in synthesis of nanoparticles of metallic alloys, there are some problems and limitations of this method. The microstructure of the milling products is very sensitive to the grinding conditions and may be affected by unwanted contamination from the milling media and atmosphere. In addition, extensive long periods of milling time may be required to obtain particles smaller than 20 nm (Pithawalla, 2000).

Bottom-Up Approach

The Bottom-up, or self-assembly, approaches to nanofabrication involve gradual additions of atoms or groups of atoms. This technique uses chemical or physical forces operating at the nanoscale to assemble basic units into larger structures. The chemical growth of nanometer-sized materials often implies colloidal or supramolecular systems and it frequently passes through phase transformations, such as sonochemical deposition on surfaces or precipitation of a solid phase from solution. The bottom-up approach is also called chemical methods. Normally chemical methods are used to produce small clusters of specific atoms, which can then self-assemble into more-elaborated structures.This approach allows a good control over the scale dimension, even from atomic or molecular level, and they are not as expensive as top-down approaches. The various techniques used in the bottom up approach are briefly discussed below.

Microemulsion/Reverse Micellar Method

The word microemulsion was originally proposed by Jack H. Schulman and the co-workers in 1959. They prepared a quaternary solution of water, benzene, hexanol, and k-oleate which was stable, homogenous, and slightly opalescent; these systems became clear as soon as a short chain alcohol was added. Schulman and co-workers also described how to prepare these transparent microemulsion systems. Basically, a coarse emulsion was prepared and the system was then titrated to clarify by adding a co-surfactant. When the combination of the four components was right, the system became transparent spontaneously. When a co-surfactant is titrated into a coarse microemulsion (composed of a mixture of water and surfactant) in a sufficient quantity to obtain microdroplet, the resultant solution is low in viscosity, transparent, isotropic, and very stable. The titration from opaque emulsion to transparent solution is spontaneous and well defined. It was found that these systems are made of spherical micro droplets with a diameter between 5 to 20 nm. It was only in 1959 that Schulman proposed to call these systems microemulsions: Previously, he used term such as transparent water and oil dispersion, oleophatic hydromicelles, or hydropathic oleo micelles.

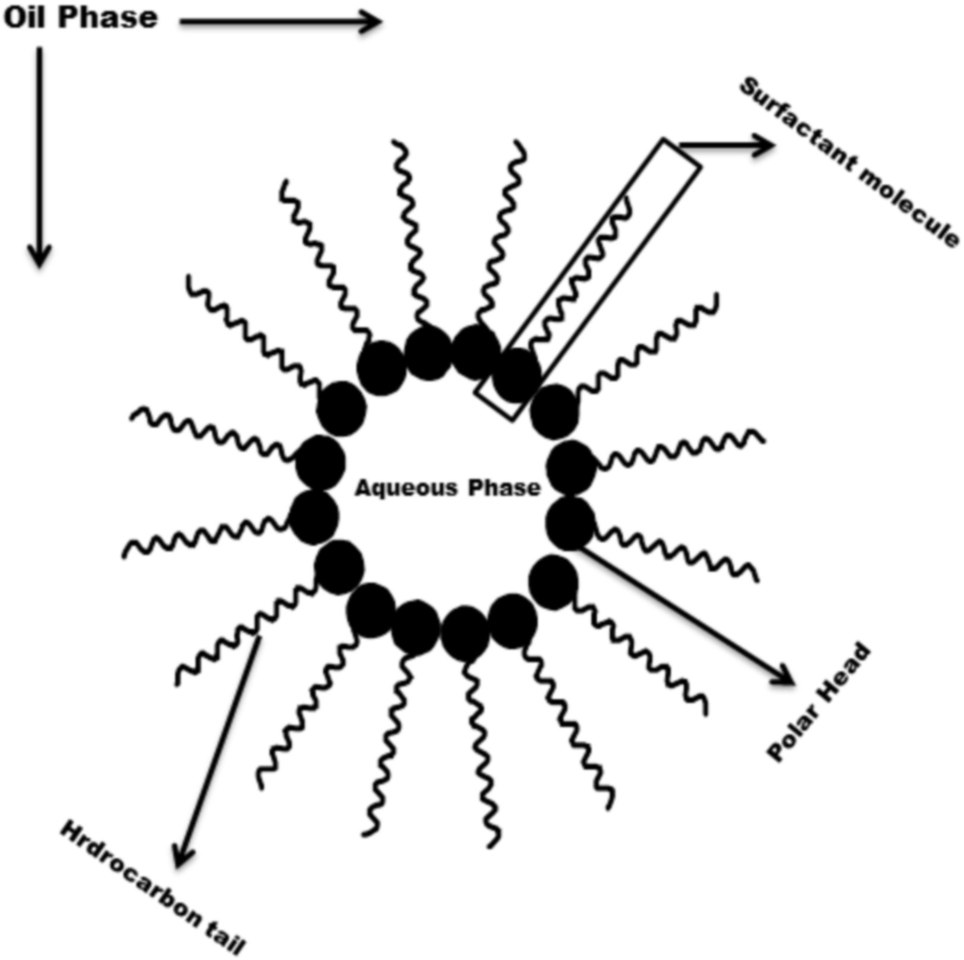
Microemulsions are isotropic, macroscopically homogeneous, and thermodynamically stable solutions containing at least three components, namely a polar phase (usually water), a nonpolar phase (usually oil), and a surfactant. On a microscopic level the surfactant molecules form an interfacial film separating the polar and nonpolar domains. This interfacial layer forms different microstructures ranging from droplets of oil dispersed in a continuous water phase (o/w-micro emulsion) over a bicontinuous "sponge" phase to water droplets dispersed in a continuous oil phase (w/o-micro emulsion). The latter can be used as nano-reactors for the synthesis of nanoparticles with a low polydispersity.

Water-in-Oil (W/O) Microemulsion

A “water-in-oil” microemulsion is formed when water is dispersed in a hydrocarbon based continuous phase, and is normally located towards the oil apex of a water / oil / surfactant triangular phase diagram. In this region, thermodynamically driven surfactant self-assembly generates aggregates known as reverse or inverted micelles(Ekwall, 1971). In a typical structure of a reverse micelle (Figure 4), the polar head groups of the surfactants attract the aqueous phase and pointed inward direction, however, the hydrocarbon chain of the surfactants attract the oil phase and pointed outward direction. It is important to note that these micelles frequently collide via random Brownian motion and coalesce to form dimers, which may exchange contents then break apart again(Bommarius, 1990; Fletcher, 1987). Clearly, any inorganic reagents encapsulated inside the micelles will become mixed. This exchange process is fundamental to nanoparticle synthesis inside reverse micellar ‘templates’, allowing different reactants solubilized in separate micellar solutions to react upon mixing. Reverse micelles are also described as “nanoreactors”, because the typical diameter of the aqueous core is 5-10 nm. Hence the micelles provide a suitable environment for controlled nucleation and growth. In addition, at the latter stages of growth, steric stabilization provided by the surfactant layer prevents the nanoparticles from aggregation (Lopez, 2004). In general there are two methods for nanoparticle synthesis using micro emulsion techniques (Asare, 1990). The first method is called the one micro emulsion method. This method includes “energy triggering” and the “one microemulsion plus reactant” method. In the energy triggering method, the reaction is initiated by implementing a triggering agent into the single microemulsion which contains a reactant precursor. This fluid system is activated in order to initiate the reactions that eventually lead to particle formation. Besides the energy triggering method, the other method is the one microemulsion plus reactant method. In this method, the reaction is initiated by directly adding the pure reactant (liquid or gaseous phase) into the micro emulsion containing another reactant. The ions e.g. metal salts are first dissolved in the aqueous phase of a w/o micro emulsion. Then the precipitating agent, in the form of an aqueous solution (e.g. salt NaOH) or a gas phase [e.g. NH_3 (g), $CaCO_3$ (g)], is fed into the microemulsion solution. Another scenario within the one microemulsion-plus reactant method is that the precipitating agent is first dissolved in the polar core and a metal-containing solution (e.g. organic precursor) is subsequently added into the microemulsions. The one-microemulsion method generally is driven by the diffusion-based process, since the second trigger/reactant is diffusing into the droplets containing the reactant in the used microemulsion. The second method which is also often used for preparing nanoparticles is the two microemulsion method. In this method two reactants, A and B are dissolved in the aqueous nanodroplets of two separate microemulsions and are then mixed together.

In the microemulsions mixing method, the two reactants are premicellized in two separate microemulsions and are brought into contact through intermicellar exchange to conduct the reaction. In some cases, where reaction rates are very rapid, the overall reaction rate is governed by the intermicellar exchange rate. The intermicellar exchange rate plays a significant role in the nanoparticle formation(Bagwe, 2000). Different research groups have obtained trends for the effect of intermicellar exchange rate(Bagwe, 2000), water-to-surfactant molar ratio and concentration of reactants (Monnoyer, 1995). Several reports are available in

Figure 4. Structure of a reverse micelle



the literature on the synthesis of titanium and zirconium based dielectric oxides and transition metal oxalate nanorods and their nanoparticles (Ahmad, 2004; Ahmad, 2006; Ganguli, 2007, Vaidya, 2008) through the reverse micellar route using various surfactants.

Sonochemical Method

Sonochemistry is the research area, in which molecules undergo chemical reactions due to the application of powerful ultrasound radiation. Ultrasound is defined as a sound of frequency beyond which the human ear can respond. The normal range of hearing is between 16 Hz to 18 kHz and ultrasound is generally considered to lie between 20 kHz to 100 MHz. Sonochemistry uses frequencies between 20 kHz and 40 kHz because this is the range employed in common equipments. High frequency ultrasound above 5 MHz does not produce any cavitation in the chemical reactions and therefore this frequency range is used normally in medical imaging.

The ultrasound irradiation in chemical processes principally derives from two main processes:

1. Acoustic streaming.
2. Acoustic cavitation.

1. **Acoustic Streaming:** A sound wave loses its momentum when travelling through a liquid, e.g. due to viscous friction (Lighthill, 1978). The momentum is transferred to the liquid, resulting in the formation of liquid motion in the direction of wave propagation. This sound induced flow is often referred to as acoustic streaming. Typically, streaming velocities of a few centimetres up to a meter per second can be obtained. In the presence of a small particle, friction between the fluid and the particle can also give rise to micro streaming (Peuker, 2006). Due to these phenomena, ultrasound provides a non invasive means for enhancing mass and heat transfer (Riera, 2004).However, the energy efficiency of ultrasound-induced mixing is rather low compared to conventional mechanical stirring, since a substantial part of the sound energy (~99%) is converted into heat and used for other processes, e.g. acoustic cavitation.
2. **Acoustic Cavitation:** A liquid contains gas cavities stabilized against dissolution by adherence to a surface or an impurity (Leighton, 1994). Under the influence of the rarefaction pressure from a sound wave, cavities can also arise from gas dissolved in the liquid as well as by partial vaporization of the liquid. Depending on the size of these cavities, the ultrasound frequency and the pressure amplitude, the pressure variations from the sound wave set the cavities into radial motion. During the rarefaction phase, the negative pressure

> from the sound wave induces expansion of the cavity until a maximum radius is observed. For specific conditions, the cavity is set into nonlinear motion and the cavity collapses in a relatively short period of time as compared to the expansion phase. It is the fate of these cavities when they collapse which generates the energy for chemical and mechanical effects. Temperatures of several thousands of Kelvins, pressure of hundreds of bars, and extreme heating and cooling rates can be obtained and for these conditions the collapsing cavity is often referred to as hot spot (McNamara, 1999; Suslick, 1991).The collapse is followed by a repeated oscillation, denoted as the after bounce, until the rarefaction phase of the sound wave sets in again and a new cavitation cycle starts.

The chemical reactions driven by intense ultrasonic waves that are strong enough to produce cavitations are oxidation, reduction, dissolution, and decomposition. Other reactions such as promotion of polymerization have also been reported to be induced by ultrasound (Tavakoli, 2007). The main advantages of the sonochemical method are its simplicity, operating conditions (ambient conditions) and easy control of the size of nanoparticles by using precursors with different concentrations in the solution (Umer, 2012).

Solvothermal Method

In the solvothermal processes, the chemical reaction takes place in a sealed vessel such as bomb or autoclave, where solvents are brought to temperatures well above their boiling points (Umer, 2012). Consequently a solvothermal process involves high pressures. The selected temperature depends on the required reactions for obtaining the target material through the involved process. When water is used as a solvent in the process, then this method is called hydrothermal process, however, when solvent is other than water, then it is called as solvotherrmal process. This method exploits the solubility of almost all inorganic substances in water at elevated temperatures and pressures and subsequent crystallization of the dissolved material from the fluid. Water at elevated temperatures plays an essential role in the precursor material transformation because the vapor pressure is much higher and the structure of water at elevated temperatures is different from that at room temperature. The properties of the reactants, including their solubility and reactivity, also change at high temperatures (Tavakoli, 2007). This method has been used to synthesize a variety of nanoparticles ranging from metal nanoparticles to ferrites and oxides (Ahmad, 2013; Ataie, 1996; Wani, 2010; Mishra, 2004)

There are several parameters which are involved in the solvothermal process to produce the nanomaterials of desired size and shape. Among them chemical and thermodynamic parameters are important.

1. **Chemical Parameters:** Two different parameters can be taken into account: The chemical composition of the precursors must be appropriate to that of the target materials. In addition, the concentration of the precursors, the nature of the reagents and the nature of the solvent play an important role on the control of the shape and size of nanocrystallites e.g. CdSe and CeTe nanocrystals have been prepared through the solvothermal route (Wang, 2006) and their crystallites-shape is controlled with the concentration of the precursors. The interactions between the reagents and solvents play an important role in the solvothermal reactions. The selection of the solvent also plays a key role to control the chemical mechanisms of the target material.
2. **Thermodynamic Parameters:** The parameters such as temperature, pressure and the reaction time are called the thermodynamic parameters. The solvothermal reactions normally occur in mild temperature conditions, (T <400°C). Temperature and pressure conditions are used to improve the solubility; the increase of such parameters induces an enhancement of the precursors-concentration into the solvent and then favours the growth process of the nanomaterials formation.

Sol-Gel Method

The sol-gel methods, or *"chimie douce"*, was developed in the 1950s and 60s (Roy, 1954; Roy, 1956; Roy, 1969), but the first reported studies of sol-gel synthesis goes back to the middle of the nineteenth century (Ebelmen, 1846; Graham, 1864). By definition, a sol is a colloidal dispersion of small solid particles in a liquid, and a gel is a pseudo-solid where the solvent is dispersed in a polymeric network. Sol-gel processing is a popular processing route for the synthesis of a wide variety of materials in desired shapes (particles, fibers, or films). The formation of a sol by dissolving the metal alkoxide, metal-organic, or metal-inorganic salt precursors in a suitable solvent is the primary step in a sol-gel process. Upon drying the sol, a polymeric network is formed in which the solvent molecules are trapped inside a solid (gel) (Livage, 1988; Brinker, 1990). Subsequent drying of the gel followed by calcination and sintering leads to the final ceramic product. As the reacting species are homogenized at the atomic level in a sol-gel process, the diffusion distances are considerably reduced compared to a conventional solid-state reaction; thereby the product forms at much lower temperatures.

Depending on the nature of the precursor, which can be an aqueous solution of an inorganic salt or metal-organic compound, the species involved in the intermediate steps of the sol-gel process differ. The nature and composition of the intermediate species formed also depend on the oxidation state, pH, or the concentration of the solution. These factors are crucial in the formation of a colloid and its stability. Metal alkoxides are noted for the very high reactivity toward hydrolysis and are, therefore, being used as a common starting material for the sol-gel synthesis (Bradely, 1978). Electronegativity, valence states, and the coordination number of the metal affect the rate of hydrolysis and hence the nature of the colloidal solution. The resultant properties of the synthesized powder depend on the colloidal aggregate formed as a result of the hydrolysis step.

The sol-gel process includes four steps: hydrolysis, polycondensation, drying, and thermal decomposition. Precursors of the metal or nonmetal alkoxides hydrolyze with water or alcohols according to the hydrolysis process (shown in Box 1).

After the solution has been condensed to a gel, the solvent must be removed. Higher temperature calcinations is needed to decompose the organic precursor. The size of the sol particles depends on the solution composition, pH, and temperature (Burda, 2005; Nagineni, 2005). By controlling these factors, one can tune the size of the particles (Tavakoli, 2007).

Polymeric Citrate Precursor Method

In 1967, Pechini developed a modified sol-gel process for materials that are not suitable for traditional sol-gel type reactions due to their unfavorable hydrolysis equilibria (Pechini, 1967). Although Pechini's original method was developed specifically for the preparation of thin films, it was later adapted to the synthesis of powdered products. The Pechini method, as it is now referred to, relies on the formation of complexes of alkali metals, alkaline earths, transition metals, or even nonmetals with bi and tri-dendate organic chelating agents such as citric acid. A polyalcohol such as ethylene glycol is added to establish linkages between the chelates by a polyesterification reaction, resulting in gelation of the reaction mixture. The function of citric acid is to chelate the metal cations. After drying, the gel is heated to initiate pyrolysis of the organic species, resulting in agglomerated sub-

Box 1.

$$M(OR)x + mH_2O \longrightarrow M(OR)x\text{-}m(OH)m + mROH$$

where if *m* is up to *x*, the reaction is total hydrolysis, followed by either a water condensation or an alcohol condensation

$$2M(OR)x\text{-}m(OH)m \longrightarrow (OH)m\text{-}1(OR)x\text{-}m\text{-}M\text{-}O\text{-}M(OR)x\text{-}m\text{-}1 + ROH$$

The total reaction can be expressed as

$$M(OR)x + x/2H2O \longrightarrow MOx/2 + xHOR$$

In addition to water and alcohol, an acid or a base can also help to hydrolyze the precursor. In case of an acid, a reaction takes place between alkoxide and the acid.

$$\text{-}M\text{-}OR + AOH \longrightarrow \text{-}M\text{-}O\text{-}A + ROH$$

micron or nanosized oxide particles. The advantage of the Pechini method lies in the elimination of the requirement that the metals involved form suitable hydroxo complexes. Chelating agents tend to form stable complexes with a variety of metals over fairly wide pH ranges, allowing for the relatively easy synthesis of oxides of considerable complexity.

The literature contains numerous variations of the Pechini method, most involving alternative chelating agents. The Pechini method does afford some control over particle size, but this is primarily achieved by variation of the calcination temperatures. If a pure product (free of organic contaminants) is to be obtained, calcination temperatures of at least 300 °C are usually necessary, and some chelating agents require substantially higher decomposition temperatures (Cushing, 2004).

Co-Precipitation

Many of the earliest synthesis of nanoparticles were achieved by the co-precipitation of sparingly soluble products from aqueous solutions followed by thermal decomposition of those products to oxides. Co-precipitation reactions involve the simultaneous occurrence of nucleation, growth, coarsening, and/or agglomeration processes. Due to the difficulties in isolating each process for independent study, the fundamental mechanisms of co-precipitation are still not thoroughly understood. In general, co-precipitation reactions tend to exhibit the following characteristics:

1. The products of precipitation reactions are generally sparingly soluble species formed under conditions of high supersaturation.
2. Such conditions dictate that nucleation will be a key step of the precipitation process and that a large number of small particles will be formed.
3. Secondary processes, such as Ostwald ripening and aggregation, will dramatically affect the size, morphology, and properties of the products.
4. The supersaturation conditions necessary to induce precipitation are usually the result of a chemical reaction. As such, any reaction conditions influencing the mixing process, such as rate of reactant addition and stirring rate, must be considered relevant to product size, morphology, and particle size distribution (Cushing, 2004).

Beyond simple addition/exchange reactions, precipitation can be induced by numerous other methods, such as chemical reduction, photoreduction, oxidation, and hydrolysis. Alternatively, precipitation can be induced by altering other parameters related to solubility, most notably temperature and concentration. Merely inducing precipitation of a compound, however, does not guarantee that the product will be nanoparticulate and/or monodispersed. The processes of nucleation and growth govern the particle size and morphology of products in precipitation reactions. When precipitation begins, numerous small crystallites initially form (nucleation), but they tend to quickly aggregate together to form larger, more thermodynamically stable particles (growth).

Due to the various thermodynamics parameters like nucleation, growth and Ostwald ripening of the primary seeds to form nanoparticles of maximum surface/volume ratio, the agglomeration of small particles precipitated from solutions is practically inevitable in the absence of a stabilizer (Reetz, 1995). There are generally two approaches to nanoparticle stabilization: (a) steric repulsion between particles caused by surfactants, polymers, or other organic species bound to the nanoparticles' surfaces (generically referred to as *capping ligands*) and (b) electrostatic (van der Waals) repulsions resulting from the chemisorption of charged species (usually, though not necessarily, H^+ or OH^-) at the surfaces.

Limitations, Possible Solutions, and Future Perspectives

The physical and chemical methods described above, although, versatile are costly and sometimes hazardous. Therefore, in search of cheaper pathways for the synthesis of nanoparticles, scientists and researchers all over the world are now focusing their attention on the biomemetic approach for nanoparticle synthesis using microorganisms and plant extracts. Nature has devised various pathways for the synthesis of various micro and nano-scale length inorganic materials which have contributed to the development of new and largely unexplored area of research based on the biosynthesis of nanoparticles. Biosynthesis of nanoparticles is a kind of bottom up approach where the main reaction occurring is reduction/oxidation (Umar A, 2012). The microbial enzymes or the plant phytochemicals with anti oxidant or reducing properties are usually responsible for reduction of metal compounds into their respective nanoparticles. The three main steps in the preparation of nanoparticles that should be evaluated from a green chemistry perspective are the choice of the solvent medium used for the synthesis, the choice of an environmentally benign reducing agent and the choice of a non toxic material for the stabilization of the nanoparticles. Most of the synthetic methods reported to date rely heavily on organic solvents. This is mainly due to the hydrophobicity of the capping agents used (Raveendran, 2002). Synthesis using bio-organisms is compatible with the green chemistry principles: the bio-organism is (i) eco-friendly as are (ii) the reducing agent employed and (iii) the capping agent in the reaction (Li, 2007). Often chemical synthesis methods lead to the presence of some toxic chemical species adsorbed on the surface that may have adverse effects in medical applications (Parashar, 2009). This is not an issue when it comes to biosynthesized nanoparticles as they are eco friendly and biocompatible for pharmaceutical applications. Keeping the above discussion in consideration thus, the nanotechnologists need to focus attention on the discovery of new green methods or significant improvement in the already known or available methods to (1) eliminate the use of toxic reagents and solvents, (2) afford higher yields and fewer byproducts, (3) provide better control of particle size dispersity, (4) reduce the need for purification or the amount of solvent needed to carry out purification, and (5) enhance material utilization (e.g., in assembly reactions).

CHARACTERIZATION TECHNIQUES

The exciting developments in nanoparticle research must be effectively supported by a variety of structural characterization tools, as the characterization of nanoparticles provides invaluable information on the various microstructural, crystallographic, molecular, and atomic features, which can shed light on unique properties exhibited by these fascinating materials. In this section we will discuss some important characterization tools employed in nanoparticle research.

X-Ray Diffraction

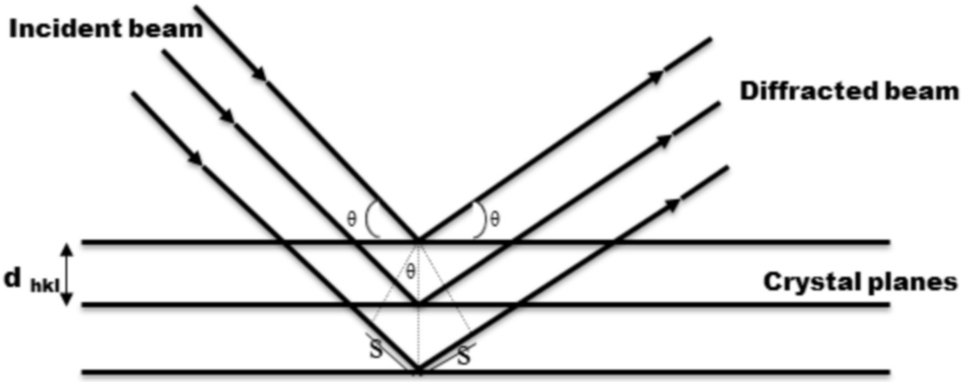
Any solid material with a periodically ordered atomic or molecular structure diffracts electromagnetic radiation of wavelengths of about the same length as the interatomic distances. In X-ray diffraction, the wavelength is ~1 Å (1.5406 Å for Cu$K\alpha1$ radiation). The diffracted radiation gives rise to specific patterns (diffraction patterns), which contain information of both the size and symmetry of the unit cell, as well as the location of the atoms within the cell.

When a beam of X-rays is falling on the surface of the crystal, then the diffraction occur from the crystal planes as shown in the Figure 5. Thus Bragg's derived a mathematical relationship between the X-ray wavelength, λ, the interplanar distance of the lattice planes (*hkl)*, $d_{hkl,}$ and the angle of the incident beam to the lattice planes, θ, is given by the following expression.

$$2d_{hkl}\,\mathrm{Sin}\,\theta = n\lambda$$

where n is the diffraction order. For very small crystallites such as nanocrystals or the particles of sizes less than 100 nm, then an additional peak broadening occurs in powder X- ray diffraction. The reason for this is that for very small crystallites, the number of parallel crystal planes *hkl* is too limited and the Bragg condition,

Figure 5. Diffraction phenomenon observed from the crystal planes



therefore, is not fulfilled. The peak broadening, however, can be used to estimate the average size of the crystallites from the Scherrer equation (Birks, 1946).

$$t = \frac{0.9\lambda}{BCos\theta}$$

where t = Grain size in Å,
λ = Wavelength of X-rays,
θ = Angle of diffraction.

B is the full width at half maximum and can be calculated with the help of Warren's formula (Warren, 1952).

$$B^2 = (B_M^{\ 2} - B_S^{\ 2})$$

where B_M and B_S are the FWHMs (full width at half maximum) in radians for the material or sample and a standard. The standard is needed to correct for instrumental broadening. The standard quartz of grain size of 2 μm is used in the diffractometer.

Electron Microscopy

In electron microscopy, high energy electrons are generated from a filament by using a large accelerating voltage (up to ~400 kV). According to the de Broglie equation, the high momentum of such electrons corresponds to very short wavelengths (λ is ~0.025 Å for an accelerating voltage of 200 kV). Relativistic effects have to be considered when the accelerating voltage is higher than ~100 kV, so the wavelength is calculated as in Eq.

$$\lambda = \frac{h}{(2em_0U + e^2U^2 / c^2)^{1/2}}$$

where h is the Planck constant, c is the speed of light, e is the electron charge, m_0 is the electron rest mass, and U is the accelerating voltage.

Electron microscopy is further extended to Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM) and Atomic Force Microscopy (AFM) on the basis of their resolution and various applications in Nanosicence and Nanotechnology.

Transmission Electron Microscopy (TEM)

Transmission electron microscope is a type of microscope that uses electrons to create an image of the target. It has a much higher magnification or power than a normal light microscope. Although modern electron microscopes can magnify objects up to two million times, they are still based upon Ruska's prototype and his co-relation between wave length and resolution.

Modern transmission electron microscopes can be used for a number of sophisticated modes, however, the most frequently used modes are object imaging and electron diffraction. In imaging mode, a transmission electron microscope is constituted of: (1) two or three condenser lenses to focus the electron beam on the sample, (2) an objective lens to form the diffraction in the back focal plane and the image of the sample in the image plane, (3) some intermediate lenses to magnify the image or the diffraction pattern on the screen. If the sample is thin (< 200 nm) and constituted of light chemical elements, the image presents a very low contrast when it is focused. To obtain an amplitude contrasted image, an objective diaphragm is inserted in the back focal plane to select the transmitted beam (and possibly few diffracted beam): the crystalline parts in Bragg orientation appear dark and the amorphous or non Bragg oriented parts appear bright. This imaging mode is called bright field mode BF. If the diffraction is constituted by many diffracting phases, each of them can be differentiated by selecting one of its diffracted beams with the objective diaphragm. To do that, the incident beam must be tilted so that the diffracted beam is put on the objective lens axis to avoid off axis aberrations. This mode is called dark field mode DF. The BF and DF modes are used for imaging materials to nanometer scale.

In diffraction mode the selected area diaphragm is used to select only one part of the imaged sample, for example, a particle or a precipitate. This mode is called selected area diffraction SAED. The spherical aberrations of the objective lens limit the area of the selected object to few hundred nanometers. Nevertheless, it is possible to obtain diffraction patterns of a smaller object by focusing the electron beam with the projector lenses to obtain a small spot size on the object surface (2-10 nm). The spots of SAED become disks whose radii depend on the condenser diaphragm. This is called microdiffraction. SAED and microdiffraction patterns of a crystal permit to obtain the symmetry of its lattice and calculate its interplanar distances with the Bragg law. This is useful to confirm the identification of a phase, after assumptions generally based on the literature of the studied system and on chemical analyses.

Scanning Electron Microscopy (SEM)

The scanning electron microscope (SEM) is one of the most versatile instruments available for examination and analysis of the microstructure morphology and chemical composition for the nanomaterials. The principal difference between TEM and SEM is that in SEM the electron beam is scanned over the sample surface, instead of being passed through the sample. The accelerating voltage used is also considerably lower (usually 5-20 kV). When the electron beam hits the atoms in the sample, both electrons and photons are emitted. The emitted electrons are collected and used to form a 3D picture of the sample, providing both topographical and structural information. Different kinds of electromagnetic radiation are emitted from the sample, and one of them is X-rays. Since the emitted X-ray photons have energies characteristic for each element, they can be used to determine the chemical composition of the sample, qualitatively and quantitatively, by a technique called energy dispersive X-ray spectroscopy (EDX).

Atomic Force Microscopy (AFM)

The atomic force microscope (AFM) measures the forces acting between a fine tip and a sample and the instrument was invented by Binning et al. in 1986. The tip is attached to the free end of a cantilever and is brought very close to a surface. Attractive or repulsive forces resulting from interactions between the tip and the surface will cause a positive or negative bending of the cantilever. The bending is detected by means of a laser beam, which is reflected from the back side of the cantilever (Clemente, 2008).

In an AFM the probe is very sharp; typically less than 50 nanometers in diameter and the areas scanned by the probe are less than 100 nm. In practice the heights of surface features scanned with an AFM are less than 20 nm. Scan times can range from a fraction of a second to many 10’s of minutes depending on the size of the scan and the height of the topographic features on a surface. Magnifications of the AFM may be between 100 X and 100,000,000 X in the horizontal (x-y) and vertical axis (West, 2009).

Components of the AFM Microscope

1. **Piezocrystals:** Piezocrystals are ceramic materials that expand or contract in the presence of voltage gradient and conversely, they develop an electrical potential in response to mechanical pressure. In this way, movements in x, y and z direction are possible.
2. **Probe:** The probe represents a micromachined cantilever with a sharp tip at one end, which is brought into interaction with the sample surface. Each probe has different specifications and shape. V-shaped cantilevers are the most popular (but also there are rectangular), providing low mechanical resistance to vertical deflection, and high resistance to lateral torsion. Cantilevers typically range from 100 to 200 μm in length (l), 10 to 40 μm in width (w), and 0.3 to 2μm in thickness (t). Integrated cantilevers are usually made from silicon (Si) or silicon nitride (Si_3N_4). They are characterized by their force constant and resonant frequency, which have to be chosen according to the sample to be studied.

AFM provides a number of advantages over conventional microscopy techniques. AFMs probe the sample and make measurements in three dimensions, *x, y,* and *z* (normal to the sample surface), thus enabling the presentation of three-dimensional images of a sample surface. This provides a great advantage over any microscope available previously. With good samples (clean, with no excessively large surface features), resolution in the *x-y* plane ranges from 0.1 to 1.0 nm and in the *z* direction is 0.01 nm (atomic resolution). AFMs require neither a vacuum environment nor any special sample preparation, and they can be used in either an ambient or liquid environment. With these advantages AFM has significantly impacted the fields of materials science, chemistry, biology, physics, and the specialized field of semiconductors.

Modes of Operation

1. **Contact Mode:** In the so-called contact-AFM mode, the tip makes soft “physical contact” with the surface of the sample. The deflection of the cantilever Dx is proportional to the force acting on the tip, via Hook’s law, F = -k. x, where k is the spring constant of the cantilever. In contact-mode the tip either scans at a constant small height above the surface or under the conditions of a constant force. In the constant height mode the height of the tip is fixed, whereas in the constant-force mode the deflection of the cantilever is fixed and the motion of the scanner in z-direction is recorded. By using contact-mode AFM, even “atomic resolution” images are obtained. For contact mode AFM imaging, it

is necessary to have a cantilever which is soft enough to be deflected by very small forces and has a high enough resonant frequency not to be susceptible to vibrational instabilities. Silicon Nitride tips are used for contact mode.

2. **Non Contact Mode:** In this mode, the probe operates in the attractive force region and the tip-sample interaction is minimized. The use of non-contact mode allowed scanning without influencing the shape of the sample by the tip-sample forces. In most cases, the cantilever of choice for this mode is the one having high spring constant of 20- 100 N/m so that it does not stick to the sample surface at small amplitudes. The tips mainly used for this mode are silicon probes.
3. **Tapping Mode (Intermittent Contact Mode):** The force measured by AFM can be classified into long-range forces and shortrange forces. The first class dominates when we scan at large distances from the surface and they can be Van der Waals force, capillary forces (due to the water layer often present in an ambient environment). When the scanning is in contact with the surface the short range forces are very important, in particular the quantum mechanical forces (Pauli Exclusion Principle forces). In tapping mode-AFM the cantilever is oscillating close to its resonance frequency.

UV-Visible Spectroscopy

Well separated metal nanoparticles and nanostructures with dimensions significantly smaller than the wavelength of exciting light are characterized by broad, intense absorption band in the UV- Visible range of the spectrum. The band width, peak height and position of the absorption maximum depends markedly on the size, size distribution, surface state, surface coverage and surrounding environment of the given nanoparticles and nanostructures (Brust, 1994; Qu, 2004). The optical properties of such small nanostructures are dominated by the collective oscillation of conduction electrons resulting from the interaction with electromagnetic radiation. Among the metal nanoparticles these optical properties are mainly observed in Au, Ag, and Cu, because of the presence of free conduction electrons. The electric field of the incoming radiation induces the formation of a dipole in the nanoparticle. A restoring force in the nanoparticles tries to compensate for this, resulting in a unique resonance wavelength (Liz-Marzan, 2004). The spectrophotometer is the instrument used for recording such absorption or transmittance of the solids as a function of wavelength of the electromagnetic radiation. The key components of a spectrophotometer are (Burgess, 1984):

1. **Sources:** The ideal light source would yield a constant intensity over all wavelengths with low noise and long-term stability. Two sources are commonly

used in UV-visible spectrophotometers. The first source, the deuterium arc lamp, yields a good intensity continuum in the UV region and provides useful intensity in the visible region. Although modern deuterium arc lamps have low noise, noise from the lamp is often the limiting factor in overall instrument noise performance. Over time, the intensity of light from a deuterium arc lamp decreases steadily. Such a lamp typically has a half-life (the time required for the intensity to fall to half of its initial value) of approximately 1,000 h. The second source, the tungsten-halogen lamp, yields good intensity over part of the UV spectrum and over the entire visible range. This type of lamp has very low noise and low drift and typically has a useful life of 10,000 h. Most spectrophotometers used to measure the UV-visible range contain both types of lamps.

2. **Dispersion devices:** Dispersion devices cause different wavelengths of light to be dispersed at different angles. When combined with an appropriate exit slit, these devices can be used to select a particular wavelength (or, more precisely, a narrow waveband) of light from a continuous source. Two types of dispersion devices i.e., prisms and holographic gratings, are commonly used in UV-visible spectrophotometers. Most modern spectrophotometers contain holographic gratings instead of prisms. These devices are made from glass blanks, onto which very narrow grooves are ruled. The dimensions of the grooves are of the same order as the wavelength of light to be dispersed. Finally, an aluminum coating is applied to create a reflecting source. Light falling on the grating is reflected at different angles, depending on the wavelength. Holographic gratings yield a linear angular dispersion with wavelength and are temperature insensitive.
3. **Detectors:** A detector converts a light signal into an electrical signal. Ideally, it should give a linear response over a wide range with low noise and high sensitivity. Spectrophotometers normally contain either a photomultiplier tube detector or a photodiode detector. Photodiodes are now a day's used as detectors in spectrophotometers. Photodiode detectors have a wider dynamic range and, as solid-state devices, are more robust than photomultiplier tube detectors.
4. **Optics:** Either lenses or concave mirrors are used to relay and focus light through the instrument. Simple lenses are inexpensive but suffer from chromatic aberration, that is, light of different wavelengths is not focused at exactly the same point in space. However, with careful design, the chromatic aberrations of individual lenses in an optical system can be used to cancel each other out, and an effective optical system can be constructed with these simple and inexpensive components.

CONCLUSION

This book chapter provides a brief discussion of the various aspects and dimensions of nanotechnology. A brief discussion is provided about the nanoparticles and its dimensions, with main focus on inorganic nanosystems and the distinctive features arising from the size reduction towards nanoregime. We have also highlighted the various aspects of synthesis of nanomaterials either in the form of thin films or bulk shapes with fairly good yields and short reaction times. These synthetic routes range from the simplest possible solution techniques like microemulsion, sonochemical, solvothermal, solgel which has been discussed under the category of chemical methods to some sophisticated processes/techniques like Chemical Vapour Condensation (CVC), Spray pyrolysis, Arc discharge etc., which come under the domain of physical methods of nanparticle synthesis. Over the years, each processing route has been modified to prepare nanoparticles with desired dimensions. In particular, plasma-assisted processing, sonication, hydrothermal, and sol-gel (colloidal) processing have been regularly used for the synthesis of a wide variety of oxide nanoparticles. Being one of the earliest well-established methods, sol-gel (colloidal) processing has been proven to be very effective for the synthesis of oxide nanoparticles and their self-assembly, which is currently being pursued as one of the frontier areas in the processing of nanostructured materials.

As the dimensions of the nanoparticles are progressively scaled down, highly accurate characterization techniques and spectroscopic measurements are often required for obtaining crucial information about the phase purity, structure and composition of the nanoparticles. Frequently used characterization techniques have been reviewed based on the developments in nanoparticle characterization. X-ray diffraction (XRD) continues to be the most common technique for the determination of grain size, strain, and phase characterization of the nanomaterials. Electron microscopy has proved to be an advanced characterization technique to clarify the materials structure at the nanometric scale. Transmission Electron Microscopy (TEM) is an advanced technique for observing the atomic arrangements. The Scanning Electron microscopy (SEM) has revolutionized the study of surface features and made an enormous contribution to science and engineering. Atomic force microscopy has an advantage over the previous electron microscopic techniques as it is now possible to probe the sample and make measurements in three directions, thus producing three dimensional image of the sample surface. Although electron microscopy provides essential information for the development of nanoscale materials and devices for various applications, complementary spectroscopic techniques like UV-Visible spectroscopy must also be incorporated to properly characterize the structure, offering many additional insights into their phenomena. Thus, it is anticipated that the role and capability of all these techniques and their combinations will only continue to increase in the future.

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KEY TERMS AND DEFINITIONS

Agglomeration: The term refers to the formation of agglomerates (secondary particles) when primary particles are held together by weak surface forces (soft agglomerates) such as van der Waals forces or capillary forces or by strong chemical bonds (hard agglomerates) during the synthesis of ceramic powders.

Domains: Under favorable energetics, certain regions termed domains are formed in materials within which a given property is identical with respect to magnitude and direction. For example, the formation of domains, wherein each domain has identical electric or magnetic dipole moments aligned in a particular direction, in ferroelectric or ferromagnetic samples.

Grains: Individual crystals, which combine to form a polycrystalline structure. The sizes of the grains in a material can be estimated from the broadening of the peaks in X-ray diffraction (XRD) patterns.

Nanomaterials: A broad class of materials that includes nanometer-sized crystallites, nanometer-sized powders, macroscopic objects, and films composed of nanometer sized particles or any phases combined with a spatial distribution that involves nanometer length scale of less than 100 nm in at least one dimension.

Nanoparticles: The term refers to particles of sizes in the range of 1–100 nm. Depending on the preparative conditions, nanoparticles may have polycrystalline or single crystalline structure. Nanoparticles of sizes less than 5 nm are termed as quantum dots.

Nanoscale Devices: Nanostructure-based devices that exhibit unique characteristics such as multistate switching phenomena, resonant tunneling, quantum interference, and single electron effects due to quantum size effect.

Nanostructure: Typical structure of a material with nanometer-sized microstructure.

Nanotechnology: a manufacturing technology able to inexpensively fabricate most structures consistent with natural law, and to do so with molecular precision.

Ostwald Ripening: Large precipitates (islands, in our case) grow larger by consuming small precipitates. As a result of the ripening, the average precipitate size is increased at the expense of precipitate density.

Chapter 2

Nanomechanical Characterization of Cement-Based Materials

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ABSTRACT

Nanoindentation technique is used to assess the mechanical properties of materials at nano-level. A very small tip (usually diamond) produces indents at the surface of the material to be tested. A load vs. deflection curve is generated and is used to study the elastic properties of materials. Generally, it is used for obtaining the hardness and Young's modulus of materials at nano-meter scale. Currently, the method to evaluate the mechanical properties by nanoindentation is restricted to homogeneous materials. Cement-based materials are heterogeneous in nature. Therefore, nanoindentation study of cement-based materials is critical and requires several important steps, which need to be performed accurately. This chapter provides a review of the theory of nanoindentation, instruments being used for nanoindentation, sample preparation techniques, indentation strategy, and determination of nanomechanical properties and data analysis for cement-based materials.

INTRODUCTION

Concrete is the most widely used construction material made commonly by mixing Portland cement, sand, crushed rock and water. The total world consumption of concrete is very high and man consumes no material except water in such tremendous quantities (Mehta and Monteiro, 2004). Present concrete consumption is much

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higher than what it was almost 40 years ago. In 2000, consumption of concrete in the world was of the order of 11 billion metric tons per year. The amount of world trade associated with concrete is estimated to be about 13 to 14 trillion dollars, providing jobs to 1% of the world's population. Over the past 100 years, concrete has made major progress in quality and performance through scientific and technological innovations. Nevertheless, little is known about the properties of concrete at the micro- and nanoscale, which governs its overall properties such as strength, ductility, durability etc. Concrete is the material of choice for new construction of high-rise buildings, roadway pavements, and bridges.

The construction industry is facing an escalating need for high-performance, durable and sustainable construction materials for buildings and roadway pavements. This need, in turn, is driving research to develop the next generation of materials. In Civil Engineering, the traditional method of designing a concrete mix is by trial and error where different additives are used to achieve a set of final properties. Recently, however the construction industry has recognized the need to investigate the science and fundamental properties of concrete and other construction materials.

HETEROGENEITY OF CEMENTITOUS COMPOSITES

Cementitious materials, like many other materials exhibit heterogeneous features over a wide range of length scales, from the nano-scale of the elementary chemical components to the macroscopic scale of the aggregate-mortar composite. This multi-scale heterogeneity ultimately determines the in vivo mechanical performance (stiffness, strength), and degradation (damage, fracture, failure) of cementitious materials. While most codes of practice in concrete engineering account for this heterogeneity through probability theory to achieve certain macroscopic material properties with some certainty, current trends in concrete science and engineering aim at a better representation of this heterogeneity at multiple length scales, to ultimately identify the scale where physical chemistry meets mechanics. The rationale behind this approach is that the different chemical components of cement-based materials are defined by specific chemical equilibrium states, for which the probability that some solid chemical compounds go into the solution is smaller than the probability that the same chemical species in the solution precipitates onto the solid. Such an equilibrium state is associated with a stable material state. Hence, if it were possible to break down the heterogeneities of cement-based materials to this scale, where the solid material manifests itself in a chemically stable state, and to assess, at this scale, the mechanical material properties, it would be possible to translate with high confidence chemical equilibrium states into macroscopic material properties.

The expected outcome of such an endeavour is a blueprint of the elementary chemo mechanical components of cementitious materials, which do neither change in time, nor from one cementitious material to another.

The indentation test provides a P - h curve, and the extraction of material properties requires an inverse analysis of these data. The theoretical foundation of elastic indentation is set by Boussinesq's problem and the Hertz contact problem: Boussinesq's stress and displacement solution of an elastic half-space loaded by a rigid, axisymmetric indenter, which was subsequently extended for conical and cylindrical indenter geometry, provides a linear P - h relation. Hertz's elastic contact solution of two spherical surfaces with different radii and elastic constants provides a means of evaluating the contact area of indentation, and forms the basis of much experimental and theoretical work in indentation analysis based on contact mechanics. Subsequently, Sneddon (1965) derived general relationships among load, displacement and contact area for any indenter describable as a solid of revolution.

Incorporating plasticity phenomena in the indentation analysis is a much more complex problem. As a result, much of our knowledge of the importance of plasticity in indenter contact problems has been derived through experimentation, and more recently through finite element simulations. Various researchers (Pharr et al., 1992; Giannakopoulos and Suresh, 1999; Dao et al., 2001) have proposed semi-analytical procedures by which the experimental p - h response can be used to calculate elastic properties such as the elastic modulus e, pseudo-properties characterizing resistance to deformation such as hardness h, and plastic properties such as yield stress and strain hardening exponents. Experimental data have demonstrated that analysis of indentation data via elastic solutions provides reasonable estimates of the elastic modulus and hardness of the indented material, provided that the contact area is measured or calculated accurately.

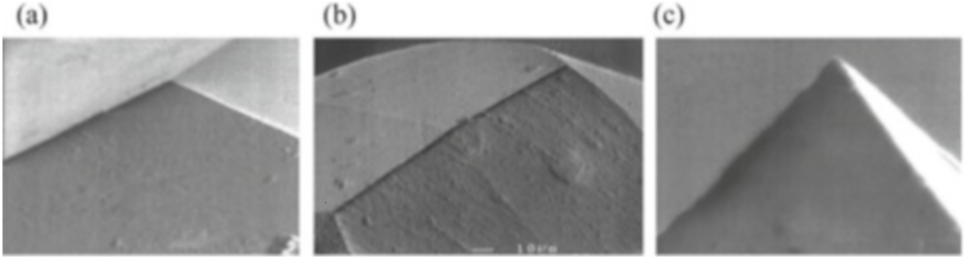
BASIC THEORY OF NANOINDENTATION

The goal of the majority of nanoindentation tests is to extract elastic modulus and hardness of the specimen material from load-displacement measurements. Conventional indentation hardness tests involve the measurement of the size of a residual plastic impression in the specimen as a function of the indenter load. This provides a measure of the area of contact for a given indenter load. In a nanoindentation test, the size of the residual impression is often only a few microns and this makes it very difficult to obtain a direct measure using optical techniques. In nanoindentation testing, the depth of penetration beneath the specimen surface is measured as the load is applied to the indenter. The known geometry of the indenter then allows the size of the area of contact to be determined. The procedure also allows for the modulus of the specimen material to be obtained from a measurement of the stiffness of the contact, that is, the rate of change of load and depth.

Nanoindentation hardness tests are generally made with either spherical or pyramidal indenters. Consider a Vickers indenter with opposing faces at a semi-angle of θ = 68° and therefore making an angle β = 22° with the flat specimen surface. For a particular contact radius a, the radius R of a spherical indenter whose edges are at a tangent to the point of contact with the specimen is given by $\sin \beta = a/R$, which for β = 22° gives $a/R = 0.375$. It is interesting to note that this is precisely the indentation strain at which Brinell hardness tests, using a spherical indenter, are generally performed, and the angle θ = 68° for the Vickers indenter was chosen for this reason.

The Berkovich indenter, in Figure 1, is generally used in small-scale indentation studies and has the advantage that the edges of the pyramid are more easily constructed to meet at a single point, rather than the inevitable line that occurs in the four-sided Vickers pyramid. The face angle of the Berkovich indenter normally used for nanoindentation testing is 65.27°, which gives the same projected area-to-depth ratio as the Vickers indenter. Originally, the Berkovich indenter was constructed with a face angle of 65.03°, which gives the same actual surface area todepth ratio as a Vickers indenter. The tip radius for a typical new Berkovich indenter is on the order of 50–100 nm. This usually increases to about 200 nm with use. The Knoop indenter, (b) in Figure 1, is a four-sided pyramidal indenter with two different face angles. Measurement of the unequal lengths of the diagonals of the residual impression is very useful for investigating anisotropy of the surface of the specimen. The indenter was originally developed to allow the testing of very hard materials where a longer diagonal line could be more easily measured for shallower depths of residual impression. The cube corner indenter, (c) in Figure 1, is finding increasing popularity in nanoindentation testing. It is similar to the Berkovich indenter but has

Figure 1. SEM images of the tips of (a) Berkovich, (b) Knoop, and (c) cube-corner indenters



a semi-angle at the faces of 35.26°. Conical indenters have the advantage of possessing axial symmetry, and, with reference to Figure 1, equivalent projected areas of contact between conical and pyramidal indenters are obtained when:

$$A = \pi h^2 \tan^2 \alpha \tag{1}$$

where h is depth of penetration measured from the edge of the circle or area of contact. For a Vickers or Berkovich indenter, the projected area of contact is $A = 24.5h^2$ and thus the semi-angle for an equivalent conical indenter is 70.3°. It is convenient when analysing nanoindentation test data taken with pyramidal indenters to treat the indentation as involving an axial-symmetric conical indenterwith an apex semi angle that can be determined from Equation 1.

SAMPLE PREPARATION TECHNIQUE

One of the main challenges in applying nanoindentation to characterize cementitious material is preparing the sample surface. Contact mechanics theory used in the analysis of nanoindentation data is based on indentation on a flat surface. In reality, extremely flat surfaces can be achieved only in very rare occasions. The sample preparation for nanoindentation consists of mechanical polishing with diamond paste followed by chemical polishing in 50% phosphoric acid, 28% acetic acid and 22% nitric acid, which is used to remove the strain hardened layer due to mechanical polishing and to etch slightly the microstructure. Micrometer-grained pre-eutectoid phase has unique island-shaped aggregates of grains with 5 x10 mm diameter, which are embedded inside a sea of UFG eutectoid matrix with grain size less than 1 mm (Figure 2). However, the surface roughness of the UFG matrix is obviously very high due to the selective etching of Al-rich phase from the eutectoid structure during chemical polishing. To eliminate the influence from roughness to nanoindentation, the UFG matrix with low roughness through lightly etching was prepared for nanoindentation (Figure 3).

INDENTATION STRATEGY

In contrast to usual indentation on homogeneous materials (e.g. glass, films, and coatings), structural materials (e.g. cement paste, alkali-activated materials, and gypsum) are much more complex in their microstructure and mechanical performance. The situation is further complicated by their time-dependent load response

Figure 2. Typical microstructure in Cu-10.8 mass%Al alloy with bimodal distribution of grain size

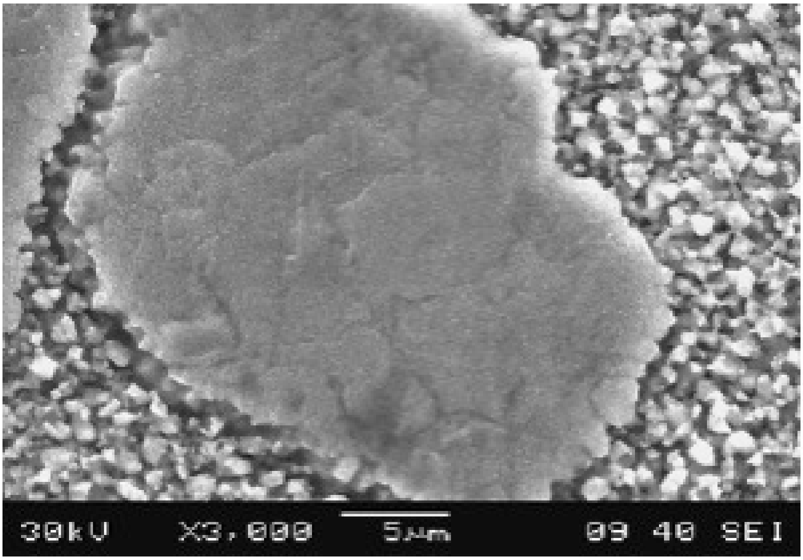
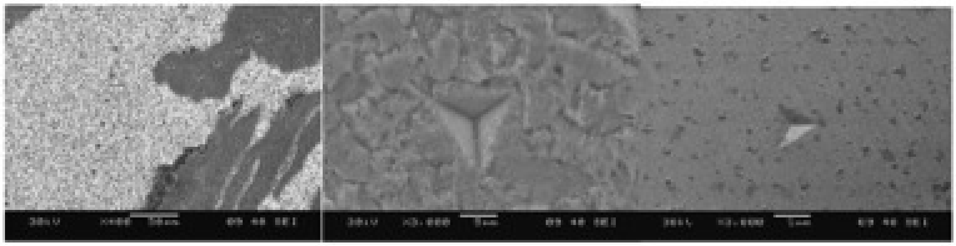


Figure 3. Residual indentation at different constitutional regions



(Němeček, 2009), aging and property fluctuations due to temperature or humidity (Beaudoin et al., 2010). The evaluation methodology however, is currently restricted mostly to homogeneous isotropic systems. The indentation response in the form of force-penetration (P-h) curves is characterized by two elastic constants, indentation modulus:

$$E_r = \frac{1}{2\beta}\frac{\sqrt{\pi}}{\sqrt{A}}\frac{dp}{dh} \qquad (2)$$

where *dp/dh* is the contact stiffness evaluated from the initial slope of the unloading branch of the force-penetration curve, P is the indentation force, A is the projected contact area and β is the correction factor for indenters with non-symmetrical shape (β=1.034 for Berkovich tip). Direct application of these equations to heterogeneous materials poses several difficulties, as the underlying analysis relies on the self-similarity of the indentation test, which holds only for homogeneous materials (Borodich et al., 2003; Constantinides and Ulm, 2007). The interaction of phases in heterogeneous materials is unavoidable but depending on the length scale it can be more or less important. Properties extracted from indentation data of a heterogeneous solid can be treated as averaged quantities dependent on the depth. Therefore, the choice of an indentation depth directly determines the length scale of the tested material volume. For example, the effective volume affected by an indent can be estimated as 3×h for the Berkovich indenter (Constantinides et al., 2006). Composite structural materials are multiphase materials in which distinct phases are intermixed spatially and chemically. Taking the microstructural heterogeneity into account one can formulate basically three testing strategies to obtain mechanical properties of a composite or its phase properties:

1. Averaged (effective) composite properties can be found if the indentation depth is much larger than the characteristic phase dimension (h>>D). In this case, a phase compound is indented and thus, physically averaged properties are obtained. This strategy does not give access neither to distinct phases' properties nor to their volume fractions.
2. Another possibility is to perform pointed indentation to a specific material phase with individual indent's dimension much smaller than the characteristic dimension of the tested phase (h<<D). In this case, intrinsic properties of the distinct phase (which may also include phase porosity smaller than the tested size h) are obtained. This strategy can be used, provided the material phase can be distinguished prior to indentation by some other means (e.g. optical microscope, SEM), which is not always the case. It gives access to the distinct phase properties but not to volume fraction of the phase compared to other phases.
3. The last one, but for structural materials probably the most powerful technique, is based on the statistical (massive grid) indentation in which small indents are produced over a large area to capture the sample heterogeneity, but the dimension of a single indent is kept still smaller than the characteristic dimension of an individual phase (h<<D). In this case, the results provide information on all phases' properties as well as their volume ratios, but without any knowledge

which indent belongs to which phase. The properties can be evaluated in terms of property histograms for which subsequent de convolution techniques can be employed and individual phase properties assessed.

The extraction of material properties of a heterogeneous system from nanoindentation in cases of (2) and (3) relies on the fact that the volume affected by an indenter is small enough not to mechanically interact with other phases. As a rule of a thumb, the indentation depth is usually chosen as 1/10 of the characteristic size of the measured inclusion or phase D. Applying (2) strategy to cement paste, for example, where calcium-silica-hydrates of different densities (low and high) are intermixed with $Ca(OH)_2$ zones in hydrated cement matrix (Thomas et al., 1998; Taylor, 2003) is not an option due to impossible differentiation of the reaction products in optical microscope or SEM. Therefore, it is advantageous to perform massive grids (hundreds of indents) on large sample area containing all material phases. Then, the indentation offers statistical set of data, which can be analyzed by the de convolution technique.

NANOMECHANICAL PROPERTIES FROM NANOINDENTATION

Nanoindentation testing is a technique that determines the mechanical properties of a material in the submicron/nano scale. The test involves penetrating a sample material using an indenter, while the penetration depth and load are recorded so that the stiffness and hardness of the indented location can be subsequently calculated. The indenter head can be 100 nm in radius (in the case of Berkovic indenter), and the penetration can be up to one or two micrometers in depth, with the resulting indent having a linear dimension in the order of micrometers. In particular, the continuous nanoindentation technique is one of the significant improvements in nanoindentation testing. The continuous measurement technique offers a tool to probe stiffness as a function of indentation depth in one single experiment. That is, cycles of indentation, each of which consists of incremental loading and partial unloading, are performed until a final desired depth is attained. Each loading-and-partial unloading cycle provides a value of hardness and stiffness; hence as the penetration progresses, various hardness or stiffness values were determined as a function of the indentation depth.

Continuous nanoindentation was performed as following six steps: approaching to surface as accurately as possible, loading to peak load, holding the indenter at peak load, unloading 90% of peak load for 50 seconds, holding the indenter after 90% unloading for 100 seconds, and finally, unloading completely. An arrayed line of indents was made from fiber and matrix with different spacing, depending on indentation depth. The load-displacement data from the nanoindentation tests can be used to calculate hardness and elastic modulus. The hardness (H) of the samples for an indentation depth (h) can be calculated from the following equation:

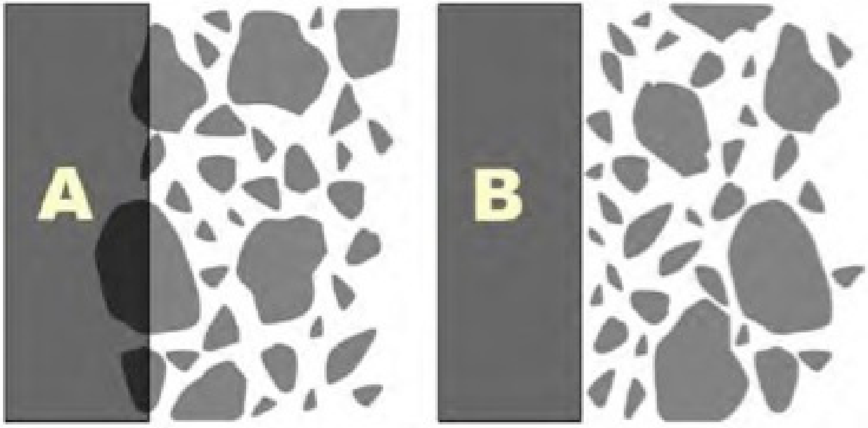
$$H = \frac{P_{\max}}{A} \tag{3}$$

where P_{max} refers to the load measured at a maximum depth of penetration (h) in an indentation cycle, while A refers to the projected area of contact between the indenter and sample at P_{max}.

In concrete, paste works as the glue that holds aggregates together to behave as a whole. However, this composite action depends on a thin layer that is believed to exist between the aggregates and the paste matrix, referred to as the interfacial transition zone (ITZ). This is the region of cement paste around aggregates developed due to the so called "wall effect" (Breton, 1993; Bentz, 1995). Relatively smooth surfaces of large aggregates act as wall and interfere with the packing of cement particles against it (Figure 4).

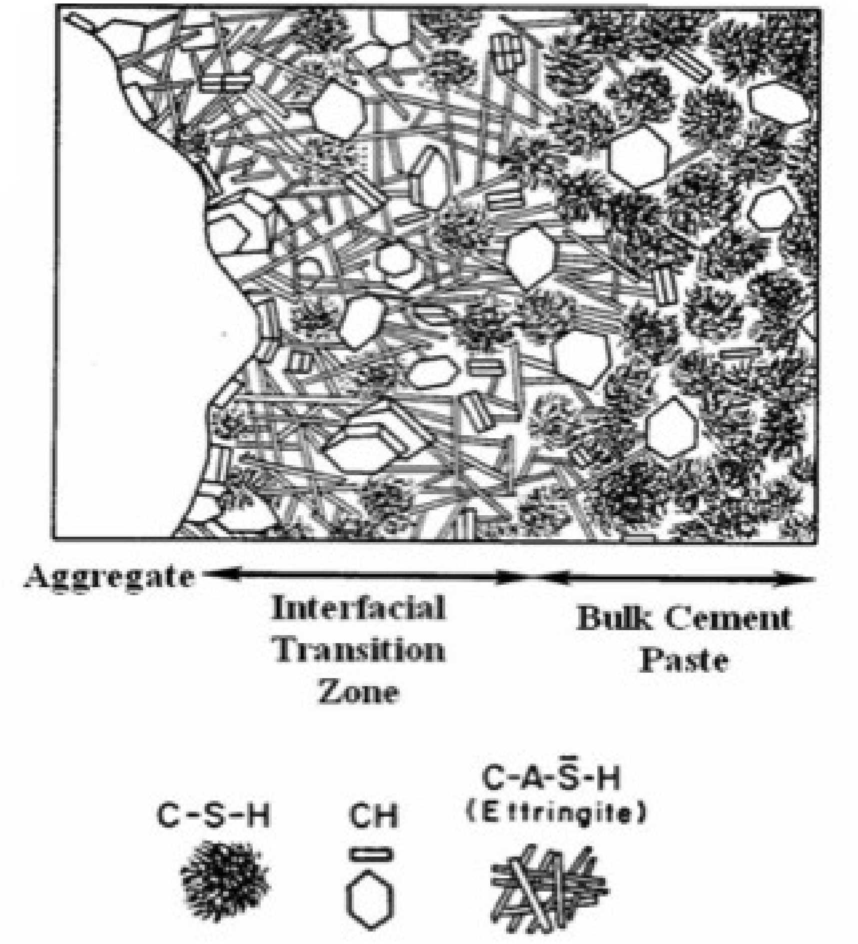
According to the literature, the w/c within the ITZ is higher than elsewhere in the paste matrix and the large crystals of $Ca(OH)_2$ introduce higher porosity at the interface (Neville, 1995).This is a region of gradual transition where the effective thickness of the region varies with the microstructural feature being studied, and with degree of hydration (Scrivener, 2004). In many studies, it was concluded that in ordinary Portland cement concrete, the ITZ consists of a region up to 50µm around

Figure 4. Schematic diagram showing wall effect of aggregates



each aggregate with fewer un-hydrated particles, less calcium-silicate-hydrate, higher porosity, and greater concentration of calcium hydroxide and ettringite. The microstructure of an interfacial transition zone in concrete is presented schematically in Figure 5. The ITZ is believed to be weaker than the bulk paste matrix. When the material is subjected to loads, micro-cracks may appear within the region of the ITZ. This leads to the quasi-brittle nature of concrete. Development of micro-cracks also reduces both the strength and the stiffness of the composite (Mehta and Monteiro, 2004). In normal strength concrete, the failure plane always passes through the ITZ.

Figure 5. Schematic diagram of interfacial transition zone (Mehta & Monteiro, 2004)



The quality of the bond between the paste matrix and aggregate is influenced by the shape, size, surface roughness, mineral and chemical composition, porosity, and surface moisture content of aggregates. Generally, a rougher surface of crushed particles results in a better bonding due to mechanical interlocking. Limestone, dolomite, and siliceous aggregates may have stronger ITZ because of the existence of chemical bonds. Lightweight aggregates with a porous outer layer lead to the migration of mobile ions towards the surface to form a dense ITZ, so that a better bond can be obtained. There are a lot of arguments about the effect of aggregate size on the properties of the ITZ. Some researchers argued that the thickness of the ITZ depends largely on the size of the aggregate. During mixing, dry cement particles are unable to become closely packed against the relatively large aggregate, thus a coarse aggregate may have a thicker ITZ (Elsharief, 2003).

It is reported that the influence of ITZ on the overall elastic properties of mortar and concrete (Simeonov and Ahmad, 1995). In normal strength concrete, it is considered to be the weakest link in the mechanical system. Although it is widely accepted that the properties of the ITZ have to be taken into account in modeling the overall mechanical properties of concrete, it is difficult to determine its local mechanical properties because of the complexity of the structure and the constraints of existing measurement techniques. Most of the time, the modulus of the ITZ is assumed to be uniform and less than that of the paste matrix by a constant factor (Li et al., 1999). This factor is assumed to have a value between 0.2 and 0.8, although there is not enough theoretical or experimental evidence to support this assumption (Sun et al., 2007). In their model, Lutz et al. assumed that the elastic properties vary smoothly as a power law within the ITZ. By fitting macroscopic bulk modulus data, they found that the modulus of the ITZ is 30-50% less than that of the bulk matrix. In some recent studies, attempts were made to determine the local mechanical properties of the ITZ using micro-indentation or micro-hardness testing (Zhu and Bartos, 2000; Zhu et al., 2004). Nadeau (2002) reported that elastic modulus of the ITZ in mortar is 10 to 20% that of the bulk paste based on his generalized self-consistent model. As bridge et al. reported about 20 percent reduction in Knoop micro-hardness in the ITZ than the bulk matrix at w/c of 0.4 and 0.5. At w/c 0.6, however, they reported similar Knoop micro-hardness at the ITZ and the bulk matrix. In their study, the width of indentation was reported as 10-15 μm, which is comparable with the width of the ITZ itself. Therefore, though it revealed some information, effects of adjacent phases on hardness results makes micro-hardness test not suitable for determining local properties of the ITZ. There is still very little information available at the nano-scale properties of the ITZ.

CONCLUDING REMARKS

The major challenge of applying nanoindentation to characterize cementitious material is preparing the sample surface. The surface preparation is very important, as it will affect the overall properties of material specially the nanomechanical properties. The theory of nanoindentation is developed based on the assumption of indentation on a flat surface. Therefore, the accuracy of nanoindentation experiments on cementitious materials depends on reducing surface roughness to a tolerable level without causing any damage to the sample.

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KEY TERMS AND DEFINITIONS

Cement-Based Materials: Includes concrete, mortar and paste. Cement-based material is one of the most widely used construction materials in the world.

Hardness: Hardness is a measure of how resistant slid matter is to various kinds of permanent shape change when a force is applied.

Interfacial Transition Zone: The region of the cement paste around the aggregate particles, which is perturbed by the presence of the aggregate.

Nanoindentation: A variety of indentation hardness tests applied to small volumes. In nanoindentation small loads and tip sizes are used, so the indentation area may only be a few square mm or even nm.

Nanomechanics: Nanomechanics is a branch of nanoscience studying fundamental mechanics (elastic, thermal and kinetic) properties of physical systems at the nanometer scale.

Stiffness: Stiffness is the rigidity of an object - the extent to which it resists deformation in response to an applied force.

Young's Modulus: Young's modulusis a measure of the stiffness of an elastic material material and is a quantity used to characterize materials. It is defined as the ratio of the stress along an axis over the strain along that axis in the range of stress in which Hooke's law holds.

Chapter 3

Carbon Nanotubes:
Basics, Biocompatibility, and Bio-Applications Including Their Use as a Scaffold in Cell Culture Systems

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ABSTRACT

Carbon-based nanotechnology has been rapidly developing, with a particular interest in the bio-application of carbon nanotubes (CNTs) as a scaffold in tissue engineering. It is essential that the materials used in scaffold fabrication are compatible with cells, as well as with the biological milieu. Many synthetic polymers have been used for tissue engineering so far; however, many lack the necessary mechanical strength and may not be easily functionalized, in contrast to CNTs, which have shown very attractive features as a scaffold for cell culture system. In spite of many attractive features, the toxicity of CNTs is a prime concern. The potential applications of CNTs seem countless, although few have reached a marketable status so far and there is need of more studies on CNTs biocompatibility issues. This chapter aims to revisit the basics of CNTs with their bio-applications including their use as a scaffold in cell culture systems.

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INTRODUCTION

Nanotechnology is a creation and utilization of materials measured in billionths of a meter. Nanotechnology is poised to make potentially revolutionary innovations in areas of biomedical science such as, diagnostics, drug therapy, imaging and tissue engineering. Following the discovery of carbon nanotubes by lijima (1991), carbon-based nanotechnology has been rapidly developing as a platform technology for variety of uses including biomedical applications. A particular area that is generating particular interest as illustrated by an increasing publication rate is the bio-application of carbon nanotubes as a scaffold in tissue engineering (Edwards *et al.,* 2009). The core of the tissue-engineered replacement is the biomaterial construct or scaffold, in which a given cell population is seeded. Ideally, a biomaterial scaffold should have well-controlled microarchitectures with well controlled pore sizes and porosity, reproducibility, biocompatibility, thermal and biochemical stability.

In tissue engineering, carbon nanotubes have been mainly used for structural support. There are various reports which suggest use of carbon nanotubes as a scaffold for cell culture (Harrison and Atala, 2007; Edwards et al., 2009, Rafeeqi and Kaul, 2010a). While popular synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA) and poly(lactic-acid) (PLA) have been used for tissue engineering, they lack the necessary mechanical strength. In addition, such polymers cannot easily be functionalized in contrast to carbon nanotubes which can be readily functionalized. In spite of many attractive features, the toxicity of CNTs is a prime concern, with several groups pointing to their similarity to asbestos fibers. CNT toxicity in both *in vivo* and *in vitro* studies has been attributed to various factors and there is need of more studies on CNT toxicity and biocompatibility issues. We should appreciate the pros and cons of each system and should make every effort to refine them to further enhance their therapeutic potential.

As we continue exploring nanotechnology for biomedical applications, it is essential for us to ensure that the nanotechnologies developed are safe. The focus of this book chapter is on basics of carbon Nanotubes with their method of preparation and purification, which is fundamental prerequisite for applications of carbon Nanotubes in biological system. Further, this chapter also deals with biocompatibility and bio-applications of carbon Nanotubes with emphasis on its use as a scaffold in cell culture systems.

BACKGROUND

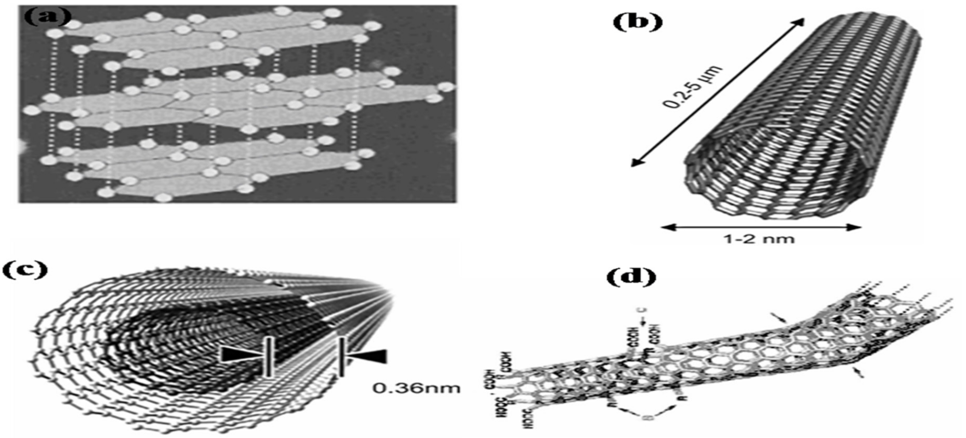
Carbon Nanotubes (CNTs)

Carbon nanotubes have been synthesized for a long time as products originating from the thermal decomposition of hydrocarbons. However following the discovery of carbon nanotubes by lijima (1991), carbon-based nanotechnology has been rapidly developing as a platform technology for a variety of uses including biomedical applications. Carbon nanotubes are hollow graphitic cylinders of nanoscale dimensions of different types (Figure 1). They are electrically conductive, chemically and thermally stable, and exceptionally strong and these properties are defined by their diameter, length, and chirality or twist. Given this unique combination of properties there has been much interest in CNTs, and finding applications for them. An emerging area that is generating particular interest is the use of carbon nanotubes in tissue engineering with the expanding range of tissue types being considered.

Types of CNTs

Comprised entirely of carbon, the structure of pure CNT can be visualized as a single sheet of graphite (graphene, being the same polyaromatic mono-atomic layer

Figure 1. Schematic representation of graphite sheets and different forms of carbon nanotubes. (a) Graphite, showing graphene sheets (b) single-walled carbon nanotube (SWNT), conceptually a SWNT is formed by rolling up graphene to form a cylinder (c) multi-walled carbon nanotube (MWNT) and (d) functionalized carbon nanotube (COOH- labelled).



made of a hexagonal display of carbon atom) rolled to form a seamless cylinder. Generally there are two classes of CNT: single-walled carbon nanotubes (SWNTs) and multi-walled carbon nanotubes (MWNTs). MWNT are larger and consist of many single-walled tubes stacked one inside the other. CNT are distinct from carbon fibers, which are not single molecules but strands of layered graphite sheets. CNT are reported to be physically strong and stiff as SWNT can be as much as 10 times as strong as steel and 1.2 times as stiff as diamond (Walters et al., 1999; Yu et al., 2000).

Structure of CNTs

It is simple to imagine a single-wall carbon nanotube (SWNT). Ideally, it is enough to consider a perfect graphene sheet to roll it into a cylinder. There is no such restriction for nanotube length, which only depends on limitations brought by the preparation method and the specific conditions used for the synthesis (thermal gradients, residence time, etc.). Geometrically, there is also no restriction regarding the tube diameter. But calculations have shown that collapsing the single-wall tube into a flattened two-layer ribbon is energetically more favourable than maintaining the tubular morphology beyond a diameter value of 2.5nm (Tersoff and Ruoff, 1994). These features make single-wall carbon nanotubes a unique example of single molecules with huge aspect ratios. Though carbon atoms are involved in aromatic rings, the C=C bond angles are no longer planar as they should ideally be. This means that the hybridization of carbon atoms is no longer pure *sp*2 but get some percentage of the *sp*3 character, in a proportion that increases as the tube radius of curvature decreases. On the one hand, this is supposed to make the SWNT surface (though consisting of aromatic ring faces) a bit more reactive than regular, planar graphene. The easiest MWNT to imagine is the concentric type, in which SWNTs with regularly increasing diameters are coaxially displayed according to a Russian-doll model into a multiwall nanotube (Bhushan, 2004). The number of walls (or number of coaxial tubes) can be anything, starting from two, with no upper limit. The intertube distance is approximately that of the intergraphene distance in turbostratic, polyaromatic solids, i. e. 0.34 nm (as opposed to 0.335 nm in genuine graphite). In contrast to SWNTs, whose aspect ratio is so high, aspect ratio for MWNTs are generally lower. Except for MWNTs from electric arc that grow following a catalyst-free process, nanotube tips are frequently found associated with the catalyst crystal from which they have been formed. Both texture and nanotexture depend on the processing conditions. While the texture type is a permanent, intrinsic feature only able to go toward complete alteration upon severe degradation treatments (e.g., oxidation), however, nanotexture can be improved by subsequent thermal treatments at high temperatures (e.g., > 2,000°C) or by chemical treatments (e.g., slight oxidation conditions).

Size of CNTs

CNT vary significantly in length and diameter depending on the synthetic procedure. Lengths are generally dependent on synthesis time but are typically tens of microns, although significantly shorter and longer nanotubes have been made (Puretzky et al., 2002; Motta et al., 2005). Cleaned and processed CNT are usually shorter than as-produced nanotubes due to the destructive conditions used in purification (Liu et al., 1998). The diameters of SWNT are controlled by the sizes of the metal nanoparticles (NP) from which they are grown, which vary between about 0.7 and 3 nm (Jorio et al., 2001). MWNT generally range from 10 to 200 nm in diameter (Hou et al., 2003). More important, there is the strong tendency of both SWNT and MWNT to bundle together in ropes as a consequence of attractive van der Waals forces analogous to forces that bind sheets of graphite (Thess et al., 1996). Bundles typically contain many tens of nanotubes and can be considerably longer and wider than the nanotubes from which they are formed. This could have important toxicological consequences. Much research has focused on creating homogeneous dispersions of CNT in various solvents. More complete dispersion is generally achieved by prolonged sonication, but dispersions of CNT tend to aggregate over time. As a consequence of their dimensions, CNT have very high surface areas. The available surface area is dependent on the length, diameter, and degree of bundling. Theoretically, discrete SWNT have surface areas of ~ 1300 m^2 g^{-1}, whereas MWNT generally have surface areas of a few hundred m^2 g^{-1} (Peigney et al., 2001). As a result of bundling, the surface area of most samples of SWNT is dramatically lowered to ~ 300 m^2 g^{-1}, or less, which is still a very high value (Ye et al., 1999).

Synthesis and Purification of CNTS

Carbon nanotubes are generally prepared via three methods: arc-discharge (Journet et al., 1997), laser ablation (Thess et al., 1996), and chemical vapor deposition (CVD) (Cassell et al., 1999). CVD is the most widely used commercial method of producing carbon nanotubes. A good overview of these methods is provided by Thostenson et al., (2001). The common feature of these methods is addition of energy to a carbon source to produce fragments (groups or single C atoms) that can recombine to generate CNT. The energy source may be electricity from an arc discharge, heat from a furnace (~ 900°C) for CVD, or the high-intensity light from a laser (laser ablation). The mechanisms of CNT formation are widely debated (Cassell et al., 1999; Sinnott et al., 1999). Where metal catalysts are used, it is thought that carbon is deposited on a catalyst NP, from which the C network finally extrudes to form a graphite tube (Vinciguerra et al., 2003; Helveg et al., 2004). The size of the metal particle determines the diameter of the tube; SWNT grow from metal particles a few nanometers in diameter, while larger particles tend to produce wider MWNT. The methods of laser ablation and electric arc are based on an essential mechanism, i. e. the energy transfer resulting from the interaction between either the target material and an external radiation laser beam or the electrode and the plasma. Generally laser is being used as a means of concentrating a large quantity of energy inside a very small volume within a relatively short time. During the interaction between the laser beam and the material, numerous phenomena superimpose and/or follow each other within the time range, for instance, the solid target can merely heat up, or melt, or vaporize depending on the power (watts) provided. The principle of arc discharge technique is to vaporize carbon in the presence of catalysts (iron, nickel, cobalt, etc) under reduced atmosphere of inert gas (argon or helium). In this method a plasma is formed (consists of carbon vapor, the rare gas and catalyst vapors) after triggering the arc between two electrodes. The vaporization is the consequence of the energy transfer from the arc to the anode made of graphite doped with catalysts. Commercially available CNT are often synthesized by CVD as this process is easily scaled up and low cost processes for industrial production. The high-pressure carbon monoxide method, which uses iron as the catalyst and carbon monoxide as the carbon source is commonly employed (Bronikowski *et al.*, 2001). The synthesis of both single-walled or multiwalled carbon nanotubes by CVD methods involves the catalytic decomposition of a carbon containing source on small metallic particles or clusters and is low temperature process (600°C – 1000°C) compared to arc-discharge laser ablation methods. Further, CNTs produced by CVD process are generally longer (10 – 100 micrometeres) than those obtained by arc discharge (few micrometeres) and may contain more structural defects due to low temperature reaction. However, these defects can be removed by subsequently applying the heat treatments in inert atmosphere or vacuum.

After synthesis, CNT are usually purified to remove amorphous carbon (‘‘soot’’), free residual catalyst (metal from which nanotubes failed to grow), and any support material. Chemical methods have been applied for purifying SWNTs. A generalized method for SWNT purification developed by Smalley and co-workers (Liu et al., 1998) consists of refluxing as-grown SWNTs in nitric acid solutions. Subsequently, more-effective purification techniques have been developed with minor physical damage of the tubes (Bandow et al., 1997; Rinzler et al., 1998; Dillon et al., 1999). Chattopadhyay et al., (2002) reported the complete removal of metallic impurities through a sonication mediated treatment of as-grown SWNTs in a mixture of hydrofluoric and nitric acids. Also, Martinez et al., (2002) reported a combined technique of high-temperature air oxidation in conjunction with microwave acid treatments, thus removing a high portion of metal particles in relatively short periods of time. For MWNTs, high-temperature treatments in an inert atmosphere (graphitization or annealing) are the most effective methods for removing structural defects (heptagons and heptagon–pentagon pairs) or impurities such as metallic compounds (Andrews et al., 2001). One of the effective methods used for purification of MWNTs is by acid purification as has been reported by Sato et al., (2005). Since purification also destroys CNT, the removal of impurities must be balanced against the introduction of defects into tubes. Many attempts have been made to produce carbon nanotubes by various other ways in addition to the above three major techniques with specific goal by various groups. However none has been sufficiently convincing so far.

Properties of CNTs

Carbon nanotubes have variety of structures and these various structures have different properties. Generally nanotubes are closed at both ends and the tubes are essentially cylinders with each end attached to half of a large fullerene like structure. Carbon nanotubes are significantly unreactive; e.g., SWNT must be heated to 500°C before they burn in air (Zhang et al., 2002). However, there are points in the structure of CNT which are more reactive than others, such as defects due to missing carbon atoms and the more strained curved-end caps (Lin et al., 2003). Carbon nanotubes are metallic or semiconducting depending on the diameter and chirality of the tube. Synthesis of carbon nanotubes generally results in a mixture of tubes two-thirds of which are semiconducting and one-third metallic. In metallic state the conductivity of the nanotubes is very high. One reason for the high conductivity of carbon nanotubes is because of their very low resistance as compared to copper wires which fails because resistive heating melts the wire. Nanotubes are also very good conductors of heat as their thermal conductivity is almost a factor of 2 more than that of diamond. Further, nanotubes have a current carrying capacity of 1 billion amps per square centimeter much higher than copper wires which burn out at one million amps per square centimeter. The tensile strength of carbon nanotubes are about 20 times more than that of high steel alloys and are lighter than almunium. It is likely that carbon nanotubes are likely to remain stable at higher temperatures than metal wires and can transmit twice as much heat as pure diamond (Bhushan, 2004). The chemistry of pure CNT is surprisingly uninteresting. They are significantly unreactive; e.g., SWNT must be heated to 500°C before they burn in air (Zhang *et al.*, 2002). However, there are points in the structure of CNT which are more reactive than others, such as defects due to missing carbon atoms and the more strained curved-end caps (Lin *et al.*, 2003). Smaller nanotubes are more ‘‘strained’’ because they deviate further from the ideal planar structure of graphite. Purified nanotubes are likely to contain additional defects in the form of carboxylic acid (-COOH) residues. A sample of CNT invariably contains a variety of residual impurities. As discussed above the postproduction processing removes the majority of metal catalyst.

Fictionalization of CNTs

Much research on CNT focuses on modifying these ‘as produced’ tubes by the addition of different chemical groups, leading to a significant change in many of their properties (Banerjee et al., 2003). Pristine, as-produced CNTs tend to bundle up and are insoluble in most types of solvents (Tasis et al., 2003) making it difficult to use them in biological systems. Therefore, to integrate CNTs into biological systems, CNTs need to be functionalized. Functionalization can make CNTs soluble and improve their biocompatibility properties. In addition, through functionalization, bioactive agents can be conjugated to CNTs which can serve as a carrier for drugs, antigens and gene delivery. Many companies sell these ‘‘derivatized’’ or ‘‘functionalized’’ nanotubes including fluorine groups as a starting point for various other chemical modifications. Functionalization with different groups is likely to result in different toxicity (Sayes et al., 2005) since the particle surface is important for interaction with biological systems. Different functionalization strategies have been pursued and they can be divided into two main approaches: (i) additional reactions to the sidewalls and tips of CNTs and (ii) oxidation followed by carboxyl based couplings. In the first approach, additional reactions are employed to attach some organic groups to the sidewalls and/or tips of the CNTs. Briefly, purified SWNTs and aniline are mixed together. Under the pressure from the mixing force, the outermost nanotubes from the bundle will be “librated” and become exposed to the reactive agent. Thus, the individual nanotube is covalently functionalized thereby preventing itself from bundling up with others. Preventing bundling up of CNTs is very important as more CNT surface area will be available for the attachment with active molecules and the solubility of the CNTs can also be improved. The advantages of this functionalization strategy include its simplicity, its ability to produce highly soluble materials and its ease to implement on the industrial scale (Dyke and Tour, 2004). However, this simple functionalization method has the disadvantage of not allowing for many desirable further modifications of the tubes. The second functionalization strategy is through oxidation and carboxyl-based couplings. It involves the selective breaking of $C = C$ bonds in the CNT resulting in carboxyl groups that could then be used as subsidiary sites for addition reactions. In this method, the tube cap openings are created and holes in the side walls are formed by an oxidation process in which strong acids are used. In addition to opening tube caps and creating side wall holes, the oxidation introduced to the caps and side walls with carboxylic groups enhances the solubility of CNTs in aqueous solutions (Liu et al., 1998). The carboxylic groups also allow for covalent couplings with other molecules through amide and ester bonds. Through this method, CNTs can be conjugated with various functional groups such as bioactive agents (for example, peptides, proteins, and nucleic acids) and therapeutic agents such as anti-cancer drugs. Importantly, by bonding with suitable groups, CNTs can become soluble in aqueous or organic solvents (Tran et al., 2009). The presence of carboxylic groups on the sidewalls of CNTs reduces van der Waals interactions between the tubes, enabling separation of nanotube bundles into individual separated tubes (Balasubaramanian, 2005).

Biocompatibility of Carbon Nanotubes

It is essential that the materials used in scaffold fabrication are compatible with cells, the biological milieu in which cells are residing and surrounding tissue. A large number of CNT biocompatibility studies have been conducted that introduces carbon nanotubes to cells in a variety of ways. These include at different concentrations, different degrees of purity, various chemical modifications, and both directly, or within composites. We have demonstrated the interaction between MWNTs and cell culture medium and subsequently correlated with biocompatibility of this nano material. Our study (Rafeeqi and Kaul, 2011) along with other reports support the use of MWNTs for bio-applications especially as scaffold for cell culture system. In general biocompatibility studies can be grouped into either loose CNTs in suspension, or CNTs physically contained within a structure. Studies of loose CNTs in cell culture generally found that nanotube concentration caused a dose and time dependent decrease in cell viability. This has been accompanied by observations of nanotubes bound to the cell membranes (Garibaldi et al., 2006), within the cytoplasm (Yokoyama et al., 2005), and lying close to the nucleus (Monteiro-Riviere et al., 2005), impairing the cells ability to engulf (phagocytose) materials (Jia et al., 2005) after being exposed to CNTs. Conversely cells seeded directly onto the CNT containing structures exhibited good cell adhesion, spreading and proliferation (Galvan-Garcia et al., 2007), with cells extending projections onto (Zhang et al., 2006), and intermingling with, the filamentary CNT surface. When considering these results it should be noted that these studies were performed on CNTs of different types (either SWNTs or MWNTs), of varying aspect ratios, functionalization (chemical modification) and levels of purity that may have influenced CNT biocompatibility.

Carbon Nanotubes as a Scaffold in Cell Culture Systems

The core of the tissue-engineered replacement is the biomaterial construct or scaffold, in which a given cell population is seeded. One of the challenges in tissue engineering is to find a more suitable method for the fabrication of scaffolds of defined architecture to guide cell growth and development. Ideally, a biomaterial scaffold should have well-controlled microarchitectures, including well controlled pore sizes and porosity, reproducibility, biocompatibility, thermal and biochemical stability with no/minimal toxicity. A tissue engineered construct that has a well-controlled microstructure will better maintain cell morphology, differentiation, and functionality over long periods of time. A key feature of these constructs will be the replication of *in vivo* geometry and dimensional size scale that will aid in the maintenance of an *in vivo*-like cell phenotype (Desai, 2000). Other important fundamental requirements of scaffold are that it is fabricated from a biocompatible material that supports cell and tissue growth, with 3D structure mimicking the *in vivo*, with an interconnected network of suitably sized pores (Edwards et al., 2009). The matrix plays a critical role in tissue engineering. It is responsible for defining the space the engineered tissue occupies and aiding the process of tissue development. While popular synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA) and poly(lactic-acid) (PLA) have been used for tissue engineering, they lack the necessary mechanical strength. In addition, such polymers cannot easily be functionalized in contrast to carbon nanotubes which can be readily functionalized (Harrison and Atala, 2007). Further CNTs have been lauded as promising material to create the next-generation matrix for growing various cell types due to their necessary strength and favourable electrical conductivity in comparison to current alternatives.

There are various reports which suggest use of carbon nanotubes as a scaffold for cell culture which we have also reviewed earlier elsewhere (Rafeeqi and Kaul, 2010a). One of the first studies using microfabricated substrates to study cellular behavior was performed by Brunette and colleagues (Brunette et al., 1983). Further Mattson et al., (2000) reported for the first time the application of carbon nanotubes as substrate for neuronal growth. They reported that neurons can attach and grow across the surfaces of carbon nanotubes and when nanotubes were coated with bioactive molecule 4-hydroxynonenal, neurite branching and total neurite outgrowth were greatly enhanced. Because MWNTs can have diameters approximately 100 nm, they can possibly be used to mimic neural fibers for neuronal growth. It has been shown that hippocampal neurons from 0- to 2-day old Sprague-Dawley rats were able to grow on carbon nanotubes coated with 4-hydroxynonenal (Hui et al., 2004). Lovat et al. (2005) also reported the biocompatibility of carbon nanotubes with neuronal cells. They demonstrated the possibility of using CNTs as potential device to improve neural signal transfer as well as helps in dendrite elongation and cell adhesion. Ni et al. (2005) have shown that how different groups added to carbon nanotube surface, such as poly(*m*-aminobenzene sulfonic acid) or ethylenediamine, affect neurite outgrowth and branching. They concluded that more positively charged groups incite greater neurite length and more numerous growth cones. Mazzatenta et al., (2007) have developed an integrated SWNT–neuron system and their results indicate that SWNTs can directly stimulate brain circuit activity. To that aim, hippocampal cells were grown on pure SWNT substrates and patch-clamped. The use of neurotrophin coating in MWNTs as a biologically active substrate to stimulate neuronal neurite outgrowth has been also demonstrated (Matsumoto et al., 2007).

Bardi et al., (2009) suggested that the presence of MWNTs might decrease considerably the toxicity of conjugated composites such as Pluronic F127 *in vivo*. *In vitro* studies showed that the presence of a higher dose of MWNTs compared to Pluronic F127 decreased cell death. Polysaccharide agarose/CNT hybrid materials for applications involving neural tissue engineering and bio-interfacing with the nervous system have also been tested. It has been reported that the agarose/CNT materials are not only conductive and nontoxic, but their functionalization can facilitate cell attachment and response both *in vitro* and *in vivo* (Lewitus et al., 2011). It has been recently reported that the long-term impact of an artificial MWNT meshwork characterized by large surface roughness and conductivity favours neurite regrowth in spinal explants, with the appearance of increased growth-cone activity (Fabbro et al., 2012). In order to achieve conductive scaffold for neural tissue, Kabiri et al., (2012) studied the growth and neural differentiation of mouse embryonic stem cells on three different aligned nanofiber scaffolds (poly L lactic acid, SW- and MW- carbon nanotubes). They have showed that Nanotubes confer conductivity as well as promote mouse embryonic stem cells neural differentiation. Further to maintain potential use of amorphous carbon nanofibrous scaffolds as artificial nerve implants Jain et al., (2013) have reported that these scaffolds support cell adhesion and proliferation of neuronal cells.

The first application of carbon nanofibres in osteoblast culture has been reported by Elias et al., (2002). They showed the enhanced long-term (days to weeks) functions of osteoblasts as well as the evidence of enhanced osteoblast proliferation on carbon nanofibres and predicted carbon nanofibres as a promising class of orthopedic as well as dental implant formulations. Aoki et al., (2005) formed the CNT scaffolds on porous polycarbonate membrane to study the osteoblast-like cells (Saos2) interaction with CNTs. They reported that the osteoblast-like cells showed excellent proliferation with extension of cell morphology in all directions as well as their tight interactions with CNT scaffold. The functionalization of carbon nanotubes have demonstrated excellent growth of certain cell types e.g., osteosarcoma ROS 17/2.8 cells were successfully cultured on chemically modified single-walled and multi-walled CNTs. CNTs carrying neutral electric charge sustained the highest cell growth (Zanello et al., 2006). The high level of viability of fibroblast and osteoblast in contact with nanotubes, the slight increase of collagen formation, the lack of pro-inflammatory IL-6 cytokine as well as the induction of free radicals, confirm a good biocompatibility of nanotubes (Chlopek et al., 2006). Aoki et al., (2006) reported that the CNTs as the best scaffold material for cell culture in comparison with other isomorphs of carbon. The morphology of cells cultured on CNTs scaffolds investigated using confocal laser scanning microscope and scanning electron microscope revealed that the cells extended strikingly in all directions. Further Aoki et al., (2007) studied the response of osteoblast cells on SWNTs, MWNTs and graphite (all forms of carbon) scaffold. Their results have shown the good biocompatibility of CNT scaffold in terms of cell morphology, cell proliferation. The CNTs have been expected to influence osteoblast behaviour because of their high textured surfaces as well as their roughness might contribute to higher adsorption of proteins, thus increasing the adhesion of cells. Supporting the use of CNTs as scaffold, Eliason et al., (2008) reported the interaction between osteoblast cells and micropatterned CNTs on a polymer cell substrate and cell response to a wider range of patterns of micro and nano scale lengths. Adhesion of osteoblast-like cells to a multi-walled and single-walled CNT sheets has been recently reported and compared with that of cell culture polystyrene dishes. The number of attached cells on the MWNT sheets seemed to be greater than on SWNT sheets and cell culture polystyrene and the cell adhesion to CNT sheets were influenced by serum proteins (Akasaka et al., 2009). Watari et al., (2009) performed cell proliferation on the scaffolds of single-walled CNTs, multiwalled CNTs, and on graphite and their scanning electron microscopy observation of osteoblast-like cells (Saos2) showed the morphology fully developed for the whole direction. Proliferated cell numbers were reported largest on SWNTs, followed by MWNTs, and are very low on graphite. In addition, the concluded the nanosize meshwork structure with large porosity responsible for the excellent cell adhesion and growth on CNTs. Tutak et al., (2009) have tested the cytotoxicity of CNTs on osteoblast and osteoblast-like cultures. They have showed that when CNTs were firmly attached to a substrate such as glass, no cytotoxic effects or enhanced growth or differentiation in cells were observed. The introduction of cell lysate into cultures without the presence of CNTs mimicked its effects on total protein assay, producing no reduction in cell viability. Verdejo *et al.,* (2009) evaluated the cytotoxicity of polyurethane CNT foams over osteoblasts. They observed that increasing the CNT loading fraction did not cause cytotoxicity to osteoblasts, nor did it has any detrimental effect on osteoblast differentiation or mineralization. The effects of a layer-by-layer assembled carbon nanotube composite on osteoblasts in vitro and bone tissue in vivo in rats were studied. And it has been reported that cell differentiation and matrix mineralization, was good on the CNT-composite. Further when implanted in critical-sized rat calvarial defect, the CNT-comp permitted bone formation and bone repair without signs of rejection or inflammation, thus supporting its use as a bone implant or as a scaffold for tissue engineering (Bhattacharya et al., 2011). Shao et al., (2011) fabricated poly-DL-lactide (PLA)/MWNT nanofiber meshes by direct electrospinning of PLA solution containing MWNTs. Further, in the presence of direct current, the osteoblasts on all samples grew along the electrical current direction. These nanofiber meshes maintained the conductive property of MWNTs and offered a unique system to study the synergistic effect of topographic cues and electrical stimulation on osteoblast outgrowth, as a way of exploring their potential application in bone-tissue engineering. Bone regeneration, fracture healing, and more recently stem cell differentiation could be directed with the use of an electric field (Tonelli et al., 2012). Recent study with multiwall carbon nanotubes/nanohydroxyapatite/chitosan scaffolds have demonstrated their good biocompatibility with human cells from periosteum biopsy and have been considered as promising biomaterials for bone tissue engineering applications (Fonseca-García et al., 2013).

Apart from neuronal and osteoblasts, other cell types have been successfully grown on carbon nanotubes or nanocomposites. For example L929 mouse fibroblasts have been successfully grown on carbon nanotube scaffolds (Correa-Duarte et al., 2004), blends of SWNT with collagen support smooth muscle cell growth (MacDonald, et al., 2005). Li et al., (2005) used mesenchymal stem cells from adult bone marrow for the generation of chondrocytes and cultured on a three-dimensional nanofiber scaffold. They reported that this scaffold was a potential candidate for tissue engineering aimed at cartilage repair. Garibaldi et al. (2006) have used cardiomyocytes to assess nonfunctionalized SWNT cytotoxicity *in vitro*. They have reported that SWNTs bind to the cell membrane, making it hard to detach them by normal washing. The results also showed little toxicity even after 3 days, with the viability and cell number decreasing slightly. However, after reseeding, changes in cell morphology and a considerable decrease in cell viability was noticed. Supporting the use of CNTs in tissue engineering Galvan-Garcia et al. (2007) demonstrated that highly oriented CNT sheets and yarns, produced with a minimal residual content of catalytic transition materials, support the long-term growth of a variety of cell types ranging from skin fibroblasts and Schwann cells, to postnatal cortical and cerebellar neurons. Cell adhesion, viability and proliferation onto the MWCNT/Chitosin scaffolds with C2C12 cell line (myoblastic mouse cell), which is a multipotent cell line has been evaluated recently. The results have supported the use of MWNTs as scaffold for cell culture (Abarrategi et al. 2008). Further Lobo et al. (2008) reported growth of Fibroblast L929 mouse cells on vertically aligned CNTs used. Their results show high cell viability (close to 100%) after 96 h of incubation, proper cell adhesion and spreading on the surface formed by nanotube tips. Oh et al. (2009) reported that by changing the dimensions of the nanotubular scaffold, it is possible to increase adhesion of human mesenchymal stem cells (hMSCs) as well as allows their differentiation into the osteoblasts. They demonstrated that a narrow range of CNT dimensions led to a dramatic change in hMSC behavior. Further CNTs have also been shown to favour the differentiation of human embryonic stem cells (hESCs) into neurons. It has been shown that the stem cells were favourably directed towards the neural lineage, with an enhancement double that of poly-L-ornithine – the conventional polymer for growing neurons with no decrease in cell viability or adhesion (Chao et al., 2009). Fung et al. (2010) have reported that the interactions of cultured cardiac myocytes with nanotubes were optimized when CNTs were vertically aligned (so the position is important for interactions to be established). In that position, they were able to penetrate the membrane of neonatal rat ventricular myocytes, while the randomly oriented ones remained external to the cells. We also tried to explore the usefulness of these nano scaffolds and have successfully grown spermatogonial cells on the nano scaffolds for the first time. Our results provide an appreciable degree of biocompatibility between spermatogonial cells and CNTs (Rafeeqi and Kaul, 2010b). McKeon-Fischer et al., (2011) used co-axially electrospun poly(ε-caprolactone), acid MWNT, and a hydrogel consisting of polyvinyl alcohol and polyacrylic acid (PCL-MWNT-H) to create a self-contained nanoactuating scaffold for skeletal muscle-tissue replacement. This nanocomposite was biocompatible, and the acid MWNT increased its conductivity and acted as an inner electrode. It has been observed that the adhesion, growth, and differentiation of stem cells on CNT matrices were increased (Holy et al., 2011). Namgung et al., (2011) have reported that the alignment of the individual CNTs can affect the growth and differentiation of the hMSCs. The hMSCs on the aligned CNT networks were stretched along the alignment direction of the individual CNTs in the networks. They further observed the enhanced proliferation and osteogenic differentiation of the hMSCs on the aligned CNT networks, and that the osteogenic differentiation could be related to the upregulation of genes involved in the mechanotransduction pathways in the hMSCs.

To support the biocompatibility of glass-ceremic scaffolds coated with carbon nanotubes Meng et al., (2011) reported that these scaffold systems are biocompatible with mesechymal stem cells and they support the *in vitro* cellular activity. Recently by electrospinning methodology carbon nanotube composite nanofibers has been fabricated and their cellular response with mice L929 fibroblasts has been studied. It has been reported that these composite nanofibers provide a better environment as a 3D scaffold for the cell proliferation and attachment suitable for tissue engineering applications (Sharma et al., 2012). These reports and many others have shown that carbon nanotubes have the ability to serve as multifunctional structural materials and may be able to provide the initial structural reinforcement needed for newly created tissue scaffolds. The uses of CNTs as a scaffold in cell culture represent a challenging but potentially rewarding opportunity to develop the next generation of engineered biomaterials.

Other Bio-Applications of Carbon Nanotubes

The most prominent medical areas were carbon nanotubes have potential applications including tissue engineering are surgery, therapy, diagnostics, imaging, implant technology, bionics, bio-active surfaces, textiles, actuators, and delivery systems. Functionalization of carbon nanotubes has important consequences, as the ease of functionalization of CNTs gives them overwhelming advantage over spherical nanoparticles in many biological applications. For example, Kam and colleagues reported that biotin functionalized CNTs bound to fluorescent dyes were capable of intercellular transport of fluorescent streptavidin (Kam et al., 2004), DNA or siRNA can be bound to nanotubes with cleavable disulfide bonds and delivered to mammalian cells (Kam et al., 2005). Singh and colleagues have shown the biodistribution of functionalized nanotubes in BALB/c mice. These functionalized SWNTs were shown not to accumulate in any specific organ and were rapidly cleared from blood system without any toxic side effects and could be visually observed in the urine. Their work suggests that nanotubes have good biocompatibility and can be functionalized to serve as a vehicle for carrying imaging agents (Singh et al., 2006). CNTs have been also used for many other cell altering applications like localized drug delivery (Martin et al., 2003), delivery of genetic material and proposed as ion channel blockers (Joseph et al., 2003). The transporting capabilities of CNTs combined with suitable functionalization chemistry and their intrinsic optical properties had lead to new classes of novel nanomaterials for drug delivery and cancer therapy. Carbon nanotubes with unique physical property, can transform electro-magnetic energy into heat causing an increase in temperature lethal to cancer cells. This can be obtained merely by increasing the magnetic field or by irradiation with an external laser source of near-infra red (NIR) light at the very location, where these are bound to, or internalised within tumour cells. Moreover, the delivery of chemotherapy and photosensitisers to tumours, and activating them *in situ* is possible. Moreover, since carbon nanotubes fluoresce with a single wavelength of light, it may be possible to tailor different sizes of nanotubes and tune their electrical properties to seek specific targets, and thus diagnose multiple diseases in a single test. For example as selective cancer cell destruction has been achieved by functionalization of SWNT with a folate moiety, selective internalization of SWNTs inside cells labeled with folate receptor tumor markers, and NIR-triggered cell death, without harming receptor-free normal cells. A novel SWNT-based tumor-targeted drug delivery system (DDS) has been reported, which consists of a functionalized SWNT linked to tumor-targeting modules as well as pro-drug modules and shows high potency toward specific cancer cell lines (Chen et al., 2008). Further it has been demonstrated that use of MWNTs to generate heat in response to near-infrared radiation results in thermal destruction of kidney cancer *in vitro* and *in vivo.* The use of MWNTs enables ablation of tumors with low laser powers and very short treatment times with minimal local toxicity and no evident systemic toxicity. Thus making use of MWNTs with NIR is effective in anticancer therapy (Burke et al., 2009). The ability to track and monitor implanted cells in the progress of *in vivo* tissue formation is important in tissue engineered-constructs. In this relevance, the CNTs display good photostability and are feasible as imaging contrast agents for optical, magnetic resonance, and radiotracer modalities. Raman scattering and fluorescence spectroscopy may be promising methods for tracking CNTs in cells over long durations of time (Cherukuri et al., 2004, Heller et al., 2005). Carbon nanotubes have been also studied for their promising potential for nano delivery applications. Single-walled carbon nanotubes have been shown as a generic tool for delivering small peptides (Pantarotto et al., 2004) and proteins (Kam et al., 2004) into cells *in vitro* as well as *in vivo*. Cell line experiments showed that carbon nanotubes can deliver proteins that then retain their biological activity once inside the cell e.g., nanotube-bound cyt-*c* retained its biological activity and did cause significantly higher rates of apoptosis than did either cyt-*c* or the nanotubes alone (Cai et al., 1998; Zhivotovsky et al., 1998).

The exceptional electric and electronic properties of carbon nanotubes make them promising for many other applications for example Nanotube-based cold cathodes for compact, portable, and miniature X-ray generators are being manufactured. These X-ray tubes can be set up in a narrow space and possibly X-ray endoscopic imaging and provide improved high-resolution images in biological and medical applications. The unique properties of carbon nanotubes when utilized in conjunction with biomolecular recognition capabilities (e.g., antibodies) could lead to miniature electronic devices, including probes and sensors. CNTs provide several attractive features that make them ideal components for nanosensors including their electrical properties, large surface area, and the capacity to immobilize DNA or other proteins. For example, MWNTs have also been modified with putrescine oxidase for detection of putrescine (Rochette et al., 2005) and free cholesterol in blood can be measured using a MWNT electrode placed on a biocompatible substrate (Tan et al., 2005). Polyaniline and nanotube composite sensors have been shown to form flexible pH sensors (Kaempgen et al., 2006). MWNTs as well as SWNTs have been used to develop enzymatic amperometric biosensors (Joshi et al., 2005; Sotiropoulou and Chaniotakis, 2003; Wang et al., 2003) or fluorimetric biosensors (Barone et al., 2004). Nanotubes has been also used as sensors for DNA detection e.g., multiwalled nanotubes –based nanoelectrode arrays embedded in SiO2 matrix have been integrated into a electrochemical system for ultra-sensitive and rapid DNA detection (Cai et al., 2003; Koehne et al., 2004; Li et al., 2003). Carbon nanotube based sensors are being also developed for medical Capnography (measurement of CO2 concentration in human respiration during anaesthesia). This tiny low-power sensor has the potential to extend the reach of quantitative respiratory monitoring beyond the operating room. The other carbon based sensors reported have illustrated their broad potential as biosensors e.g., the simultaneous detection of dopamine and ascorbic acid for the diagnosis of Parkinson's disease (Jiang et al., 2004), and dopamine and serotonin detection (Wu et al., 2003), and a nitric oxide radical biosensor (Wang et al., 2005). Further enzyme based biosensors has been made by immobilising enzymes in redox hydrogels incorporating single-walled carbon nanotubes (Joshi et al., 2005). Application of carbon nanotubes in life sciences research sets the stage for an exciting and promising role in healthcare.

Carbon Nanotubes Toxicology

In spite of many attractive features, the toxicity of CNTs is a prime concern, with several groups pointing to their similarity to asbestos fibers (Poland et al., 2008). CNT toxicity in both *in vivo* and *in vitro* studies has been attributed to various factors, for instance, length, type of functionalization, concentration, duration of exposure, method of exposure, and even the dispersant used to solubilize the nanotubes. Yet many studies also seem to suggest that such attributes for CNT toxicity are unfounded. These inconsistencies seem to arise largely due to differences in experimental protocol, and whereas some points of view have been reconciled, most aspects of CNT toxicity remain uncertain (Firme and Bandaru, 2010). In cases where CNTs have a toxic interaction with cells, the mechanisms of toxicity are coming into focus. Results suggest CNTs may cause harm to cells by activating many pathways at once, mostly involving DNA damage (Pacurari et al., 2008). In one study, mesothelial cells exposed to SWNTs at concentrations ~25 μg cm^{-2} activated DNA recovery along with changes in the cell cycle and generation of apoptotic signals. Another approach showed that most cells incubated with CNTs halt at the G1 phase of the cell cycle (Jacobsen et al., 2008). It was also observed that CNT/ DNA interaction was the preferred route of toxicity in a 3-hour incubation study with 96 μg SWNT cm^{-2}, which induced DNA damage (through micronucleus generation) in lung fibroblasts (Ulrich et al., 1999). It should be possible, through the observation of specific toxic events that result from incubations with different types of functionalized-CNTs, to test for functional groups that reduce the severity of such events. CNTs were reported to be harmful to living organisms (Hoet et al., 2004) and consequently extensive nanotoxicological investigations are necessary to determine their biocompatibility and cytotoxicity before carbon nanotubes can be safely used as biomaterials (Colvin, 2003). Generally, metal dissolution (Uo et al., 2001) surface functional groups (Fubini, 1997) and size effects (Johnston et al., 2000) have been commonly cited as factors indicating cytotoxicity. There is need of more studies on CNT toxicity including long-term studies, with emphasis on issues such as cell specific tolerance, rates of toxic events, mechanism of cell injury, and organ-specific biodistribution before carbon nanotubes can be applied in medical tests or so. Future research into the fundamental aspects relevant for nanotube application, such as intrinsic defects, methods of synthesis, nature of the functional group, and so forth, will underlie biocompatibility, toxicological issues and eventual widespread application.

CONCLUSION AND FUTURE PROSPECTS

Carbon nanotubes are one of the most promising materials in nanobiotechnology with applications ranging from electronics to biology. Recently use of carbon nanotubes in tissue engineering as scaffolds for cell culture has shown positive results so far. Carbon nanotubes have shown as a promising material as a scaffold in cell culturing for many types of cells e.g., osteoblast, neuronal cells and stem cells. In addition carbon nanotubes, have the capacity to be used in tracking of implanted cells, cancer therapy, biological sensing and as a bioactive delivery agent for DNA and drugs into the cells. Application of carbon nanotubes in tissue engineering will provide key contribution for development of engineered biomaterials. Future research may be focused into the fundamental aspects of nanotube application, methods of synthesis, topography, and presence of impurities in as prepared- and functionalized- carbon nanotubes.

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KEY TERMS AND DEFINITIONS

Biocompatibility: Capability of coexistence with living things without causing harm.

Carbon Nanotubes(CNTs): Hollow graphitic cylinders of nanoscale dimensions.

Functionalized Carbon Nanotubes: CNTs with any functional group.

Multiwalled Carbon Nanotubes: CNTs with several nested graphene cylinders.

Scaffold: Any supporting framework.

Single Walled Carbon Nanotubes: CNTs with one cylindrical graphene sheet.

Tissue Engineering: Multidisciplinary field involving use of a combination of cells, engineering, suitable biochemical and physio-chemical factors to improve / replace biological functions.

Chapter 4

Novel Synthesis of 4nm Anatase Nanoparticles at Room Temperature Obtained from TiO_2 Nanotube Structures by Anodizing Ti

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ABSTRACT

The scope of the chapter is showing novel experimental findings on preparing anatase TiO_2 nanoparticles, first anodizing titanium into an organic media for obtaining TiO_2 nanotubes, and these used as a photo catalytic active electrode in treating water polluted with organic contaminants. The substrates were grit blasted in order to obtain mechanical fixation of the generated nanotubular TiO_2 structure. This was successfully achieved without diminishment of the nanotubes order and

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with a self-leveling of the outer surface. A new phenomenon is investigated consisting in the process of oxidation of the nanotubes in water after anodizing. Along this process, methyl orange added to the aqueous solution was discolored as part of the redox reaction involved. The final state of the modified layer was composed of conglomerates of crystalline TiO_2 *nanoparticles, around 4 nm in size, consisting of anatase. This was obtained under room conditions.*

INTRODUCTION

Nowadays, many materials with different properties have been investigated, between them, the nanomaterials, which have the potential to influence modern society in many aspects. These kinds of materials are now so interesting and both nanoscience and nanotechnology, result so attractive and exciting fields because nano-systems may not behave like their bulk counterparts. The era of dealing with tiny objects has been gaining momentum in the past few years because of the industrial progress, the scientific ability to fabricate, model and manipulate things with a small number of atoms, and the almost daily discovery of novel size-induced phenomena.

The origin of the size-induced properties in nanomaterials depends on the surface phenomena (extrinsic contribution) and quantum confinement effects (intrinsic contribution). The surface to volume ratio increases rapidly when particle size decreases (Fagan & Solange, 2011).

There are many techniques for synthesizing nanoparticles, but in this work is presented the investigation about obtaining them through the synthesis of TiO_2 nanotubes through an electrochemical method. Their analysis cover different aspects, such as morphology layer surfaces, their shape and size, chemical composition, crystalline size, study about catalytic and photocatalytic activity, morphology before and after catalytic and photocatalytic tests. These analyses allow finding and observing a complete transformation of the structure to 4nm anatase nanoparticles.

There are so many works in the nanomaterials area, but those directly related to photocatalysis are mostly associated to TiO_2 or ZnO (Chen & Mao, 2007). TiO_2 is used for many applications, such as: sunscreens, antibacterial, chemical sensors, pollutant filters, toner photoconductor, and in optoelectronics (Chen, Wang, Wei, & Zhu 2012; Chen, Liu, Zhang, & Jin, 2003; Cui, Ghao, Qi, Liu, & Sun 2012; Liang, Luo, Tsang, Zheng, Cheng, & Li, 2012; Macak, Tsuchiya, Ghicov, Yasuda, Hahn, Bauer, & Schmuki, 2007; Xie, 2006). The main use of TiO_2 is like a white dye in many products. In some cases, it is possible to find several industries spread around the world that are producing different kinds of nano-structured titanium dioxide on a large scale (Khvan, Kim, Hong, & Lee, 2011; Yam, Beh, & Hassan, 2011).

The TiO_2 semiconductor material shows a vast number of interesting properties, which are maximized when these belong to the nanostructure. However, one of the emerging and intensively explored properties of this nanostructured oxide is its photo catalytic activity, mainly for the treatment of environmental pollution.

The photo catalytic phenomena of TiO_2 occur due to the presence of a large number of defects in the crystalline structure, such as oxygen vacancies, interstitial titanium atoms from the donor states, titanium vacancies and interstitial oxygen atoms from the acceptor states.

The electronic condition created in this structural arrangement produces a band-gap, an intrinsic characteristic of semiconductor materials, by the existence of a forbidden gap between the valence and the conduction band. The photocatalytic activity of TiO_2 occurs only when photons with energies greater than its band-gap energy can result in excitation of the valence band electrons, which jump to the conduction band and then can promote a reaction. The absorption of photons with lower energy or longer wavelengths than the band-gap energy usually causes energy dissipation in the form of heat. The illumination of the photocatalytic surface with sufficient energy leads to the formation of a positive hole in the valence band and an electron in the conduction band (Nakata & Fujishima, 2012). After the light excitation, the electron-hole created pair could have an electronic recombination releasing heat or could be involved in electronic transfer with other species and interact directly or through some photosensitizers with organic substrates. The positive hole oxidizes either pollutant directly or water to produce hydroxyl radicals (•OH), whereas the electron in the conduction band reduces the oxygen adsorbed on the catalyst (Gelover, Gómez, Reyes, & Leal, 2006). Based on this principle TiO_2 and, more recently, nano-TiO_2 have received attention in research on the degradation of different organic specimens that are environmental pollutants.

BACKGROUND

For making TiO_2 more functional, suppressing electron-hole potential recombination at grain boundaries, many attempts have been carried out, such as: nanowires (Liu, Wang, Li, Zhao, Liang, Huang, & Shen, 2011; Miao, Xu, Ouyang, Guo, Zhao, & Tang, 2002; Tan & Wu, 2006; Xue, Zhang, Chen, Yin, & Lin, 2011), nanorods (Hu, Li, Jia, & Xia, 2011; Huang, Ning, Peng, & Dong, 2012; Limmer, Chou, & Cao, 2004; Yoon, Jang, Vittal, Lee, Kim, 2006), or nanotubes (Albu, Ghichov, Macak, Hahn, & Schmuki 2007; Awitor, Rafqah, Géranton, Sibaud, Larson, Bokalawela, & Jhonson, 2008; Ghicov, Tsuchiya, Macak, & Schmuki, 2005; Kılınç, Şennik, & Öztürket al, 2011; Kim, Ghicov, & Schmuki, 2008; Kwon, Kim, Lee, Chin, Seong, Lee, & Lee, 2012; Li, Wang, Huang, Sun, & Zhou, 2011; Nie, Mo, Zheng, Yuan, &

Xiao, 2013; Palmas, Da Pozzo, Delogu, Mascia, Vacca, & Guisbiers, 2012; Shankar, Mor, Prakasam, Yoriya, Paulose, Varghese, & Grimes 2007; Yang & Pan, 2010) have been explored as an alternative to nanoparticles based films. Especially, self-ordered anodic TiO_2 nanotube arrays have attracted considerable interest due to their highly aligned geometry and the simple fabrication process (J, Lin, Zheng, Zhu, & Samia, 2011; Kılınç et al, 2011; Lei, Luo, Sun, Kuang, & Su, 2013; Liu, Lee, & Schmuki, 2012; Liu, Yang, Qiang, & Wu, 2011; Yu, Li, Wlodarski, Kandasamy, & Kalantarzadeh, 2008).

For the production of TiO_2 nanotube layers some different methods have been used, such as: sol-gel methods with organic gellants as templates (Arami, Mazloumi, Khalifehzadeh, & Sadrnezhaad, 2007), pre-deposited hydrothermal TiO_2 (L. Cui et al, 2012), microwave-assisted hydrothermal (Cui, Hui, Hui, Lee, Zhou, Wan, & Thuc, 2012), sonochemical (Arami et al, 2007; Mohapatra, Misra, Mahajan, & Raja, 2007), microemulsion (Y. Li et al, 2012), solvothermal (Wang, Yang, Wang, Huang, & Hou, 2012), atomic layer deposition (ALD) (Lee, Ju, Lee, Kim, & Lee, 2010; Meng et al., 2013), Seeded growth method (Tia, Voigt, Liu, McKenzie, & Xu, 2003), by mean of ionic liquids (Li, Qu, Cui, Xu, Luo, Chi, Dai, 2011), anodized Ti (D. Gong et al, 2001), among others. The anodized Ti for obtaining TiO_2 nanotubes offers a better control over their dimensions and homogeneity. This is carry out in fluoride based electrolytes (Gong, Grimes, Varghese, Hu, Singh, Chen, & Dickey, 2001; Gong, Lay, & Lin, 2010; Y. Lai et al, 2012; Y. K. Lai et al, 2010).

In 2001, D. Gong et al. (2001) first developed titania nanotube arrays self-organized into a Ti substrate by potentiostatic anodic oxidation using HF solutions as an electrolyte and pure Ti plate as substrate, as a consequence, this lead to the rise of the research on TiO_2 nanotube arrays. Their special nano architecture offers great inner surface without a corresponding decrease in geometric and structural order (Shankar, Varghese, Mor, Paulose, Grimes, 2008). These oriented structures make them excellent electron percolation pathways for charge transfer vector between interfaces and offers improved properties for applications in many fields, such as: solar cells, photocatalysis, photolysis of water, hydrogen sensors (Albu et al, 2007; Johns, Roberts, & Owen, 2011; Macak, Tsuchiya, Ghicov, Yasuda, Hahn, Bauer, & Schmuki, 2007; Mohammadpour, Waghmare, Mitra, & Shankar, 2010; Quan, Yang, Ruan,& Zhao, 2005; Santangelo, Messina, Faggio, Donato, De Luca, Donato, Neri, 2010).

The major use on TiO_2 is the phtocatalysis, one disadvantage of TiO_2 nanoparticles is that they can only use a small percentage of sunlight for photocatalysis. Practically, there exists an optimal size for a specific photocatalytic reaction. This work is based in the results after degradation of methyl orange using TiO_2 nanotubes, however, some results of some author using TiO_2 nanotubes and under UV radiation are listed in Table 1.

Table 1.

Sample	Time of Degradation (h)	Degradation Rate (%)	Reference
TiO_2 nanotubes (film)	12	55	(Zhao et al, 2007)
TiO_2 nanotubes (film)	4	10	(Hailei Li et al, 2012)
TiO_2 nanotubes (film)	1	80	(Sohn et al, 2008)
TiO_2 nanotubes (film)	1	97	(Su et al, 2008)

Anodizing is a process in which a metal is exposed to the anode voltage (+) in an electrochemical cell configuration of at least two electrodes, where the reaction implies the oxidation of the metal:

$$M \rightarrow M^{n+} + ne^- \quad (1)$$

This method is more common for making metals more resistant against oxidation that occurs naturally. This consists in the formation of a layer over a metallic surface.

In this process, there are three possibilities:

1. Metal ions (M^{n+}) are solvated in the electrolyte. The metal is continuously dissolved.
2. Metal ions (M^{n+}) react with O^{2-} (H_2O formed by the electrolyte), forming a compact layer of metal oxide. The metal oxide is not soluble in the electrolyte.
3. Under some conditions, there is an electrochemical competition between solvated ions and the formation of oxides.

In the anodized Ti, the parameters that influence the growth of TiO_2 nanotubes are: the electrolyte composition, voltage, and time. Grimes et al (2001), observed the appearance of pores and voids in the surface of the titanium sheet in the form of nanotubes. They believed that the tube structure was the result of the depth and spread of small pores. Schmuki et al. (2005) found that the low acidity at the bottom of the pore helps sculpt the pore into a tubular structure. However, the detailed process of how the small pore becomes a large pore, and eventually into a tubular structure is not clear.

EXPERIMENTAL

TiO_2 nanotubes were synthesized by means of anodizing-dissolution. The preparation of Ti plates for the anodizing process started by removal of any rust present by polishing. Then, Ti plates were subjected to sandblasting process (Sandblast Horus Group Ltd., Tezca Mark) for generating a rough surface, which was proposed for adequately anchor the nanotubes.

The system for anodizing was an organic medium, which consisted of the following: Electrolyte (ethylene glycol 98% v/v, H_2O 2% v/v, NH_4F 0.3% wt/%) Ti plates (97.5% Ti, 2.42% C, 0.08% Sn). The anodizing time was variable, the used times were 2, 4, 8 and 16 h, being 2 h and 4 h with better degradation effect (see Figure 7). A voltage ramp about 100 mV/s (6 V/min) was used, starting from 6 V, and raising it up to 60 V (main potential used in the TiO_2 nanotubes generation process).

The experimental setup consisted of: a) an open transparent polypropylene container with a capacity of 4L; b) a central Ti plate as cathode (13 x 9 cm, thickness 1 mm), the immersed area was typically 4 x 9 cm; c) two Ti plates as anodes (4cm x 3cm, thickness 1 mm), one per each side of the cathode, with a 2cm separation between anode-cathode-anode and an immersed area typically of 2.5 cm x 3 cm (7.5 cm^2).

After obtained, TiO_2 nanotube layers were used to treat methyl orange aqueous solutions catalytically (without UV light) and photocatalytically (UV light). The methyl orange ($C_{14}H_{14}N_3NaO_3S$, Acros Organics brand), with a concentration of 20 mg/L, was used as a model contaminant. These tests were realized with 15 mL of solution into polypropylene bottles, where anodized Ti plates were immersed, and later stored into darkness within a container.

For photocatalytic degradation tests, methyl orange aqueous solutions were placed in open plastic containers. The Ti plates anodized were placed into the solution, the container was into a special cell for photocatalysis (closed black PVC container) and subjected to artificial UV light with a mercury UV lamp (GE germicide lamp, model G15T8, 15 W).

TiO_2 nanotubes were generated in an organic medium (0.3 wt/% NH_4F and 2 v/% H_2O in ethylene glycol, 60 V) with various anodizing times (0.5, 2, 4, 8 and 16 h).

There is a relationship between the pore diameter, the wall thickness and the anodizing voltage, which among other factors form part of the process of forming the TiO_2 nanotube arrays on the surface of the titanium (Roy et al, 2011). The mechanism is as follows:

1. In a first step, occurs the formation of a compact layer of titanium dioxide. It is formed due to the interaction of metallic Ti with O^{2-} and OH^-, present into the solution, under an external applied electric field (reactions 2 and 3).

$$Ti \rightarrow Ti^{4+} + 4^{e-} \tag{2}$$

$$Ti^{4+} + 2H_2O \rightarrow TiO_2 + 4H^{+} \tag{3}$$

2. TiO2 layer formed on the anode in the vicinity of this, the TiO2 surface reacts with fluoride ions with the help of the electric field forming the complex [TiF6]2- dissolved in water, resulting in surface cracks.

$$TiO_2 + 6F^{-} + 4H^{+} \rightarrow TiF_6^{2-} + 2H_2O \tag{4}$$

3. Fractures become larger pores and the pore density increases. Subsequently, the pores become evenly spread over the surface (Liu et al. 2011a).
4. When the rate of oxide growth on the metal-oxide interface, and the dissolution rate of oxide in the oxide-electrolyte interface are equal, the thickness of the barrier layer remains unchanged.
5. The length of the nanotubes increases as long as the ratio of electrochemical oxidation remains equal to the ratio of chemical dissolution in the upper surface of the nanotubes. Thus, it produces a porous self-organized structure.

Various causes influence the photocatalytic efficiency in nanotubular titania surfaces, among others, the manufacturing process, in which the factors are: current intensity, electrolyte used, impurities, treatment temperature, dissolved oxygen, experimental setup, etc.

In order to evaluate the photocatalytic activity of titanium dioxide, a single dye having a molecule with a single link azo (N=N) had been used, named methyl orange (MO).

There were some unusual conditions employed to produce the nanotubular structures.

1. **Sandblasting:** Before applying this technique, Ti plates were cleaned with a wire brush in order to remove corrosion on the surface. After cleaning, the application proceeds to sandblasting (only to the anodes). The pressure used to accomplish the surface attrition was 100 kgf/cm^2, for a period of 1 minute per side of each Ti plate. The abrasive material used was Al_2O_3 with an average particle side around 2.5 mm.

The principal hypothesis to use sandblasting is for increasing fixing the nanotubes layers modified, and resist adverse mechanical conditions. An example could be the continuous flow of water. This treatment is necessary, since after some first tests of titanium anodizing (without sandblasting), the layers made of nanotubular structures had poor adhesion, presented fractures and detached easily.

2. **Water Dosing for the System:** The experimental setup consisted of an open vessel, which allows evaporation along with water consumption by electrolysis required for providing oxygen and acidity to the bottom of the nanotubes. This made it necessary to continually add water into the system. This was done by dripping at a rate that could compensate the loss of water, and that kept the solution level. In addition, this change in the process had as a favorable consequence avoiding the rise in the electrical resistivity of the system.

The conductivity of the solution was monitored and controlled, which resulted indicative of a balance among TiF_6 resulting from the reaction, the addition of NH_4F for maintaining the fluoride level and constant water addition. After finishing each anodizing process, solutions were stored. Usually, during a period with time enough for a precipitation of a crystalline compound to occur. These crystals are composed of fluorine, ammonium and titanium (see Figure 8). After to separate the precipitate, the ethylene glycol solutions were reused for anodizing. During all the experiment, the implementation of magnetic stirring into the system was realized, this allowed a mass transport, improving homogeneity of the species concentrations in the solution.

3. **Voltage Ramp:** Applying an initial voltage ramp has been shown to promote the development of a network of interconnected cavities from the early stages of the process. This helps to release stress at the interface metal/metal-oxide (M/OM) and aiding in the retention of titania layer on top of Ti substrate. Since, at the begin of the experiment, the electrode located close to the solution are without an oxide layer, therefore requieres less current density.
4. **Adding NH_4F to the Electrolyte:** When the solution started from a new or pure ethylene glycol, usually a 0.3% w/w of NH_4F was added, according to the calculation based on the conditions of the electrolyte. However, when the electrolyte is reused, it is necessary to add NH_4F. Subsequent additions to use baths were done to keep the chemical dissolution of TiO_2. Some tests were realized for comparing nanotubes layers obtained after many anodized in a same ethylene glycol bath. By the above, the bath could be used four times without detriment in the conditions or characteristics of the resulting layers. This was done considering above described material additions and monitoring the process parameters.

5. **Ultrasonic Cleaning (Sonication) of the Nanotube-Modified Ti Plate Surface:** After anodized Ti, is necessary to apply sonication, which involves the propagation of high-intensity sound waves in liquid media. This, one of the most efficient methods of cleaning, results not abrasive and not leaving residues of chemical solutions on substrates.

The application of ultrasonic cleaning was intended to eliminate any remaining adsorbed species after anodizing process on the modified Ti plate. This cleaning was conducted immersing the nanotube-Ti plate in a beaker containing deionized water.

RESULTS AND DISCUSSIONS

SEM and HRTEM Analysis of Nanotubes

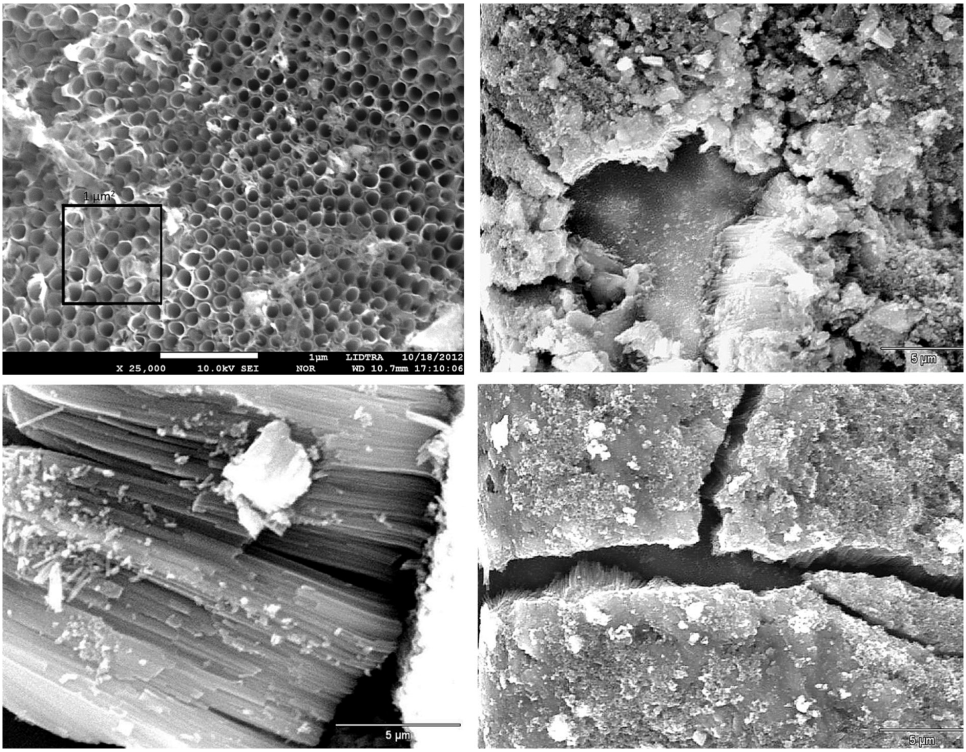
Tubular structures were observed by mean of SEM, which shows TiO_2 nanotubes formed, generated during anodizing-dissolution process in organic media.

The Figure 1 shows TiO_2 layers and nanotubes structures. In Figure1-A (top-left) is shown an area of 1 μm^2, where it is possible to look the presence of 32 nanotubes, 29 of these are surrounded by six nanotubes and 3 surrounded by five. Therefore, based in this observation, hexagonal packing factor was 0.92; meaning 92% of the nanotubes had six first neighbors. In this area, the nanotubes were not perpendicular to the surface plane but deviated to the left. This was something typical for our nano-structures with substrates subject to sandblasting. For those nanotubes normal to the surface plane, the calculated wall thickness and pore size were approximately 10-20 nm and 110-140 nm, respectively.

Figure1-B (top-right) and Figure 1-D (bottom-right) show fractures on a top modified layer, which allow seeing nanotubes formed at the bottom constituting a second modified layer. This was changed by using sandblasting as Figure 1-A show. The thickness depends on different parameters, such as time, but usually was around ten microns for two hours of anodizing. Figure 1-C shows a detached fragment of the nanotubes layer with a thickness around 17.6 μm.

HRTEM was used for samples previously used in water treatment. The nanotubular structures obtained by mean of Ti anodized, after the treatment, resulted in different morphology in comparison to others works reported. They were metastable due to their composition: fluorine, ammonium and titanium. The Figure 2 shows HRTEM images, which present nanotubes transformation to nanoparticles. Figure 2-B (top-right), 2-C (bottom-left), 2-D (bottom-right) presents fuzzy nanotubes.

Figure 1. Four SEM images corresponding to: A) sandblasted and anodized Ti substrate, B) – D) corresponding to anodized Ti without sandblasting pretreatment



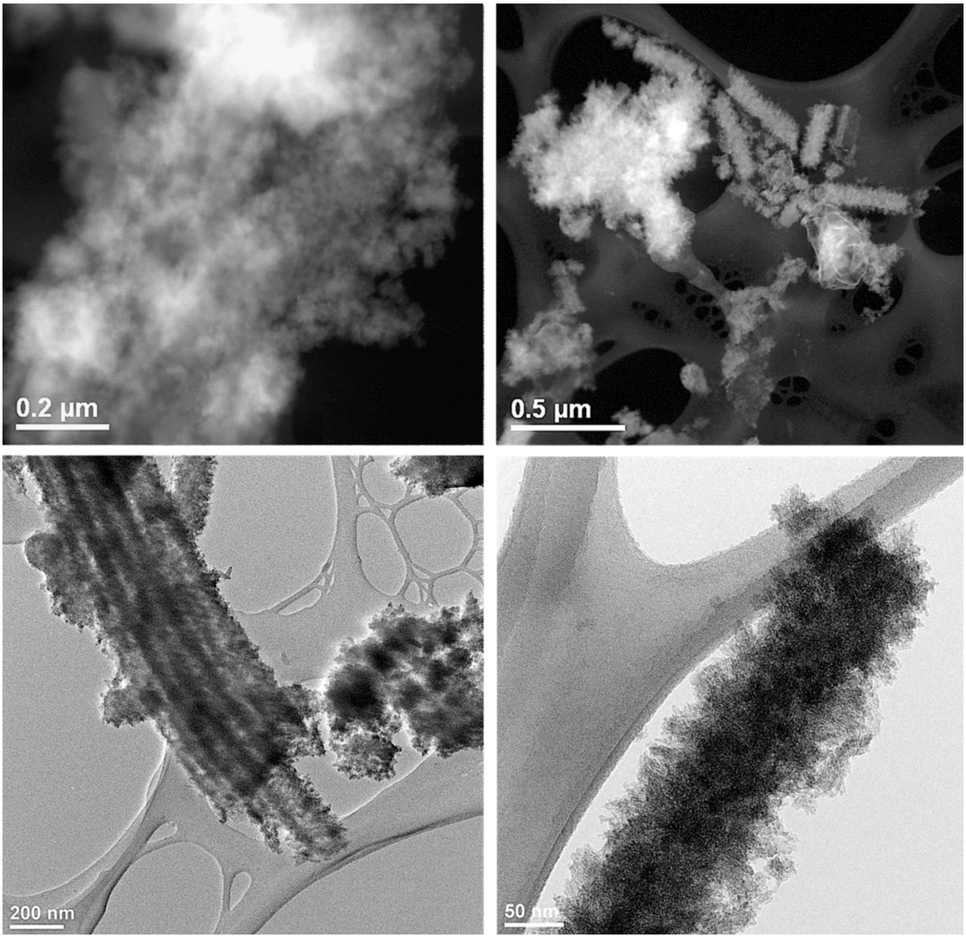
We propose that those structures underwent a transformation from a structure made of fluorine/ammonium/titanium, by slowly oxidizing in water, until reaching a titanium oxide.

The Figure 3 shows that the material is highly crystalline, the crystallite size was determined by Scherrer equation (Equation 5), the size was around 4 nm.

$$\tau = \frac{K\lambda}{\beta Cos\theta} \tag{5}$$

This was first observed on samples that had higher percentages of discoloration of methyl orange aqueous solutions, corresponding to 2 h anodizing time (Figure 2-A and 2-B). The samples were immersed in water, containing methyl orange, during around four days. This caused a solution discoloration but also a surface change. The nanotubes layer was modified to a thick, white and powdery layer.

Figure 2. Four HRTEM images corresponding to nanotubes after water exposure during 4 days. The fuzzy conformation indicates transformation of nanotubes to a particulate system.



HRTEM analysis was performed on the sample with 2 h (Figure 2-A and 2-B) and 4 h (Figure 2-C and 2-D) anodizing without the application of heat treatment. This implies the generation of the anatase nanoparticles from contact with the aqueous solution.

Those micrographs show the presence of nanotubular structures with apertures of nanotubes of about 120 nm and lengths of about 0.5 microns. The nanotubes apertures measured by HRTEM (120 nm) coincide with that obtained from SEM (110 -140 nm).

Figure 3. a and b Four HRTEM images corresponding to nanotubes after water exposure during 4 days. The fuzzy conformation indicates their transformation of nanotubes to a particulate one.

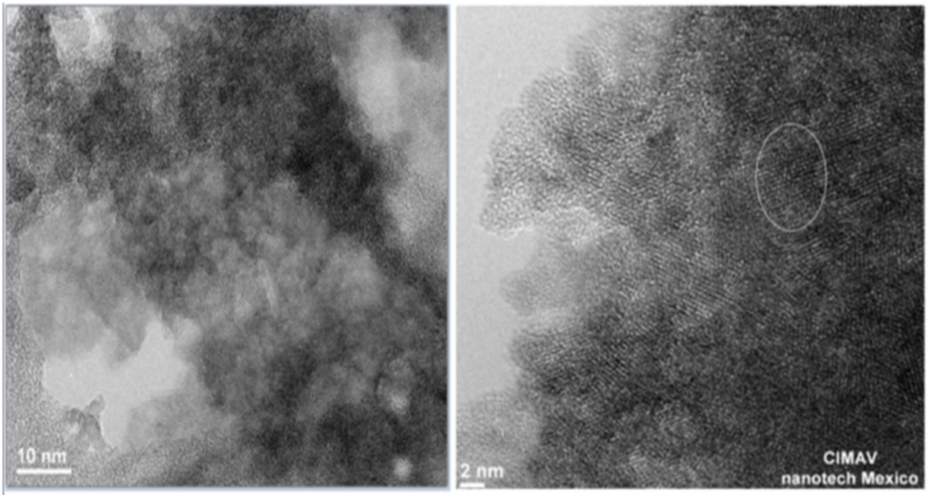


Fig-3a

Fig-3b

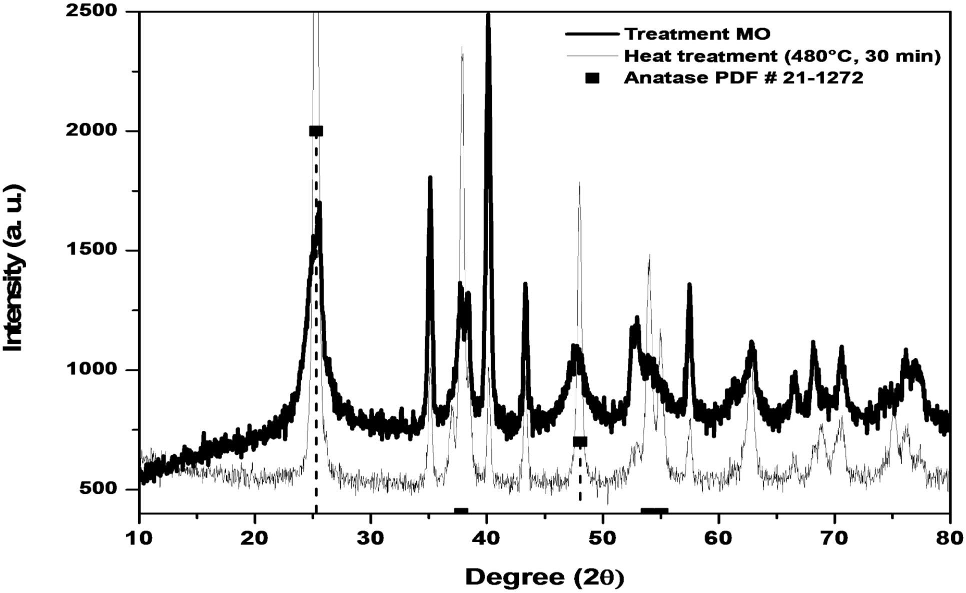
In those cases, where the nanotubular structure was desirable, heat treatments around 450 °C during 30 min were done. The crystallite size were around 25-40 nm.

Chemical Composition and Crystalline Sizes Determination

In addition to identifying the desired phase (anatase) for photocatalytic processes by mean of XRD, it is possible to determine the chemical composition in weight percent (% wt) and the size of the crystals formed (nm) by using Rietveld method. Figure 4 shows two diffractograms, one corresponding to a Ti treated plate with MO aqueous solution, and other corresponding to a similar sample but heat-treated. In addition, it shows anatase reference patron JCPS 21-1272.

This confirms that it was possible to obtain the anatase phase without heat treatment, only by oxidation in contact with the aqueous solution of NM. In both cases, some tests with (4 hours) and without application of UV light. Finally, there was a substantial crystallite size difference in the anatase phase with and without heat treatment. Larger crystallite size (26.8 nm) was obtained by using temperature in order to modify samples and a smaller size (4 nm) by immersion in aqueous MO solutions.

Figure 4. Diffractograms of anodized Ti plates with heat and water treatments. Black squares indicate the anatase peaks. The other peaks correspond to metallic Ti.



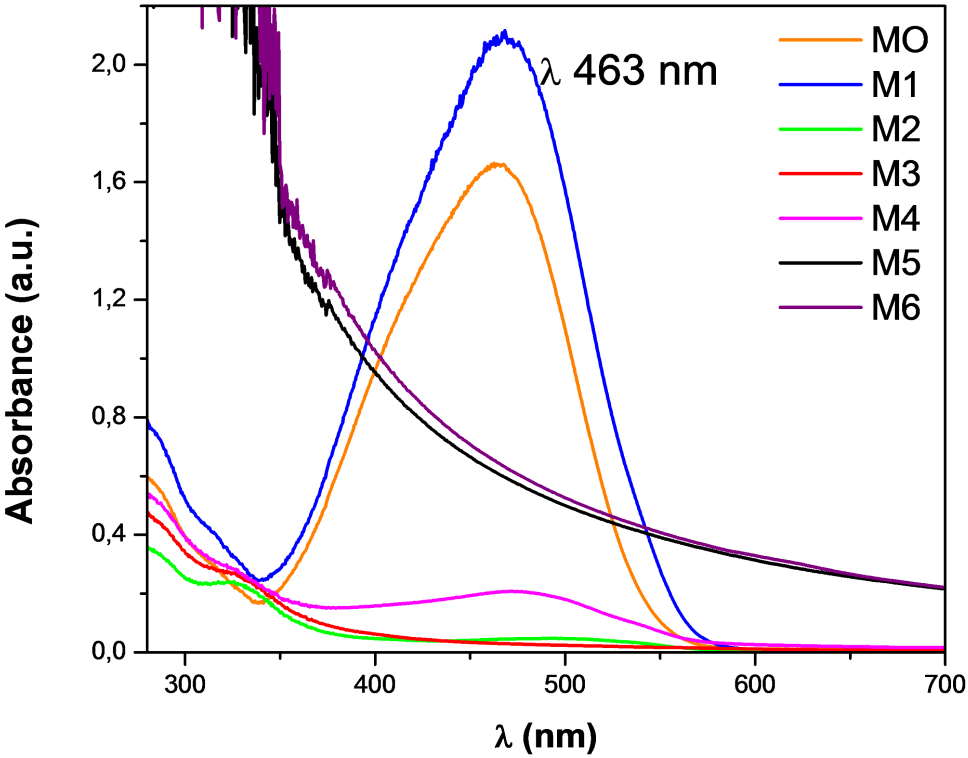
Discoloration of Methyl Orange

For determining the concentration of MO, the UV-vis spectra (absorbance vs. concentration) were acquired of aqueous dye solutions with the following concentrations: 5, 10, 20, 25 and 30 mg / L. The main absorption band was located at 463 nm (see Figure 5, label MO). The absorbances for all those concentrations were taken at that wavelength used for the calibration curve. Those samples were not exposed to UV.

Figure 5 shows absorbance spectra for a series of samples used in the catalytic tests. Sample M1 was obtained anodizing Ti 4 h but it was used previously in a discoloration test. Sample M2 was obtained anodizing Ti 4 h but it was not dryed in air before discoloration tests but kept into ethylene glycol. Samples M3 - M7 were obtained anodizing Ti during 2, 4, 8, 16h, respectively.

The samples were not exposed to UV and the discoloration was attributed to a collateral effect to the oxidation process for the nanotubes. The samples M2 and M3 had a higher degree of discoloration, corresponding to 4 and 2 h of anodizing, respectively. The contact time with the solution for all samples was around four days. Sample M2 and M3 accomplish the discoloration in two days. We propose that the oxidation process in those two samples were due to the nanotubes layer conditions, such as the fluorine/ammonium/titanium bonds and ratios.

Figure 5. UV-vis analysis show spectra corresponding to the process of methyl orange discoloration during the process of nanotubes oxidation and their transformation to anatase nanoparticles



The samples with 8 and 16 h of anodizing, the discoloration of methyl orange solutions were not as effective as for samples M2 and M3. It is important to notice that M1 sample increased NM coloring. The orange color changed started increasing its intensity with a deep red tone it was previously used in other discoloration test, which was its main difference. The other samples only diminished solutions color. Nonetheless, this capacity for discoloring the MO solution only occurred during the oxidation of the nanotubes layer process. After it was complete, the samples lost such effect without UV exposure. Therefore, it was possible to observe a loss of bleaching effect on MO when a sample was used more than once. Since the transformation makes anatase particles, they become photocatalytic but with poor cohesion among particles or adhesion to the substrate.

Kinetic Analysis

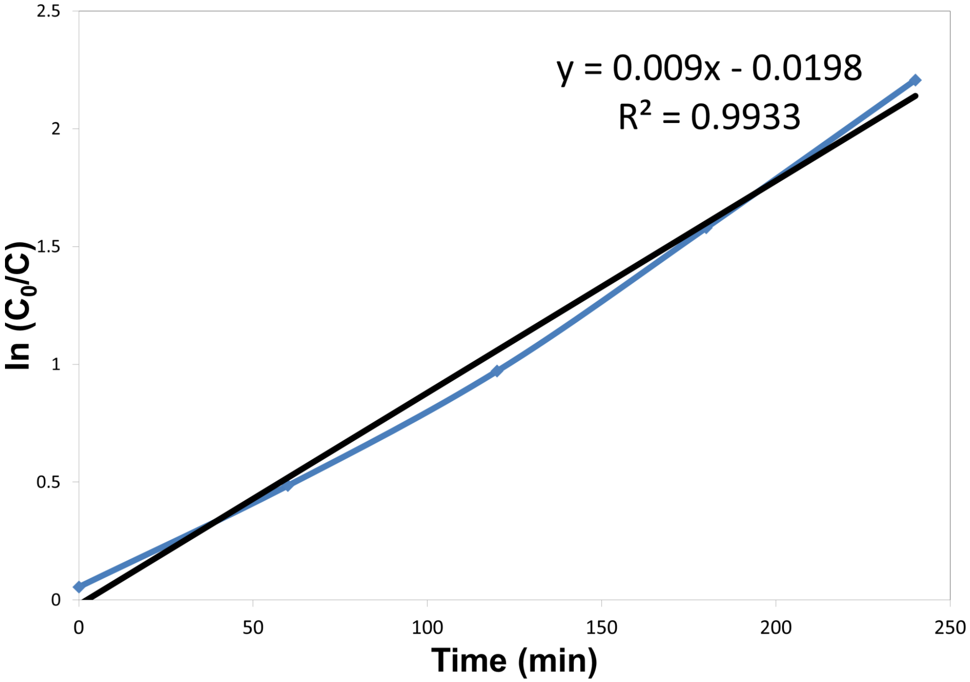
The process degradation was adjusted to a kinetic model and a constant rate of reaction kinetics was obtained by mean of Langmuir-Hinshelwood Equation (6). This equation is applicable to low dye concentrations. The concentration of MO (20 mg/L) was enough to use this equation.

$$\ln\left[\frac{C_0}{C}\right] = k_{app}t \tag{6}$$

Equation (6) was used by testing the reaction. It was plotted as ln $[C_0/C]$ vs. time (t) and 1/C vs. time (t), which represent reactions of first and second order, respectively.

The Figure 6 shows a correlation coefficient very close to 1 ($R^2 = 0.9933$). Therefore, it provides a very good fitting of the reaction to an equation of the first order. In other words, the order of reaction was 1.

Figure 6. Fitting of the ln $[C_0/C]$ vs. time (t) plot corresponding to the discoloration of methyl orange in water using nanotubes plates



Catalytic and Photocatalytic Tests

Photocatalytic Tests

Photocatalytic tests performed were of two kinds:

1. Test with 1 h of exposure to UV light and 4 days of nanotube modified plates in contact with the MO solution.
2. Test with 4 h of exposure to UV light. This was the time required for discoloration of the MO solution with the experimental setup used.

In this test, modified surfaces were exposed to ultraviolet light within MO solutions. This was performed into a closed cell for photocatalysis. The time of exposure to UV light was 1 h, whereas the contact time with the solution of MO was 96 h (4 days, as in the tests without UV exposure). MO discoloration was quantified by UV-vis analysis.

Discoloration Effect

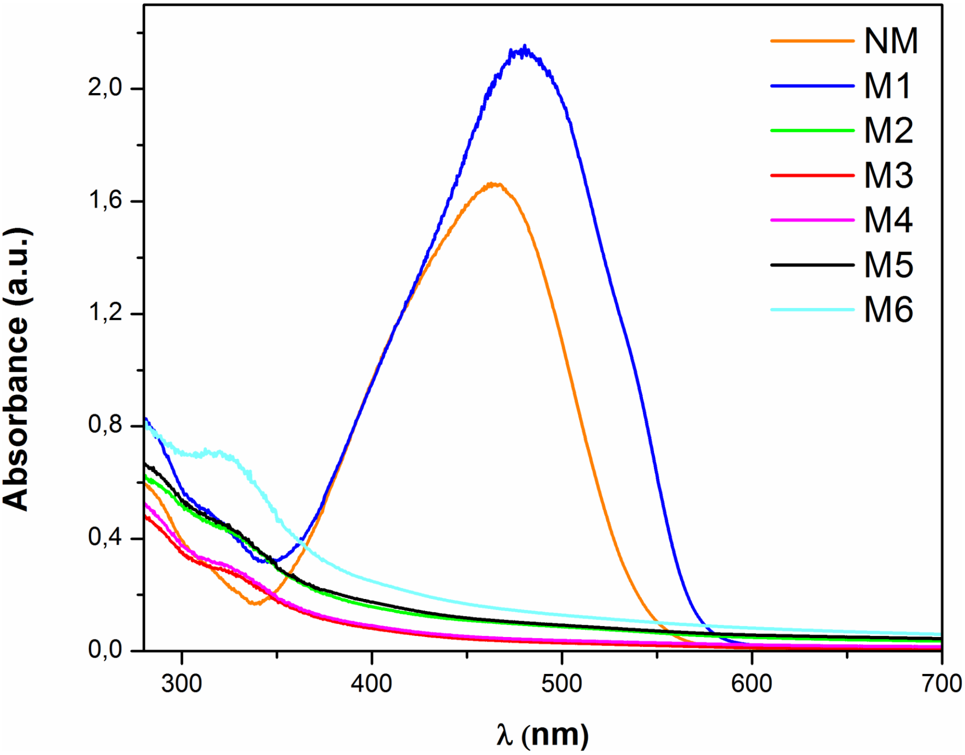
UV-vis analysis showed the effect of MO via photocatalytic discoloration. The degree of discoloration observed in samples over time generated six different conditions.

Figure 7 shows absorbance spectra for the series of photocatalytic tests. The M3 and M4 samples were those that had a higher degree of decolorizing, corresponding to 2 and 4 h of Ti anodizing, respectively. In the cases 8 and 16 h of Ti anodizing (M5 and M6, respectively), discolorations were not as effective as for M3 and M4 samples.

It is important to note that sample M1 increased MO coloring. Again, this modified Ti plate sample was previously used in other discoloration test. It was possible to observe a loss of bleaching effect on MO. One more time, the discoloration effect on the dye can be observed only when the surface was not used before. Once the oxidation of the layer was complete, such effect ends.

Ti plates can be easily cleaned, i.e. removing TiO_2 nanoparticles formed during such oxidation/discoloration effect, which is possible using sonication for approximately 20 minutes. This action would free Ti plates and allowing their use again for repeat the anodizing process.

Figure 7. UV-vis spectra of solutions with discoloration of methyl orange in a photocatalytical process



Comparison between Catalytic and Photocatalytic Tests

In previous sections, 3.3 and 3.5.2, the catalytic and photocatalytic effects by contacting nanotubes modified Ti plates with the aqueous solutions of MO was analyzed. In this way, two kind of tests were conducted, one catalytic and the other photocatalytic.

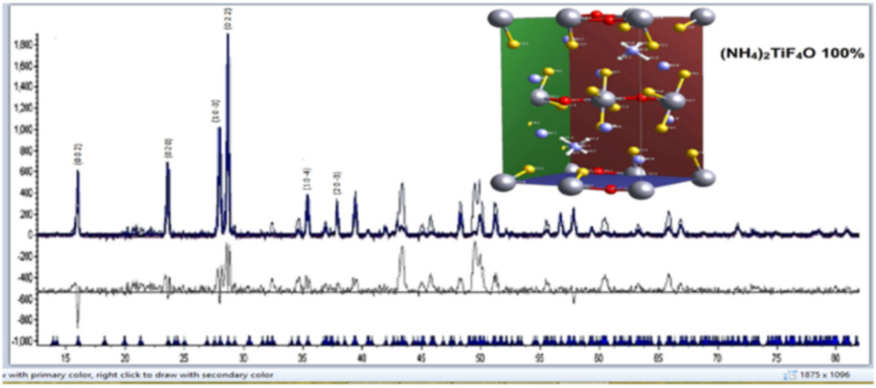
Based on the results of both sections, both processes resulted in discoloration of MO solutions. The photocatalytic discoloration was obtained within 1 h of exposure to UV light. However, the time required to performing a test with the catalytical process was 96 h. This together with the fact of a single use for each sample limits its use. In the other hand, such effect is a new observation. The collateral discoloration effect was a way to quantify and follow the transformation of the nanotubes layer by oxidation, and their loss of ammonium and fluoride that formed part of the structure.

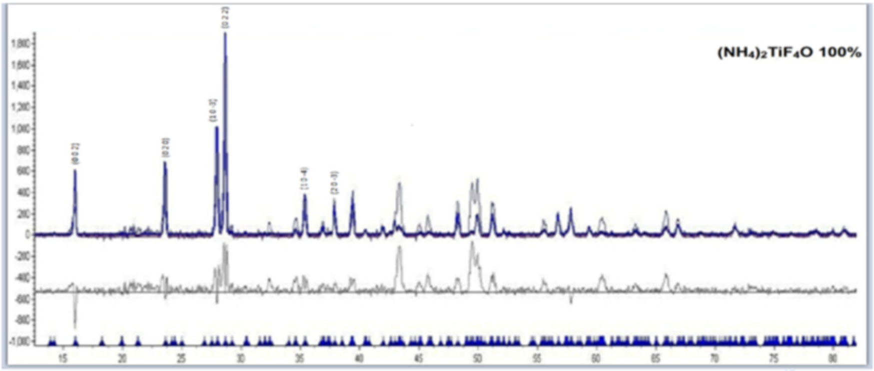
Analysis of Precipitate Formed After Anodizing in Organic Media

During the generation of nanotubes, by oxidation-dissolution of Ti-TiO_2, an organic bath was used. Their composition was: Ethylene glycol 98% v/v, H_2O 2% v/v, NH4F 0.3wt/%. These electrolytes were reused several times, according to the procedure described in the experimental section. After been used around four times, the solutions were saturated. The solutions were stored, which allow for an accumulation of a precipitate. The white powdery precipitate was abundant. It also was easy to remove and allowing re-use of those solutions for anodizing.

Figure 8 shows the fitting by Rietveld method using the TOPAS 4.2 software. The lines at the top correspond to the experimental diffractogram and the fitting. The gray line corresponds to the difference between those two.

Figure 8. The fitting of a diffractogram corresponding to a white precipitate formed at the solutions used for anodizing Ti plates. This crystalline compound was identified as $(NH_4)_2TiF_4O$.





The white precipitated was formed into the solutions used for anodizing Ti plates. The time for obtaining this precipitate depends of concentration and storage conditions of the bath previously used. After separation and cleaning, the precipitate was analyzed by X-ray Diffraction (XRD). This allowed a determination of composition. According to the above, the compound identified in the precipitate formed after anodizing Ti plates was $(NH_4)_2TiF_4O$, ammonium fluoride titanium oxide, which corresponds to 100% of its composition. Its unit cell was displayed as an insert in Figure 8.

An amorphous variant of the compound $(NH_4)_2TiF_4O$ is proposed as forming the nanotube structure shown in the SEM images, which transforms into anatase nanoparticles, as shown in the HRTEM images, by oxidation of such compound.

CONCLUSION

Nanotubes structures were generated by anodizing Ti plates using an organic solution (NH_4F 0.3 wt/%, H_2O 2% v/v, $C_2H_6O_2$ 98% v/v) using a voltage ramp of 6 V/min and finally maintaining 60 V, which was the working potential of the anodizing process. The dimensions of the nanotubes generated at room temperature were nanotube opening 110-140 nm, wall thickness 10 – 20 nm, length 5 – 20 μm.

The nanotubular structures generated were metastable. Their obtaining was under some changes incorporated into the process, such as: sandblasting of Ti plates, continuously adding water to the system, constant agitation of the electrolyte, addition of ammonium fluoride to compensate its consumption, reuse of solutions, and voltage ramps. Additionally, long periods of immersion for the modified layer plates into the aqueous MO solution (20 mg/L), ranging from 4 – 96 h. After that, samples were analyzed by XRD, SEM and HRTEM where anatase nanoparticles were identified substituting the nanotube structures.

XRD shows that before contacting the MO aqueous solution of modified Ti plates, no anatase structure appeared. However, after a slow oxidation process within an aqueous MO solution, it was possible to observe anataseTiO_2. This was independent of UV exposure. Furthermore, by employing XRD, a marked difference was observed in crystallite sizes with and without heat treatment, resulting in sizes of 26.8 and 4.7 nm, respectively.According to discoloration rates obtained, the test using 4 hours of exposure to UV light, resulted in a 95.5% of discoloration. HRTEM showed a conversion of nanotubes to TiO_2 nanoparticles, without heat treatment. An amorphous variant of the compound $(NH_4)_2TiF_4O$ is proposed as forming the nanotube structure shown in the SEM images, which transforms into anatase nanoparticles, as shown in the HRTEM images, by oxidation of such compound.

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KEY TERMS AND DEFINITIONS

Anodizing: A process that modify the surface of an electrode while acting as the positive or anode into a conducting solution.

Bandgap Energy: The required energy to move an electron from the valence band to the conduction band.

Nanotube: A tube with dimensions in the range between 1 nm and 100 nm.

Sandblasting (Grit Blasting): The mechanical surface treatment by impact of particles, such as sand, alumina, nutshells, bicarbonate, or others.

Sonication: Application sound energy to agitate particles in a sample.

TiO_2 (Titania): The dioxide of titanium with its valence +4 which is a semiconductor with a bandgap energy around 3.2 eV.

Wastewater: Water disposed after use in processes, which may content pollution, related to them.

Chapter 5

Nanotechnology, Metal Nanoparticles, and Biomedical Applications of Nanotechnology

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ABSTRACT

Nanotechnology has emerged as an important field of modern scientific research due to its diverse range of applications in the area of electronics, material sciences, biomedical engineering, and medicines at nano levels such as healthcare, cosmetics, food and feed, environmental health, optics, biomedical sciences, chemical industries, drug-gene delivery, energy science, optoelectronics, catalysis, reprography, single electron transistors, light emitters, nonlinear optical devices, and photoelectrochemical applications and other applications. Due to these immense applications of nanotechnology in biomedical science, it has became possible to design the pharmaceuticals in such a way that they could directly treat diseased cells like cancer and make microscopic repairs in hard-to-operate-on areas of the body. The nanomachines have been designed to clean up toxins or oil spills, recycle all garbage, eliminate landfills, etc. The chapter summarizes the present and future applications of nanotechnology for human welfare but needs further study in catalysis, optical devices, sensor technology, cancer treatment, and drug delivery systems.

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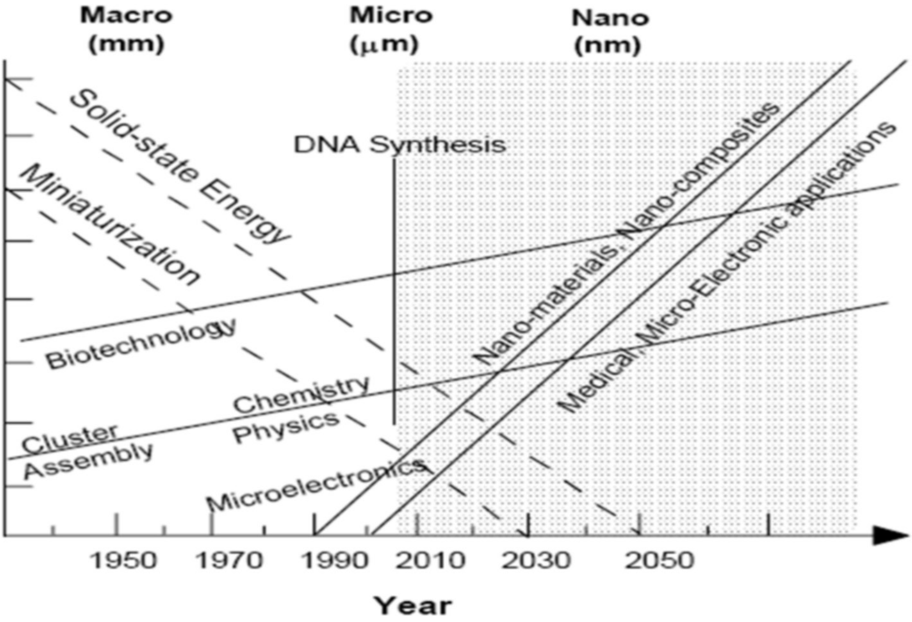
INTRODUCTION

Nowadays technical and engineering activities have a significantly greater impact on the natural laws and rules once considered as changeless. Nonetheless we have been approaching the same pattern that we followed in the past – we get inspired by the nature. Nanoscience is currently a fast growing field and Nanotechnology is at the cutting edge of this rapidly evolving area (Mandal et al., 2006). Nanomaterials and nanotechnologies include molecules and atoms, biosensors and multisensory systems measure the required biological parameters and processes with a relatively high accuracy, the electronic systems and computers create artificial intelligence that is integrated into diagnostic, measuring or control systems etc likely to change the way almost everything from vaccines to computers to automobile tires to objects not yet imagined is designed and made. Nanotechnology collectively describes technology and science involving nano-scale particles (nanoparticles) that increases the scope of investigating and regulating the interplay at cell level between synthetic materials and biological systems (Du et al., 2007), which can be applied as an efficient tool to explore the finest process in biological processes (Sondi & Salopak, Sondi, 2004) and in biomedical sciences (Hutten et al., 2004).

The word “nano” means dwarf in Greek language and is used to indicate one billionth of a meter or 10-9 and a world of things is built up from the tiny scale of nanometers. The term nanotechnology was coined by Norio Taniguchi a, researcher at the University of Tokyo, Japan. Nano science and technology is a broad and interdisciplinary area of research and development activity that has been growing explosively worldwide in the past few years and making an impact in all spheres of human-life (Vaidyanathanh et al., 2009). Besides this, It has the potential for revolutionizing the ways in which materials and products are created and the range and nature of functionalities that can be accessed. Nanotechnology plays an indispensable role in drug delivery, diagnostics, imaging, sensing, gene delivery, artificial implants and tissue engineering, has significant commercial impact, which will be assuredly increased in the future. (Marones et al., 2004).

The nanotechnology has also shown major developments in is the production and application of nanoparticles in biology. Novel techniques and methods are being are constantly being studied to produce nanoparticles. The enormous interest has developed green synthesis of NPs is due to their unusual optical (Krotiknowska et al., 2003), chemical (Kumar et al., 2003), Photochemical (Chandrasekharan et al., 2000), electronic (Peto et al., 2002) and magnetic (Watson et al., 1999), properties. In the chapter we would like the emphases the importance of metallic nanoparticles synthesised through various methods and the other applications of nanotechnology with respect to biomedical applications.

Figure 1. Evolution of science and technology and the future



HISTORICAL BACKGROUND

The history of nanoparticle research very old and the use of these particles date back to the 9th century in Mesopotamia when artisans used these to generate a glittering effect on the surface of pots. This lustre or glitter over pottery from the middle Ages and Renaissance is due to a metallic film that was applied to the transparent surface of a glazing. The lustre can still be visible if the film has resisted atmospheric oxidation and other weathering. The lustre is within the film itself which contained silver and copper nanoparticles dispersed homogeneously in the glassy matrix of the ceramic glaze. Artisans created the nanoparticles by adding copper and silver salts and oxides together with vinegar, ochre and clay, on the surface of previously-glazed pottery. Then the pots were placed into a kiln and heated to about 600 °C in a reducing atmosphere. With the heat the glaze would soften, causing the copper and silver ions to migrate into the outer layers of the glaze. Michael Faraday 1857 firstly proved scientifically that optical property of nanometals. Nanoparticles are either newly created via nanotechnology or are present naturally over the earth's crust or in the environment caused by weathering of Au deposits. The metal formed by evaporation is coupled with minerals and been deposited rapidly from saline ground water. Nanotechnology has been defined as a technology that mainly consist of the process of separation, consolidation and deformation of materials by one atom or molecule (Taniguchi, 1974). The following are the mile stones in the evolution of Nanotechnology.

- **3.5 Mrd. years:** First cells with nano-machines.
- **400 B.C:** Demokrit: Reasoning about atoms and matter.
- **1905:** Albert Einstein: Calculated molecular diameter.
- **1931:** Max Knoll, Ernst Ruska: Electron microscope.
- **1959:** Richard Feynman: There is plenty of room at the bottom.
- **1968:** Alfred Y.Cho, JohnArthur (Bell Labs): MBE (atomic layer growth).
- **1974:** Norio Taniguchi: Nanotechnology for fabrication methods below1µm.
- **1981:** Gerd Binnig and Heinrich Rohrer: Noble prize for inventing STM.
- **1985:** Robert F.Carl, Harald W.Kroto: Richard Smalley: Bucky balls.
- **1986:** K. Eric Drexler: writing with a STM tool.
- **1991:** Sumio Ligima: Carbon Nanotubes.
- **1993:** Warren Robinett, R.Stanley Williams: Combination of SEM and VR (virtual reality system).
- **1998:** Cees Dekkar et al.: Carbon nano-tube transistor.
- **1999:** James M. Tour and Mark A. Read: Single molecule switch.
- **2000:** Eigler et al.: Construction of quantum mirrors.
- **2001:** Florian Bambers: Soldering of nanotube with e-beam.
- **2004:** Intel launches the Pentium IV 'PRESCOFT' processor based on 90nm technology.

The metals like Silver, gold, Titanium, Magnesium, Selenium, Iron, Tin etc were known only as a metal till recently and it is only when the nano-era came into existence that people started to believe that could even be produced at the nanoscale. The Nanoparticles were being used by various organisms for bioremediation of various metals before the existence of nanotechnology it remained unnoticed. The number of organisms has been used to purify environment by removing various reactive metal salts from the environment. Both the Gram positive and Gram negative metals have been used for the biosorption of metals such as silver, cadmium and copper. Various organisms have been tested for their efficiency to adsorb these metal ions and these metal ions remained as a colloidal aggregate mostly on the cell surface, occasionally on the cytoplasm. The size of the nanoparticles played no significant role during those times. These capable organisms were in turn termed as the "competent organisms" which could bind large amounts of metal ions (Beveridge and Murray 1976; Mullen et al. 1989; Doyle et al. 1980). Cell walls of Gram positive bacteria such as *Bacillus subtilis* were found to bind with large quantities of metals than the Gram negative bacteria such as *Escherichia coli* (Beveridge and Fyfe 1985). The synthesis methods in the early 1980s described the reduction of metal ion as a two step procedure; in first step very small particles were synthesized, which were then enlarged to several nanometres. The difference remained in the use of the reducing agent for the synthesis where in the former step a stronger reducing agent was used, and in latter step a weaker reducing agent was used (Sintubin et al. 2009). Chemical and physical methods were used for the synthesis of nanoparticles, a controlled process mediated by the addition of specific reducing agents at raised temperatures and various pH values. Metal nanoparticles were synthesized through an array of methods such as spark discharging, electrochemical reduction, solution irradiation and cryochemical synthesis but the biosynthesis of nanoparticles has emerging and highlighted the intersection of nanotechnology and biotechnology attention due to a growing need to develop environmentally benign technologies in material synthesis (Kalish waralal et al. 2008).

The role of microorganisms for the production of nanoparticles in the fate of metals in the environment was not thoroughly examined; however, it was conceived that they represent an important component of metal dynamics. The first evidence of biosynthesis metal nanoparticles (silver) was established in 1984 using the microorganism *Pseudomonas stutzeri* AG259, a bacterial strain that was originally isolated from silver mine (Haefeli et al. 1984; Zhang et al. 2005; Nair and Pradeep 2002). The deposition of silver on bacterial cell membrane under the transmission electron microscope was confirmed which opened new avenues towards the preparation of nanostructural materials that incorporate metal-based crystalline particles

Figure 2. Nanotechnology over view

with defined structural, compositional and morphological properties. Biological methods are gaining importance because of the use of normal conditions for the synthesis that enable control over the size of the nanoparticles. The biological synthesis of nanoparticles germinated from the experiments on biosorption of metals bacteria were not identified as nanoparticles but were named as aggregates (Mullen et al. 1989). The microorganisms, such as bacteria, yeast and fungi play an important role in remediation of toxic metals through reduction of the metal ions; this was considered interesting as nanofactory, using the dissimilatory properties of fungi and hence these biological systems have been extensively used for the rapid and eco-friendly biosynthesis of metal nanoparticles (Bhattacharya and Gupta, 2005). Unicellular as well multi-cellular organisms have shown immense potential for the synthesis of nanoparticles, as they can synthesize inorganic materials either intracellularly or extracellularly. More recent and detailed investigations into the use of microbes in the synthesis of different metal nanoparticles include bacteria for gold (Beveridge and Murray, 1980; Southam and Beveridge, 1996; Fortin and Beveridge, 2000), silver (Joerger et al., 2000; Klaus et al,.1998), ZnS (Labrenz et al., 2000), magnetite (Lovley et al., 1987; Nair and Pradeep, 2002) CdS (Smith et al., 1998; Philipse and Maas,2002), iron sulfide (Watson et al., 1999, 2000), yeast for PbS (Kowshik et al., 2002a), CdS (Kowshik et al., 2002b), and silver (Kowshik et al., 2003), and algae for gold (Robinson et al., 1997). *Morganella* sp. (Parikh et al. 2008).

SYNTHESIS OF NANOPARTICLES

The synthesis and study nanoparticles, has become a major interdisciplinary area of research over the past 10 years. The size, morphology as well as the properties of nanoparticles basically depends on the methods of preparation. All the processes can be broadly divided into three processes, physical methods, chemical methods and biological methods.

Physicochemical Methods

Nanoparticles are mainly prepared by physical and chemical methods. Metallic nanoparticles, including gold, silver, iron, zinc and metal oxide nanoparticles, have shown great promise in biomedical application, due to their large surface area to volume ratio are being produced by both methods. The silver nanoparticles can also be prepared by both methods called ‘top-down’ and ‘bottomup’ methods. The top-down method mainly deals with the mechanical grinding of bulk metals and subsequent stabilization of the subsequent nanosized metal particles by the addition of colloidal protecting agents (Gaffet E et al., 1996, Amulyavichus A et al., 1998). While as bottom-up methods deal with reduction of metals by electrochemical methods, and sonodecomposition. There are also numerous physical and chemical approaches for synthesis of silver nanoparticles reported

- Spray pyrolysis.
- Gas condensation.
- Freeze drying.
- Ultrasonic methods.
- Chemical precipitation.
- Sol-gel technique.
- Polymeric precursor.
- Micro emulsion.
- Hydrothermal synthesis.
- Combustion synthesis.
- Dc Arc Plasma Process.
- Rf Plasma Process.
- Plasma Rapid Solidification Technology.
- Reactive Electrode Submerged Arc.

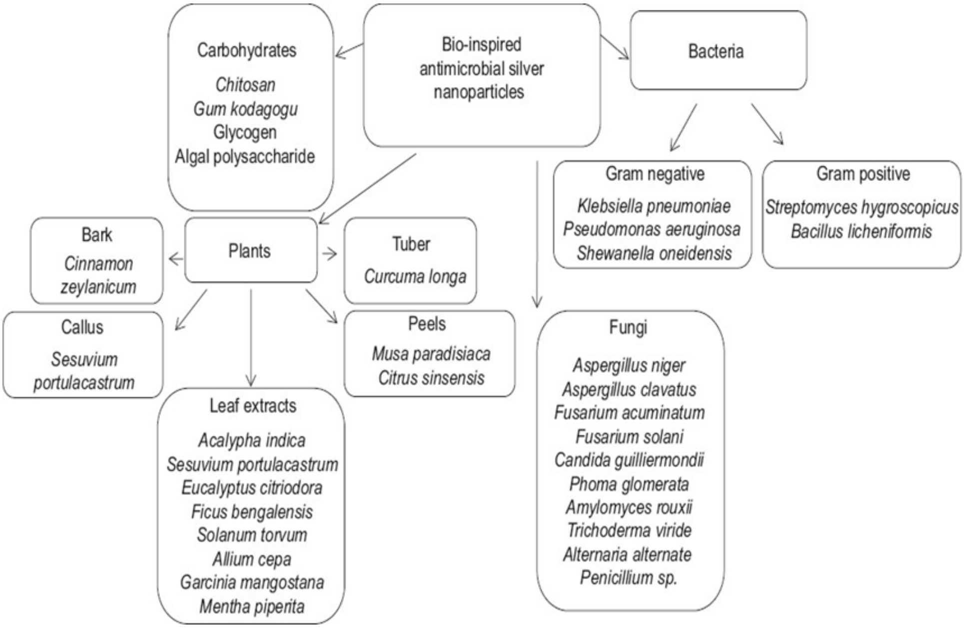
Biological Methods

The metallic nanoparticles prepared through the chemical and physical methods are costly and also include the use of toxic chemicals, thus there is a need for an environmentally and economically feasible way to synthesize these nanoparticles. The metallic nanoparticles can be synthesised by biological methods which are easy to synthesise, cost effective, ecofriendly and non toxic (Mukherjee et al., 2001) is possible with help of bacteria, fungi, and plant extracts. Biological synthesis of silver nanoparticles is a bottom-up method that includes reduction/oxidation reactions. The microbial enzymes or photochemical with antioxidant or reducing properties act on the corresponding compounds and give the anticipated nanoparticles (Kalishwaralal, et al., 2008, Parashar, UK et al., 2009).

BIOSYNTHESIS OF METALLIC NANOPARTICLES USING BACTERIA

The bacteria are most abundant microorganisms which are prokaryotic in nature and greatly diversified in size, shape, and lives in all kinds of habitats, including extreme environments that exhibit, for example, extremely high or low temperatures, acid-

Figure 3. Bioinspired nanoparticles



ity, alkalinity, and salt or sulfur concentrations are known as extremophile. Some bacterial species of bacteria have exhibited the ability to resort to specific defense mechanisms to quell stresses like toxicity of foreign metal ions or metals; even at high ion concentrations. The *Pseudomonas stutzeri* is living in soil rich in silver (Haefeli et al., 1984) and *Pseudomonas aeruginosa* have developed resistance to that metal (Bridges et al., 1979). Some bacteria are known to synthesize inorganic materials like the magnetotactic bacteria, which synthesize intracellular magnetite NPs (Lovley et al., 1987; Spring and Schleifer, 1995). Consequently, a wide number of bacterial species have been used in nanobiotechnology to research alternative methods for the production of metallic nanoparticles (Table 1).

BIOSYNTHESIS OF METALLIC NANOPARTICLES USING FUNGI

The fungi are eukaryotic organisms, mostly decomposers, having more than 70,000 species living in a wide variety of habits. As per the recent estimated data, there are as many as 5.1 million fungal species exist (Blackwell, 2011). These organisms possess the ability to digest food extracellularly, secreting special enzymes to hydrolyze complex compounds into simpler molecules, which are then absorbed and used as an energy source. Fungi are excellent candidates to explore their use

Table 1. List of bacterial strains utilised for the biosynthesis 0f metallic nanoparticles

Bacteria	Nanoparticles	Shape	Average Size (nm)	Type of Microscopic Analysis	Reference
Pseudomonas stutzeri	Ag	Triangles and hexagons	200	TEM, HRTEM	Klaus et al. 1999)
Actinobacter spp.	Fe3 O4	Quasi-spherical, cubic	10–40, 50–150	TEM	Bharde et al. (2005)
Rhodobacter sphaeroides	ZnS	Spherical	4, 8, 30 and 105	TEM	Bai et al. (2006)
Shewanella oneidensis	Au	Spherical	12 ± 5	TEM	Suresh et al. (2011)
Shewanella algae	Pt	NR	5	TEM	Konishi et al. (2007)
Thermoanaerobacter ethanolicus	Fe3 O4	Octahedral	>35	TEM, SEM	Roh et al. (2007)
Bacillus sphaericus	Pd	NR, clusters of sc	1, sc 0.6–0.8	SEM	Pollmann et al. (2006)
Plectonema boryanum	Au	Cubic, irregular, octahedral	10–25, <10, 10–25	TEM, SEM	Lengke et al. (2006a)
Shewanella sp.	Se	Spherical	181, 164, 68, 50	TEM, SEM	Lee et al. (2007)
Pseudomonas aeruginosa	Au	Quasi-spherical	40, 25, 15	TEM	Husseiny et al. (2007)
Aeromonas sp.	Ag	Clusters	20	TEM, SEM	Zhang et al. (2007)
Escherichia coli	Au	Spheres	5–50, <10	TEM	Deplanche and Macaskie -2008
Recombinant	CdZn, CdSe, CdTe, SeZn	NR	10.35, 4.99	TEM, HRTEM, CM	Park et al. (2010)
Desulfovibrio desulfuricans	Au	Spheres	5–50, <10	TEM	Deplanche and Macaskie (2008)
	Pd	NR	NR	TEM	Deplanche et al. (2008)
	Au	NR	20–50	TEM	Deplanche et al. (2008)
Thermoanaerobacter sp.	Mx Fe1−x OOH (M = Zn, Co, Mn and Ni)	NR	25, 51, 53, 75	TEM	Moon et al (2007)
Rhodopseudomonas capsulata	Au	Nanowires	50–60	TEM	He et al. (2008)

continued on following page

Table 1. Continued

Bacteria	Nanoparticles	Shape	Average Size (nm)	Type of Microscopic Analysis	Reference
Bacillus licheniformis	Ag	NR	50	SEM	Kalimuthu et al. (2008)
	Au	Cubes	10–100	SEM	Kalishwaralal et al. -2009
	Ag	NR	50	TEM	Vaidyanathan et al. -2010
	Au	NR	10–50	TEM	Kalishwaralal et al. (2010b)
Proteus mirabilis	Ag	Spherical	10–20	TEM	Samadi et al. (2009)
Bacillus cereus	Ag	Spherical	4–5	TEM, HRTEM	Ganesh Babu and Gunasekaran (2009)
Morganella sp.	Ag	Spherical	20 ± 5	TEM, HRTEM	Parikh et al. (2008)
Staphylococcus aureus	Ag	Agglomerates	160–180	AFM	Nanda and Saravanna (2009)
Bacillus subtilis	Au	Spherical	7.6 ± 1.8, 7.3 ± 2.3	TEM	Reddy et al. (2010)
Bacillus thuringiensis	Ag	Variable	15	TEM	Jain et al. (2010)
Mycobacterium smegmatis	Cu	Doughnut shape	5, 10–20	AFM	Wörner et al. (2007)
Streptomyces	Ag	Spherical	20–30	TEM, SEM, AFM	Sadhasivam et al. (2010)
Hygroscopicus	Au	Various	Various	HRTEM, FESEM, AFM	Sadhasivam et al. (2012)
Streptomyces albidoflavus	Ag	Spherical	10–40	TEM	Prakasham et al. (2012)

Abbreviations: NR, Not Reported; CS, Cellular Surface; PS, Periplasmic Space; CM, Cytoplasmic Membrane; CFE, Cell Free Extract; ICF, Inactive Cell Filtrate, SCM, Spore crystal mixture; PCS, Phytochelatin Synthease, MT, Metallothionein FESEM, Field Emission Scanning Electron Microscopy: SEM, Scanning Electron microscopy; TEM, Transmission electron microscopy; HRTEM, High Resolution Transmission Electron Microscopy; EELS, electron energy-loss spectroscopy; STEM, Scanning Transmission Microscopy; SPM, Kelvin-Probe/Surface Potential Microscopy; AFM, Atomic Force Microscopy; FM, Fluorescence microscopy; CM, Confocal microscopy. EFTEM-ESI, Energy Filtering Transmission Electron Microscopy-Element Specific Imaging in nanobiotechnology, because some species grow at fast rates and are very easy to culture and maintain in the laboratory (Castro-Longoria et al., 2011, 2012). The use of fungal species as manufactories for the production of nanoparticles has attained a great interest of nanotechnologists recently; as firstly fungal species has been utilised for biosynthesis of silver nanoparticles from the filamentous fungus *Verticillium sp*. (Mukherjee et al., 2001). The number of fungal species have been exploited their after for the production of nanoparticles. Mostly the biomass is commonly exposed to metallic ion solutions, extracellular synthesis of nanoparticles (Ahmad et al.2002). The number of fungal species have been reported for CdS nanoparticles as well as the formation of Ag, Au, PbS, ZnS, and MoS_2 etc. The presence of proteins in the aqueous solution suggested a possible sulfate reducing enzyme-based process for production of nanoparticles. Depending on the metallic ion solution and incubation conditions, diverse morphologies can be obtained, although quasi-spherical nanoparticles are the most commonly produced nanoparticles. From different species as extracellular and intracellular formation has been reported presenting different size ranges as well as varying shapes. The exact mechanism involved in synthesis of metallic nanoparticles using fungi is not clear. But it is believed that the mechanism involve in synthesis of metallic nanoparticles by fungi is trapping of Ag^+ ions at the surface of the fungal cells and the subsequent reduction of the metal ions by the enzymes present in the fungal system. Fungi can produce larger amounts of nanoparticles as compared to bacteria as they can secrete larger amounts of proteins which directly translate to higher yield of nanoparticles. *F. oxysporum*, it is believed that the NADPH-dependent nitrate reductase process is responsible for nanoparticle formation (Mohanpuria et al., 2008, Mukherjee et al., 2001, and Ahmad et al., 2003) *Penicillium glabrum*(MTCC-1985),(Nanda & Shahnaz, 2014), *Penicillium sp* (Nayak et al., 2013) and *Aspergillus Sp* (Nayak et al., 2014). Different fungi species have been exploited for the biosynthesis of metallic nanoparticles have been reported in Table 2.

BIOSYNTHESIS OF METALLIC NANOPARTICLES USING PLANTS

The plants and plant extracts have been explored under different environmental conditions to produce metallic nanoparticles. Synthesize metallic nanoparticles using microbes is very slow process when in comparison with plant extracts. The major advantage of using plant extracts for metallic nanoparticles synthesis is that they are easily available, safe, and nontoxic in most cases, have a broad variety of metabolites that can aid in the reduction of silver ions, and are quicker than microbes in the synthesis. Plant extract is the most commonly product used for the

Table 2. List of fungal strains utilized for the biosynthesis of metallic nanoparticles

	Nanoparticles	Shape	Size (nm)	Type of Microscopic Analysis	Reference
Verticillium	Ag	Spherical	25	SEM, TEM	Mukherjee et al.(2001)
Fusarium oxysporum	Ag	Highly variable	5–15	TEM	Ahmad et al. (2002)
	Au	Spherical and triangular	8–40	TEM	Mukherjee et al. (2002)
	Au	Spherical, triangular	46, 21c	TEM	Shankar et al. (2004a)
	Ag	Spherical	20–50	SEM	Durán et al. (2005)
Fusarium oxysporum	Magnetite	Irregular, quasi-spherical	20–50	TEM	Bharde et al. (2006)
Aspergillus fumigatus	Ag	Mostly spherical, some triangular	5–25	TEM	Bhainsa and D'Souza (2006)
	Ag	Mostly spherical, rectangular	15–45	TEM	Alani et al. (2012)
Lycopersici Phaenerochaete	Ag	Varying, mainly pyramidal	50–200	SEM, TEM	Vigneshwaran et al. (2006)
Chrysosporium Pleurotus sajor caju	Ag	Spherical	30.5	TEM	Vigneshwaran et al. (2007a)
Aspergillus flavus	Ag	Spherical	8.92	SEM, TEM	Vigneshwaran et al. (2007b)
	TiO_2	Spherical	62–74	SEM, TEM, AFM	Rajakumar et al. (2012)
Aspergillus niger	Au	Nonoplates	50–500	FESEM	Xie et al. (2007c)
Trichoderma asperellum	Ag	NR	13–18	TEM, HRTEM	Mukherjee et al. (2008)
Volvariella volvaceae	Ag	Spherical	15	TEM, HRTEM	Philip (2009)
Penicillium fellutanum	Ag	Mostly spherical	5–25	TEM	Kathiresan et al. (2009)
Cladosporium cladosporioides	Ag	Mostly spherical	10–100	TEM	Balaji et al. (2009)
Phoma glomerata	Ag	Spherical	60–80	SEM	Birla et al. (2009)
Aspergillus versicolor	Hg	NR	NR	SEM, AFM, FM	Das et al. (2009a)
Trichoderma viride	Ag	Spherical, rodlike	5–40	TEM	Fayaz et al. (2009a)

continued on following page

Table 2. Continued

	Nanoparticles	Shape	Size (nm)	Type of Microscopic Analysis	Reference
Fusarium spp.	Zn	Irregular, some spherical	100–200	SEM, TEM	Velmurugan et al. (2010)
Aspergillus clavitus	Ag	NR	550–650	AFM	Saravanan and Nanda (2010)
Aspergillus flavus NJP08	Ag	Spherical	17	TEM, HRTEM	Jain et al. (2011)
Aspergillus flavus	Ag	Spherical	55-70	AFM, FESEM	Nayak et al (2014)
Aspergillus oryzae var.	Au	Spheres	10–60	TEM, FESEM	Binupriya et al. (2010b)
Streptomyces sp.	Ag	Mostly spherical	15–25	TEM	Alani et al. (2012)
Aspergillus terreus	Ag	Spherical	1–20	TEM	Li et al. (2012)
Alternaria alternata	Au	Spherical, triangular	12 ± 5	AFM, TEM	Sarkar et al. (2012)
Yeast					
Candida glabrata	CdS	NR	A° NR	EFTEM-ESI	Krumov et al. (2007)

Abbreviations: NR, Not Reported; CS, Cellular Surface; PS, Periplasmic Space; CM, Cytoplasmic Membrane; CFE, Cell Free Extract; ICF, Inactive Cell Filtrate, SCM, Spore crystal mixture; PCS, Phytochelatin Synthease, MT, Metallothionein FESEM, Field Emission Scanning Electron Microscopy: SEM, Scanning Electron microscopy; TEM, Transmission electron microscopy; HRTEM, High Resolution Transmission Electron Microscopy; EELS, electron energy-loss spectroscopy; STEM, Scanning Transmission Microscopy; SPM, Kelvin-Probe/Surface Potential Microscopy; AFM, Atomic Force Microscopy; FM, Fluorescence microscopy; CM, Confocal microscopy. EFTEM-ESI, Energy Filtering Transmission Electron Microscopy-Element Specific Imaging

production of metallic nanoparticles. It has been proved through experiments that in some cases live plants show the ability to absorb metals from the outside and accumulate them in their tissues in the form of nanostructures (Gardea-Torresdey et al., 2002, 2003; Armendariz et al., 2004; Bali et al., 2006; Harris and Bali, 2008). The plant alfalfa (*Medicago sativa*) extract have been initially tested and distinctive metallic nanostructures were synthesized under diverse environmental conditions under varying pH, show differences in nanoparicle shapes and sizes are achieved (Ascencio et al., 2003, 2005; Canizal et al., 2006; Schabes-Retchkiman et al., 2006; Herrera-Becerra et al., 2007). The possible application of metallic nanoparticles synthesized using plants or plant extracts has not been entirely explored. The major phytochemical mechanism involved is the reduction of the ions involved are terpenoids, flavones, ketones, aldehydes, amides, and carboxylic acids. Flavones, organic acids, and quinones are water-soluble phytochemicals that are responsible for the immediate reduction of the ions. Studies have revealed that xerophytes contain emodin, an anthraquinone that undergoes tautomerization, leading to the formation of the silver nanoparticles. In the case of mesophytes, it was found that they contain three types of benzoquinones: cyperoquinone, dietchequinone, and remirin. It was suggested that the phytochemicals are involved directly in the reduction of the ions and formation of metallic nanoparticles. Metallic nanoparticles synthesized using plant is shown in Table 3.

Types of Nanoparticles

Extensive libraries of nanoparticles, composed of an assortment of different sizes, shapes, and materials, and with various chemical and surface properties, have already been constructed. The field of nanotechnology is under constant and rapid growth and new additions continue to supplement these libraries. The classes of nanoparticles listed below are all very general and multi-functional, however, some of their basic properties and current known uses in biotechnology, and particularly nanomedicine, are described here.

1. **Fullerenes:** Buckyballs and Carbon tubes. Both members of the fullerene structural class, buckyballs and carbon tubes are carbon based, lattice-like, potentially porous molecules. Buckyballs are spherical in shape while carbon tubes are cylindrical. The diameter of a carbon tube can be several nanometer but the length can be much greater, up to several micrometer, depending on its intended use. Carbon nanotubes have many applications in materials science due to their strength and unique electrical properties. However, they have also found use in the field of biomedicine as carriers for vaccines, drugs and other molecules. A single wall carbon tube is a one-atom-thick sheet of graphite, resembling chicken wire, rolled seamlessly into a tube. There are also multi-walled and other types of tubes depending on the shape, diameter, density (hollow versus solid) and other properties.
2. **Liposomes:** Liposomes are lipid-based nanoparticles used extensively in the pharmaceutical and cosmetic industries because of their capacity for breaking down inside cells, once their delivery function has been met. Liposomes were the first engineered nanoparticles used for drug delivery but problems such as their propensity to fuse together in aqueous environments and release their payload, have lead to replacement, or stabilization using newer alternative nanoparticles.
3. **Nanoshells:** Also referred to as core-shells, nanoshells are spherical cores of a particular compound surrounded by a shell or outer coating of another, which is a few nanometres thick. One application in biomedicine is to create

Table 3. List of plants utilized for the biosynthesis 0f metallic nanoparticles

Plant	**Nanoparticles**	**Shape**	**Size(nm)**	**Type of analysis**	**Source or Reference**
Medicago sativa	Au	NR, images presented	2–20, 20–40	TEM, HRTEM	Gardea-Torresdey et al.(2002) (2002)b
	Ag	Icosahedral	2–20, 2–4	TEM, HRTEM	Gardea-Torresdey et al. (2003)
Pelargonium graveolens	Au	Decahedral, icosahedral	20–40	TEM	Shankar et al. (2003a)
	Ag	Spherical	16–40	TEM	Shankar et al. (2003b)
Azadirachta indica	Au	Spherical, triangular, hexagonal	NR	TEM	Shankar et al. (2004b)
Avena sativa	Au	Tetrahedral, decahedral, multitwinned, irregular, rod-shaped	5–20, 25–85	TEM	Armendariz et al. (2004)
Brassica juncea	Ag, Cu, Co, Zn, Ni	Spherical (Ag)	<100	TEM	Bali et al. (2006)a
	Ag	NR	NR	TEM	Harris and Bali (2008)
Aloe vera	Au	Triangular	50–350	TEM, AFM	Chandran et al. (2006)
	Ag	Spherical	15	TEM	Chandran et al. (2006)
Cinnamon camphora	Au	Spherical, triangular	10–40, 15–25	TEM, AFM	Huang et al. (2007)
	Ag	Spherical	55–80	TEM	Huang et al. (2007)
Coriandrum sativum	Au	Spherical, triangular, truncated triangular, decahedral	7–58	TEM	Badri Narayanan and Sakthivel (2008)
Cinnamon zeylanicun	Ag	Bud-like decahedral	31–40	TEM	Sathishkumar et al. (2009)
Magnolia kobus and Diopyros kaki	Au	Triangular, pentagonal, hexagonal, spherical	5–300	TEM, SEM AFM	Song et al. (2009)
Hibiscus rosa sinensis	Au	Spherical, triangular, hexagonal, dodecahedral	14	TEM, HRTEM	Philip (2010)
	Ag	Spherical	13	TEM, HRTEM	Philip (2010)

continued on following page

Table 3. Continued

Plant	**Nanoparticles**	**Shape**	**Size(nm)**	**Type of analysis**	**Source or Reference**
Citrus sinensis (peel extract)	Ag	Spherical	35 ± 2 (25 ∘ C), 10 ± 1 (60 ∘ C)	SEM, TEM	Kaviya et al., 2011
Medicago sativa (seed exudates)	Ag	Hexagonal, triangular	5–100	SEM, TEM, AFM	Lukman et al. (2011)
Rhizophora mucronata	Ag	NR	60–95	AFM	Gnanadesigan et al. (2011)
Mimosa pudica	Ag	Spherical	25–60	SEM, TEM	Marimuthu et al. (2011)
Citrullus colocynthis (L-) Schrad	Ag	Spherical	31	AFM	Satyavani et al. (2011)
Pandanus odorifer (Forssk.)	Ag	Quasi-spherical	24–55	TEM	Panda et al. (2011)
Punica granatum	Ag	Spherical	5	TEM	Ahmad et al. (2012)
(peel extract)	Au	Spherical	10	TEM	Ahmad et al. (2012)
Citrus paradisi	Au	Mainly quasi-spherical	30	TEM, FESEM, CM	Nolasco-Arismendi et al. (2012)
Coccinia grandis	Ag	Spherical	20–30	SEM, TEM	Arunachalam et al. (2012)
Cassia fistula	Au	Various	55.2–98.4	SEM	Daisy and Saipriya (2012)
Musa paradisiaca	Ag	Rod	60–150	SEM	Jayaseelan et al. (2012)
Annona squamosa	Ag	Irregular spherical	35 ± 5	TEM	Kumar et al. (2012b)
(peel extract)	TiO_2	Spherical	23 ± 2	SEM, TEM	Roopan et al. (2012)
Ficus racemosa	Ag	Clindrical, uniform rod-shaped	250.6	SEM	Velayutham et al., 2013

Abbreviations: NR, Not Reported; CS, Cellular Surface; PS, Periplasmic Space; CM, Cytoplasmic Membrane; CFE, Cell Free Extract; ICF, Inactive Cell Filtrate, SCM, Spore crystal mixture; PCS, Phytochelatin Synthease, MT, Metallothionein FESEM, Field Emission Scanning Electron Microscopy: SEM, Scanning Electron microscopy; TEM, Transmission electron microscopy; HRTEM, High Resolution Transmission Electron Microscopy; EELS, electron energy-loss spectroscopy; STEM, Scanning Transmission Microscopy; SPM, Kelvin-Probe/Surface Potential Microscopy; AFM, Atomic Force Microscopy; FM, Fluorescence microscopy; CM, Confocal microscopy. EFTEM-ESI, Energy Filtering Transmission Electron Microscopy-Element Specific Imaging nanoshells that absorb at biologically useful wavelengths, depending on the shell thickness. One common formula for the construction of nanoshells is to use silica for the core and another sticky compound to adhere gold particles to the outside surface, creating the shell. Nanoshells such as these have been used to kill cancer cells in mice. Once injected into a tumor, radiation is applied and the nanoshells heat up enough to kill the tumour cells.

4. **Dendrimers:** Dendrimers are highly branched structures gaining wide use in nanomedicine because of the multiple molecular "hooks" on their surfaces that can be used to attach cell-identification tags, fluorescent dyes, enzymes and other molecules. The first dendritic molecules were produced around 1980, but interest in them has blossomed more recently as biotechnological uses are discovered. Nanomedical applications for dendrimers are many and include nanoscale catalysts and reaction vessels, micelle mimics, imaging agents and chemical sensors, and agents for delivering drugs or genes into cells. There are two basic structural types. One is the globular structure with a central core from which branches radiate. The second type has no central core and consists simply of a series of highly branched polymers.
5. **Quantum Dots:** Also known as nanocrystals, quantum dots are nanosized semiconductors that, depending on their size, can emit light in all colours of the rainbow. These nanostructures confine conduction band electrons, valence band holes, or excitons in all three spatial directions. Examples of quantum dots are semiconductor nanocrystals and core-shell nanocrystals, where there is an interface between different semiconductor materials. They have been applied in biotechnology for cell labelling and imaging, particularly in cancer imaging studies.
6. **Super Paramagnetic Nanoparticles:** Super paramagnetic molecules are those that are attracted to a magnetic field but do not retain residual magnetism after the field is removed. Nanoparticles of iron oxide with diameters in the 5-100 nm range have been used for selective magnetic bioseparations. Typical techniques involve coating the particles with antibodies to cell-specific antigens, for separation from the surrounding matrix. Used in membrane transport studies, super paramagnetic iron oxide nanoparticles (SPION) are applied for drug delivery and gene transfection. Targeted delivery of drugs, bioactive molecules or DNA vectors is dependent on the application of an external magnetic force that accelerates and directs their progress towards the target tissue. They are also useful as MRI contrast agents.
7. **Nanorods:** Typically 1-100 nm in length, nanorods are most often made from semiconducting materials and used in nanomedicine as imaging and contrast agents. Nanorods can be made by generating small cylinders of silicon, gold or

inorganic phosphate, among other materials. Current concerns over the safety of nanoparticles have lead to the development of many new facets of research. As a result, our collection of knowledge about nanoparticle interactions within cells is still rapidly growing.

BIOMEDICAL APPLICATIONS

In recent years, nanoparticles, coated and composite nanoparticles has been used in various fields of science, engineering and industrial applications by virtue of their specific, novel and useful properties. The unique properties of nanomaterials encourage belief that they can be applied in a wide range of fields, from medical applications to environmental sciences. Studies conducted by nanotechnology experts mapping the risks and opportunities of nanotechnology have revealed enormous prospects for progress in both life sciences and information technology. Medical applications are expected to increase our quality of life through early diagnosis and treatment of diseases, and prosthetics, among others.

Nanoscaffolds

Nanofiber scaffolds can be used to regenerate central nervous system cells and possible other organs. Experiments performed on a hamster with severed optic tract demonstrated the regeneration of axonal tissue initiated by a peptide nanofibers scaffold (Ellis-Behnke et al., 2006).

Antimicrobial Nanopowders and Coatings

Certain nanopowders, possess antimicrobial properties (Bosi et al., 2003, Koper et al., 2002). When these powders contact cells of *E. coli*, or other bacteria species and viruses, over 90% are killed within a few minutes. Due to their antimicrobial effect, nanoparticle of silver and titanium dioxide (<100nm) are assessed as coatings for surgical masks (Li et al. 2006).

Bioseparation and Biosensors

Nanotube membranes can act as channels for highly selective transport of molecules and ions between solutions that are present on both side of the membrane (Jirage et al., 1997). For example, membranes containing Nanotubes with inside diameters of molecular dimensions (less than 1 nm) separate small molecules on the basis of molecular size, while Nanotubes with larger inside diameters (20– 60 nm) can be used to separate proteins (Martin et al., 2003). Biosensor is a device for the detection of an analyte that combines a biological component with a physicochemical detector component.

NANOROBOTICS AND DRUG DELIVERY

Nanorobotics is the technology of creating machines or robots at or close to the scale of a nanometer (10-9 meters). More specifically, nanorobotics refers to the still largely theoretical nanotechnology engineering discipline of designing and building nanorobots. Nanorobots (nanobots or nanoids) are typically devices ranging in size from 0.1-10 micrometers and constructed of nanoscale or molecular components. As no artificial non-biological nanorobots have so far been created, they remain a hypothetical concept at this time. Another definition sometimes used is a robot which allows precision interactions with nanoscale objects, or can manipulate with nanoscale resolution. Nanomedicine is the medical application of nanotechnology and related research. It covers areas such as nanoparticle drug delivery and possible future applications of molecular nanotechnology (MNT) and nanovaccinology.The ability of nanoparticles to target and penetrate specific organs and cells contributes to their toxicity; however, this ability may be exploited in nanomedicine. Nanospheres composed of biodegradable polymers can incorporate drugs, allowing the timed release of the drug as the polymer degrades (Uhrich et al., 1999). When particles are set to degrade in an acid microenvironment, such as tumor cells or around inflammation sites, this allows site-specific or targeted drug delivery.

Gene Transfection

Surface-functionalized nanoparticles can be used to permeate cell membranes at a much higher level than nanoparticles without a functionalized surface (Maïté et al. 2000). This property can be used to deliver genetic material into living cells, a process called transfection. For example, silica nanospheres labelled on their outer surfaces with cationic ammonium groups can bind DNA (a polyanion) through electrostatic interactions (Kneuer et al. 2000). Then nanoparticles deliver the DNA into cells.

Medical Imaging

A variety of techniques currently called “noninvasive” have been used for more than a quarter of a century in medical imaging, for example super paramagnetic magnetite particles coated with dextran are used as image-enhancement agents in magnetic resonance imaging (Harisinghani et al., 2003). Intracellular imaging is also possible through attachment of quantum dots to selected molecules, which allows intracellular processes to be observed directly.

Nasal Vaccination

Nanospheres carriers for vaccines are in development. Antigen-coated polystyrene nanospheres, used as vaccine carriers targeting human dendritic cells, have been researched for nasal vaccination (Matsusaki et al., 2005). Nanospheres had a direct effect on human dendritic cells, inducing transcription of genes important for, e.g., phagocytosis as well as an immune response.

Nucleic Acid Sequence and Protein Detection

Targeting and identifying various diseases could be made possible by detecting nucleic acid sequences unique to specific bacteria and viruses, or to specific diseases or abnormal concentration of certain proteins that signal the presence of various cancers and diseases Nanomaterials-based assays are currently evaluated as well as more sensitive proteins detections methods. Nucleic acid sequences are currently detected with polymerase chain reaction (PCR) coupled with molecular fluorophore assays. Despite high sensitivity, PCR has significant drawbacks, such as: complexity, sensitivity to contamination, cost, and lack of portability. Current protein detection methods, such as enzyme-linked immune absorbent assay (ELISA), allow the detection of proteins concentrations at which the disease is often advanced. More sensitive methods based on nanomaterials would revolutionize physical treatment of many cancer types and diseases (Rosi et al., 2005).

Smart Nanophase Extractors

Differentially functionalized nanotubes are used as smart nanophase extractors, with molecularrecognition capabilities, to remove specific molecules from solutions (Martin & Kohli, 2003).

Treatment for Local Anaesthetic Toxicity

Local anaesthetic can be sometimes very toxic, ranging from local neurotoxicity tocardiovascular collapse and coma. In addition to conventional therapies, drug-scavenging nanoparticles have shown to increase survival rate from no animals in the control group to all animals in the treated group (Renehan et al., 2005; Weinberg et al., 2003).

Protein Microarray

It is a piece of glass on which different molecules of protein have been affixed at separate locations in an ordered manner thus forming a microscopic array.

Nanomaterials in Water Treatment

Nanosorbents are nanoscale particles of inorganic or organic materials that are capable of absorbing other substances. Most environmental applications of nanosorbents are in the field of waste water treatment and drinking water production, with other applications focused on air pollutants or ground water contamination.

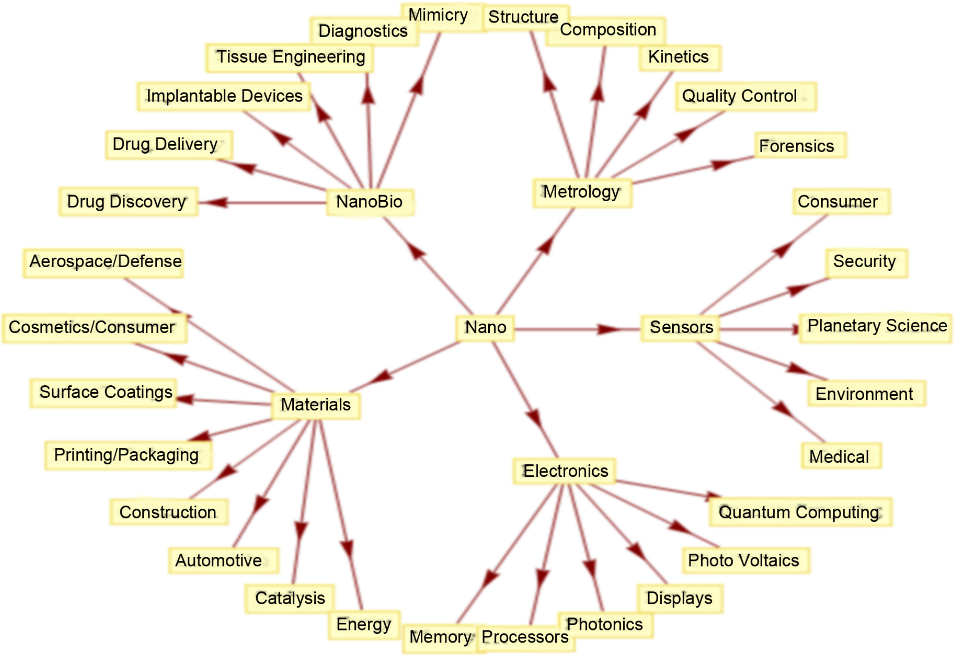
1. **Remediation:** Remediation is the science of removal or reduction of pollutants from the environment using chemical or biological means. Nanomaterials have been used for remediating contaminated groundwater and subsurface source areas of contamination at hazardous waste sites. Early treatment remedies for groundwater contamination were mainly pump-and-treat operations Due to the considerably high cost and long operating periods, the use of in-situ treatment technologies is considerably increasing.
2. **Bioremediation:** Bioremediation of harmful organic contaminants like carbazole and dibenzothiophene has been successfully reported by different groups using variety of microorganisms.

There are also numbers of applications of nanotechnology in various fields of science Figure 4, which have revolutionized the research world via various ways needs further studies.

CONCLUSION

Nanotechnology is an emerging field that is potentially changing the way we treat diseases through its diverse range of applications like Nanomedicines to control microbial pathogens, Nanorobotics and drug delivery which is having great achievement to treat targeted diseases. The tissue engineering and scaffolds nanotechnology, has made it possible to develop tissues to restore maintain and enhance tissue functions(langer and Vacanti 1993) and construction of three dimensional scaffolds from biomaterials which provide mechanical support and guide into new tissues and organs. The bacterial spore based Nano-vaccines has been tested against various diseases like tetanus with heterologous antigens and other diseases which have shown good applications eradicate the particular diseases. Quantam dots have been

Figure 4. Applications of nanotechnology in various fields



used to detect the malfunctioned cells which became possible through nanotechnology. Carbon nanotubes and biosensors have revolutionised the biomedical industry like regular self testing for glucose level, and could be used to monitor the pulse temperature diagnosing diseases etc. In the near future, the application of clean, non-toxic, and eco-friendly nanostructured material will be possible in industry and/or biomedicine. The other applications of nanotechnology like medical imaging, nucleic acid sequence and protein detection, water treatment has achieved a great success from last decade. As Feynman has predicted that there has been plenty of room at the bottom to modify and enhance existing technologies by controlling material properties at the nanoscale. This branch promises to further grow and explore many more possible applications, e.g. in catalysis, optical devices, sensor technology, cancer treatment, or drug delivery systems Therefore, with sufficient time and research the nanotechnology based biomedical applications are becoming a reality.

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KEY TERMS AND DEFINITIONS

Bioremediation: It is a waste management technique that involves the use of organisms to remove or neutralize pollutants from a contaminated site.

Carbon Nanotubes (CNTs): Hollow, cylindrical structures, with a diameter usually less than 5 nanometres. They are often but not necessarily, composed of carbon, and having remarkable strength and electrical properties.

Liposome: Phospholipid bilayer vesicle formed from an aqueous suspension of phospholipid molecules.

Nanomaterials: A broad class of materials that includes nanometre-sized crystallites, nanometre, sized powders, macroscopic objects, and films composed of nanometre sized particles or any phases combined with a spatial distribution that involves nanometre length scale of less than 100 nm in at least one dimension.

Nanomedicine: The use of nanotechnology in the improvement of a contaminated site to prevent, minimize or mitigate damage to human health or the environment.

Nanoparticles: The term refers to particles of sizes in the range of 1–100 nm. Depending on the preparative conditions, nanoparticles may have polycrystalline or single crystalline structure. Nanoparticles of sizes less than 5 nm are termed as quantum dots.

Nanosensor: A device for sensing radiation, forces, chemicals, or biological agents, in which some portion of a device operates at the nanoscale.

Nanotechnology: A manufacturing technology able to inexpensively fabricate most structures consistent with natural law, and to do so with molecular precision.

Quantum Dots: Nonocrystals or nanoparticles. Refer to confined electrons. Electrons in them occupy discrete states as in the case of atoms and therefore, quantum dots are referred to as artificial atoms.

Remediation: Remediation is the science of removal or reduction of pollutants from the environment using chemical or biological means.

APPENDIX

- Nanotechnology is technology on the atomic and molecular scale.
- A nanometre (nm) is one billionth of a meter.
- A nanoparticle is a particle with one or more external dimensions in the size range 1-100 nm.
- The aspect ratio between a nanoparticle and a football is similar to that between a football and Earth.
- Nanotechnology is working on a scale of 100 nm (which corresponds approximately to the size of a virus) down to the size of atoms, about 0.1 nm.
- Nano-scale materials and processes are present in nature, ranging from free molecules in gases and liquids to proteins and organic processes.
- Some substances are produced unintentionally, such as welding dust and diesel particulates.

Chapter 6

Nanotechnology for Environmental Control and Remediation

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ABSTRACT

The chapter emphasizes nanotechnology, which is an emerging field that covers a wide range of technologies that are presently under development in nanoscale. Nanotechnology offers the potential of novel nanomaterials for treatment of surface water, ground water, and waste water contaminated by toxic metal ions, organic and inorganic solutes, and microorganisms. The advantages of the use of nanomaterials, which are related to their properties that are completely different from the bulk materials, make them extremely attractive and give them enormous potential. Among the areas that are influenced by nanotechnology, environmental remediation is highlighted in this chapter. This chapter emphasizes several nanomaterials (Zero valent iron, titanium dioxide, nanoclays, nanotubes, dendrimers, ferritin, metalloporphyrinogens, and SAAMS) and their application in water treatment, purification, and disinfection. The use of nanoparticles in environmental remediation, which inevitably leads to the release of nanoparticles into the environment and subsequent ecosystems, is also explained.

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INTRODUCTION

Word “environment” is most commonly used to describe “natural” environment and means the sum of all living and non-living things that surround an organism, or group of organisms. Environment includes all elements, factors, and conditions that have some impact on the growth and development of certain organisms. Environment includes both biotic and abiotic factors that have influence on observed organism. Abiotic factors such as light, temperature, water, atmospheric gases combine with biotic factors (all surrounding living species). Environment often changes after some time and therefore many organisms have ability to adapt to these changes. However the tolerance range is not the same with all species and exposure to environmental conditions at the limit of a certain organism’s tolerance range represents environmental stress. Environmentalism is very important political and social movement with the goal to protect nature, environment by emphasizing the importance of nature, its role in the protection of the environment in combination with various actions and policies oriented to nature preservation. Environmentalism is movement connected with environmental scientists and many of their goals. Some of these goals include:

1. To reduce world consumption of fossil fuels.
2. To reduce and clean up all sorts of pollution (air, sea, river) with the future goal of zero pollution.
3. Emphasis on clean, alternative energy sources that have low carbon emissions.
4. Sustainable use of water, land, and other scarce resources.
5. Preservation of existing endangered species.
6. Protection of biodiversity.

The environmental impact of nanotechnology is the possible effect that the use of nanotechnological materials and devices will have on the environment. Green nanotechnology is considered to play a key role in the shaping of current environmental engineering and science & refers to the use of nanotechnology to enhance the environmental sustainability, minimize potential environmental and human health risks associated with the pollution and contamination by using nanotechnology products, and to encourage replacement of existing products with new nano-products that are more environmentally friendly throughout their Lifecycle. Nanotechnology is an emerging field that covers a wide range of technologies which are presently under development in nanoscale. The unique properties of these nanosized materials have resulted in the use of nanoparticles in various fields like biomedicine, pharmaceuticals, cosmetics, and environmental. It plays a major role in the development of innovative methods to produce new products, to substitute existing production equipment and to reformulate new materials and chemicals with improved

Figure 1. Future of our planet lies in our hands

performance resulting in less consumption of energy and materials and reduce harm to the environment as well as environmental remediation. Although, reduced consumption of energy and materials benefits the environment, nanotechnology will give possibilities for immediate problems associated with the existing processes in a more sustainable way. Environmental applications of nanotechnology address the development of solutions to the existing environmental problems, preventive measures for future problems resulting from the interactions of energy and materials with the environment. This technique has proved to be an effective alternative to the conventional practices for site remediation. Further research has also been carried out and its application is found useful in the treatment of in drinking water. Despite their potential benefits, there is a major concern over the exposure of humans and the environment to nanoparticles that may exert deleterious effects. Toxicological risk assessment demands information on both exposure and uptake of nanoparticles and their immediate effects once they enter the human system. But, the available data on these topics are very limited, to form conclusions and recommendations (Doyle, 2006). In response to these concerns, various scientific communities are gaining knowledge in exposing their toxicological effects on human (Oberdoster, Oberdoster, Oberdoster, 2005) and ecological health (Tratnyek, &

Johnson, 2006). This chapter focuses on various research and experimental works regarding the use of nanotechnology for environmental cleanup, particularly in their application in ground water and drinking water remediation with the help of nanoparticles such as Zero valent iron, titanium dioxide, dendrimers, ferritin, metalloporphyrinogens, SAAMS and bioremediation. It also focuses on the deleterious effects of using these nanoparticles.

BACKGROUND

Remediation is the science of removal or reduction of pollutants from the environment using chemical or biological means. Recent advancements have made the control and reduction of contaminants in soil, sediments and water, which are the major environmental issues. The conventional techniques like disposal to landfill, isolation is somewhat effective, but expensive and take a long time to achieve target goals (Salipira, Mamda, Krause, Malefetse, Durbach, 2007). These techniques also produce undesirable by-products, like during trichloroethylene in-situ remediation where dichloroethylenes and vinyl chloride are usually intermediate by-products. Also, contaminants like chlorinated hydrocarbons migrate to the water table, and sometimes reach the underlying zone, making it extremely difficult to remediate aquifers with standard existing procedures. All these limitations can be effectively targeted by nanotechnology (Masciangioli, & Zhang, 2003). Nanoparticles offer numerous advantages owing to their small size and high surface area These nanoparticles can offer numerous advantages owing to their small size and high surface area These nanoparticles can be easily transported with the flow of water (Karn, Kuiken, & Otto, 2009) and hence can be used for treating underground contaminants without excavation Because of their extremely small size, these particles can be injected into very small spaces and even remain active for a long duration of time (Zhang, 2003). The movement of these miniscule particles is largely controlled by gravitational sedimentation and the large surface area leads to high enzymatic activity In addition, to being used as free particles, nanoparticles can be anchored on a solid matrix and can be used for wastewater treatment or gaseous stream treatment (Zhang, 2003).

Nanomaterials have been used for remediating contaminated groundwater and subsurface source areas of contamination at hazardous waste sites. Previously, conventional methods include primarily pump and treat operations. This method involves extraction of groundwater through wells and trenches and treating groundwater by above-ground (*ex situ*) processes such as air stripping, carbon adsorption, biological reactors or chemical precipitation (U.S. EPA,2001). But unfortunately, most of these methods produce highly contaminated waste which then has to be disposed off, resulting in high operation time (U.S. EPA, 2004).

Air pollution is another potential area where nanotechnology has great promise. Filtration techniques similar to the water purification methods described above could be used in buildings to purify indoor air volumes. Nanofilters could be applied to automobile tailpipes and factory smokestacks to separate out contaminants and prevent them from entering the atmosphere. Finally, nanosensors could be developed to detect toxic gas leaks at extremely low concentrations. Overall, there is a multitude of promising environmental applications for nanotechnology. Much of the current research is focused on energy and water technologies.

From the early 1990s, site, project managers have taken advantage of metallic substance properties such as elemental iron for the degradation of chlorinated solvent plumes in groundwater. One instance of an in situ treatment technology for chlorinated solvent plumes is installing a trench with macroscale zero-valent iron to form a permeable reactive barrier.

MAIN FOCUS OF THE CHAPTER

Nanomaterials in Water Treatment

Nanosorbents are nanoscale particles of inorganic or organic materials that are capable of absorbing other substances. Most environmental applications of nanosorbents are in the field of waste water treatment and drinking water production, with other applications focused on air pollutants or ground water contamination.

Nanosorbents have been shown to have better properties than traditional solvents, such as a large surface area and high substance specificity. They also provide the ability to combine a number of reactive agents together, and allow fine control over mass transport properties.

Because of these advantageous properties, nanosorbents can quickly and specifically remove or recover target contaminants.

Key applications of nanosorbents are:

- Groundwater/soil remediation by carbo-iron.
- Nanoclays for adsorbing phosphorus and organic contaminants.
- Nano-aerogels for removing uranium from groundwater.
- Nano-iron oxides for the adsorption of hormones and pharmaceuticals from waste water.
- Dendrimers, nano-metal oxides and polymer nanofibres for removing heavy metals and arsenic.

Figure 2. The properties of many nanomaterials make them ideal for absorbing environmental pollutants in waste water treatment

NANOREMEDIATION

In recent years, nanoremediation has become the main focus of research and development. There is great potential to use this technology to clean up the contaminated sites and protect the environment from pollution. This eco-friendly technology is considered to be an effective alternative to the current practices of site remediation. Nanoremediation methods involve application of reactive materials for the detoxification and transformation of pollutants. These materials initiate both chemical reduction and catalysis of the pollutants of concern (Karn, Kuiken, & Otto, 2009). The unique properties of nanomaterials make them best suited for *in situ* applications. Their small size and novel surface coatings enable them to achieve farther and wider distribution when compared to large-sized particles (Tratnyek, & Johnson, 2006).

The use of nanotechnology for site remediation could potentially provide a solution for faster and more cost-effective site remediation. Many different nanomaterials have been evaluated for use in nanoremediation. They include nanoscale zeolites, metal oxides, carbon nanotubes,noble metals and titanium dioxide. Among the many applications of nanotechnology that have environmental implications, remediation of contaminated ground water using nanoparticles containing zero-valent iron is one of the most prominent examples of a rapidly emerging technology with considerable potential benefits.

Zero-Valent Iron Nanoparticles (ZVI)

Zerovalent iron (ZVI) is used to treat recalcitrant and toxic contaminants such as chlorinated hydrocarbons and chromium in ground water (Sellers, Boca, & Raton, 1999). The initial applications used granular iron, alone or mixed with sand to make “magic sand,” to treat extracted groundwater. Later, engineers installed flow-through ZVI cells in the ground, using slurry walls or sheet piling to direct the flow of ground water through the treatment cells. However, these walls were expensive and sometimes difficult to construct, and often incurred long-term costs for maintenance and monitoring. Injectable forms of ZVI, most recently nanozero-valent iron (nZVI) and its variations were developed to surmount these problems. In these applications, nanoscale iron particles are injected directly into an aquifer to effect treatment in situ. The core consists primarily of zero-valent or metallic iron, whereas the mixed valent [i.e., Fe (II) and Fe (III)] oxide shell is formed as a result of oxidation of the metallic iron. nZVI are generally preferred for nanoremediation because of the larger surface area of nanoparticles and more number of reactive sites than micro-sized particles and it posses dual properties of adsorption and reduction, as shown in figure 3. As described below, nZVI is commercially available and has been used on more than 30 sites as of this writing.

Zero-valent iron (Fe^0) enters oxidation-reduction (redox) reactions that degrade certain contaminants, particularly chlorinated hydrocarbons such as trichloroethylene (TCE) and tetrachloroethylene. ZVI also has been used to treat arsenic and certain metals (Zhang, 2003). In the presence of oxygen, nZVI can oxidize organic compounds such as phenol (Joo, Feitz, Sedlak, Waite, 2005).

Reductive dehalogenation of TCE generally occurs as follows (Liu, & Lowry, 2006):

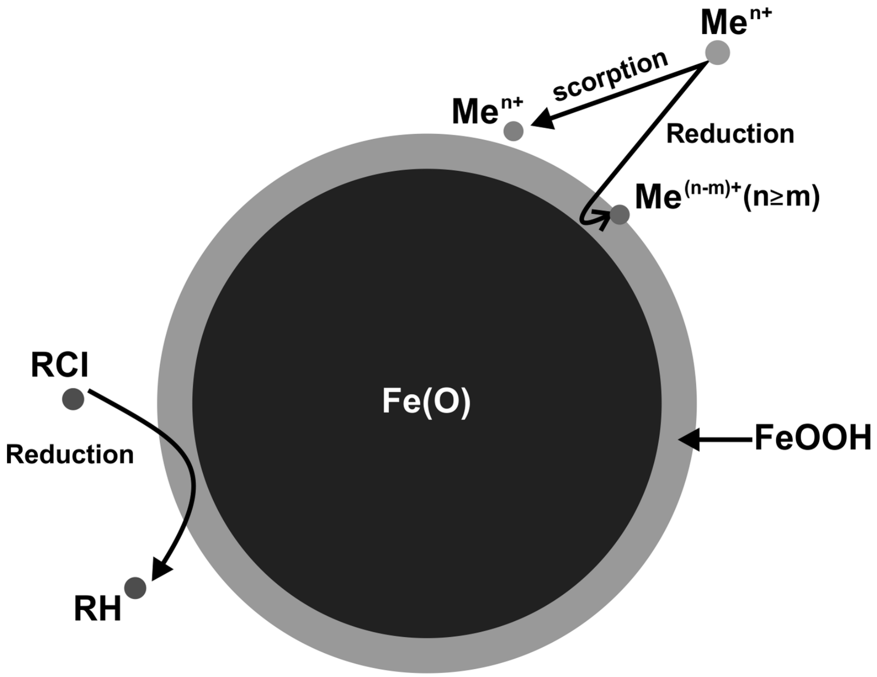
$$Fe^0 \rightarrow Fe^{2+} + 2e-$$

$$3Fe^0 + 4H_2O \rightarrow Fe_3O_4 + 8H^+ + 8e-$$

$$TCE + n\bullet e- + (n-3)H^+ \rightarrow Products + 3Cl-$$

$$H^+ + e- \rightarrow H^\bullet \rightarrow \tfrac{1}{2}H_2 \uparrow$$

Figure 3. Schematic diagram of zero valent iron (Li, 2006)



where the value of n depends on the products formed. As indicated by these half-reactions, nZVI can be oxidized to ferrous iron or to Fe_3O_4 (magnetite); the latter is more thermodynamically favored above pH 6.1. As the reaction proceeds, ZVI particles can become coated with a shell of oxidized iron (i.e., Fe_3O_4 and Fe_2O_3). This coating can eventually reduce the reactivity of (or "passivate") the nZVI particles (Joo, Feitz, Sedlak, Waite, 2005 Liu, & Lowry, 2006). Passivation can begin immediately upon manufacture, depending on how the material is stored and shipped; the oxidation reaction continues after environmental application.

The efficiency of treatment depends on the rate of TCE dechlorination relative to nonspecific corrosion of the nZVI to yield H_2. In one study with granular ZVI, the latter reaction consumed over 80% of Fe^0. The solution pH and the Fe^0 content of the particles may affect the balance between nonspecific corrosion and reduction of TCE.

The effectiveness of in situ treatment using nZVI also depends on the characteristics of the aquifer. The pattern and rate of groundwater flow affect the distribution of nZVI. The geochemical characteristics of the groundwater — including pH, relative degree of oxygenation, and the presence of naturally occurring minerals — also affect the reactivity and distribution of nZVI.

nZVI can be manufactured using different processes that convey different properties to the material. These properties include particle size (and size distribution), surface area, and the presence of trace constituents. Reagents for environmental remediation often contain materials other than iron to enhance the mobility or reactivity of nZVI. In general, four processes are used to manufacture nZVI (Zhang, 2005, Vance, 2005 & Wiesner, Lowry, Alvarez, Dionysiou, & Biswas, 2006):

1. Heat iron pentacarbonyl.
2. Ferric chloride + sodium borohydride.
3. Iron oxides + hydrogen (high temperatures).
4. Ball mill iron filings to nano-sized particles.

For the commercial production processes (2 and 3) are currently used. Researchers have modified nZVI particles to increase their mobility and/or reactivity. Coating the nZVI particles can limit agglomeration and deposition, and enhance their dispersion. These particle treatments include emulsified nZVI, polymers, surfactants, and polyelectrolytes (Salch, Sirk, & Liu, 2007).

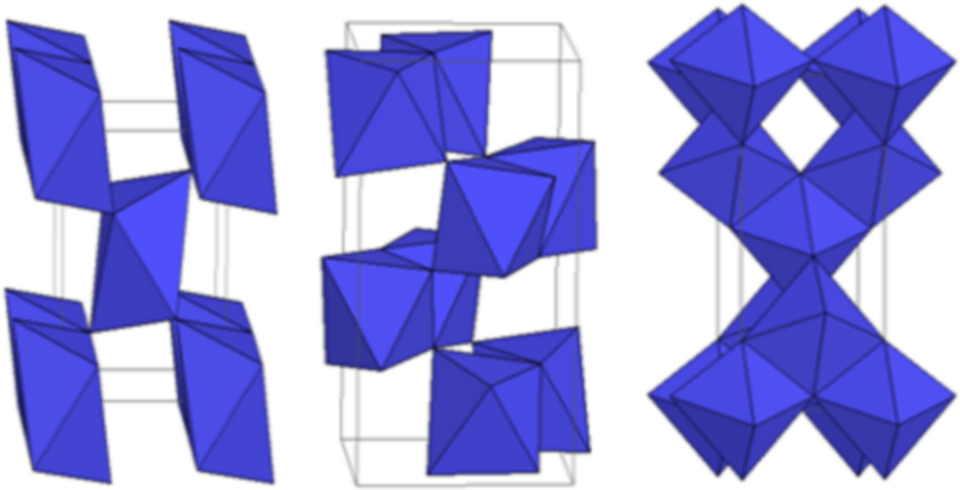
Bimetallic nanoscale particles (BNPs) have a core of nZVI with a trace coating of a catalyst such as palladium, silver, or platinum (Gavaskar, Tatar, & Condit, 2005). This catalyst enhances reduction reactions. PARS Environmental markets a BNP developed at Penn State University. This BNP contains 99.9 wt% iron and 0.1 wt% palladium and polymer support. The polymer is not toxic; the U.S. Food and Drug Administration have approved the use of the polymer as a food additive. The polymer limits the ability of the nZVI particles to agglomerate and adhere to soils.

Titanium Dioxide (TiO_2) Based Nanoparticles

Titanium dioxide (TiO_2) is one of the popular materials used in various applications because of its semiconducting, photocatalytic, energy converting, electronic and gas sensing properties. Titanium dioxide crystals are present in three different polymorphs in nature that in the order of their abundance, are Rutile, Anatase and Brookite (Figure 4) (Diebold, 2003 & Educational materials Colorado University).

Many researchers are focused on TiO_2 nanoparticle and its application as a photocatalyst in water treatment. Nanoparticles that are activated by light, such as the large band-gap semiconductors titanium dioxide (TiO_2) and zinc oxide (ZnO), are frequently studied for their ability to remove organic contaminants from various media. These nanoparticles have the advantages of readily available, inexpensive, and low toxicity. The semiconducting property of TiO_2 is necessary for the removal of different organic pollutants through excitation of TiO_2 semiconductor with a light energy greater than its band gap, which could generate electron hole pairs.

Figure 4. The crystal structures of A) rutile, B) anatase, C) brookite (http://ruby.colorado.edu/~smyth/min/tio2.html)



These may be exploited in different reduction processes at the semiconductor/solution interface.

A semiconductor can adopt with donor atoms that provide electrons for the conduction band where they can carry a current. These materials can also adopt with acceptor atoms that take electrons from the valence band and leave behind some positive charges (holes). The energy levels of these donors and acceptors fall into the energy gap.

The most affecting properties of semiconducting nanoparticles are distinguished changes in their optical properties compared to those of bulk materials. In addition, there is a significant shift in optical absorption spectra toward the blue shift (shorter wavelengths) as the particle size is reduced (Poole, & Owens, 2003).

Stathatos et al. (Stathatos, Tsiourvas, & Lianos., 1999) used reverse micelle technique to produce TiO_2 nanoparticles and deposited them as thin films. They deposited TiO_2 mesoporous films on glass slides by dip-coating in reverse micellar gels containing titanium isopropoxide. The films demonstrated a high capacity in the adsorption of several dyes from aqueous and alcoholic solutions. It had also a rapid degradation of the adsorbed dyes when the colored flames were exposed to the visible light. It is known that, the semiconducting properties of TiO_2 materials is responsible for the removal of various organic pollutants, but the rapid recombination of photo-generated electron hole pairs and the non-selectivity of the system are the main problems that limit the application of photocatalysis processes (Makarova, Rajh, Thurnauer, Martin, Kemme, & Cropek, 2000). It was suggested that, replacing adsorbed solvent molecules and ions by chelating agents, i.e. surface modification, changes the energetic situation of surface states and considerably alters the chemistry, which is taking place at the surface of titanium dioxide (TiO_2). Phenol is one of the toxic materials found in municipal and waste waters. Synthesized titanium dioxide nanoparticles of both Anatase and Rutile forms were used for wet oxidation of phenols by hydrothermal treatment of microemulsions and their photocatalytic activity (Andersson, Osterlund, Ljungstrom, & Palmqvist, 2002). Such treatment has the advantage that the size of particles is affected by the ratio of surfactant to water. Size of water droplets in the reverse microemulsions is found to be almost the same as that of formed particles. The main reactions proposed for phenol degradation are (Andersson, Osterlund, Ljungstrom, & Palmqvist, 2002).

$TiO_2 + h\upsilon \rightarrow TiO_2\ (h)^+ + e^-$

$TiO_2\ (h)^+ + H_2O\ (ads) \rightarrow$

$OH\bullet + H^+ + TiO_2$

$OH\bullet + \text{Phenol} \rightarrow$

intermediate products (e.g., benzoquinone)

$TiO_2\ (h)^+ + \text{intermediate products} \rightarrow$

$CO_2 + H_2O + TiO_2$

Nanoclay

Nanoclays are natural nanomaterials that occur in the clay fraction of soil, among which montmorillonite and allophane are the most important species. Montmorillonite is a crystalline hydrous phyllosilicate (layer silicate). Recently Organically modified montmorillonites or organoclays are develop in the form of polymer-clay nanocomposite.

Clays are layered minerals with space in between the layers where they can adsorb positive and negative ions and water molecules. Clays undergo exchange interactions of adsorbed ions with the outside too. Although clays are very useful for many applications, they have one main disadvantage i.e. lack of permanent porosity. To overcome this problem, researchers have been looking for a way to prop and support the clay layers with molecular pillars. Most of the clays can swell and thus increase the space in between their layers to accommodate the adsorbed water and ionic species. The composite structures, known as pillared clay, could stabilize TiO_2 particles and give access of different molecules to the surface of TiO_2 crystals. Ooka et al. (Ponder, Darab, and Mallouk, 2000) prepared four kinds of TiO_2 pillared clays from Montmorillonite, saponite, fluorine hectorite and fluorine mica serves as nanoclay for water remediation.

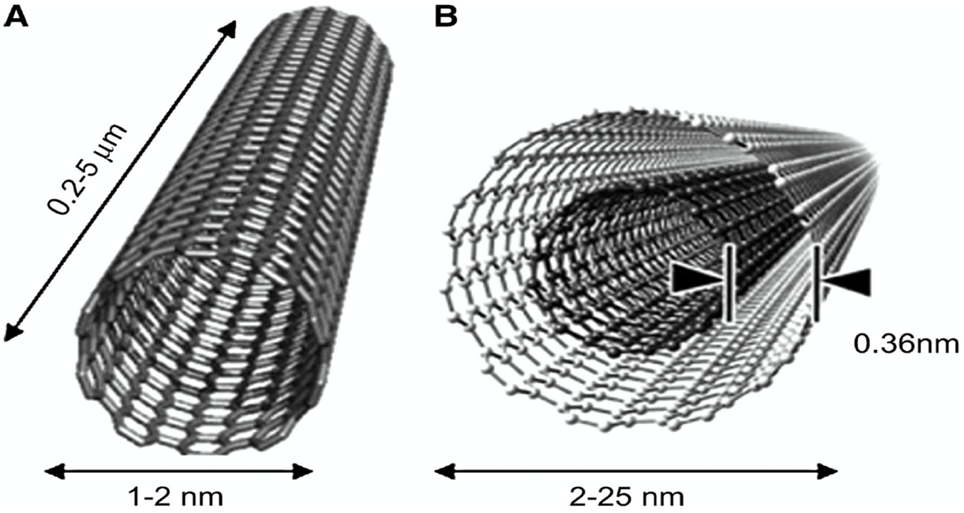
They have tested the surface hydrophobicities and performances of clays in adsorption-photocatalytic decomposition & it was found that surface hydrophobicity can be enhanced by the presence of polyethylene oxide (PEO) surfactants (Ooka, Yoshida, Suzuki, & Hattori, 2004). It resulted in forming larger precursors of TiO_2 nanoparticles and condensing them on the fragmented pieces of the silicate. Nanoclays found potential application in the petroleum industry for removing hydrocarbons from refinery process water and also been tested for treating ground and surface water and for other toxic organic chemicals from pharmaceuticals and pesticides industries. Nanomer® and Cloisite® are the popular nanoclays available in the market.

Carbon Nanotubes

The properties of nanotubes sound like science fiction; these tiny cylinders can have extraordinary strength and unusual electrical properties. Their characteristics depend on their composition, size, and orientation, as described below (Dresselhaus, Dresselhaus, Eklund, & Saito, 1998 & Helland, Wick, Koehler, Schmid, & Som, 2007). This discussion focuses on carbon nanotubes (CNTs) rather than metal-based nanotubes. CNTs consist of one or more thin sheets of graphite, one atom thick, known as graphene, which are rolled to create a hollow cylinder (Figure 5). A single-walled carbon nanotube (SWNT) contains one layer of graphene; a multiwalled carbon nanotube (MWCNT) comprises concentric cylinders of graphene. SWNT diameters generally range from 0.4 to 2.5 nm; MWCNT, up to several hundred nanometers.

The hexagonal aray of carbon atoms in graphite sheets of CNTs surface has a strong interaction with other molecules or atoms, which makes CNTs a promising adsorbent material substituted for activated carbon in many ways (Liang, Liu, Guo, Zeng, Hanbing, 2004). Carbon nanotubes act like as nanosorbent, and hold tremendous potential for applications because of their unique properties, such as strong antimicrobial activity, higher water flux than other porous materials of comparable size, tunable pore size and surface chemistry, high electrical & thermal conductivity, special adsorption properties and their ability to be attached to a functional group to increase the affinity towards the target molecule (Zhu, Li, Zhaob, & Churchman, 2005) makes CNTs as a promising material for water remediation. Some studies showed that un-functionalized CNTs tend to be water insoluble and toxic. Carbon nanotubes, in order to be highly dispersed in water and to be easily sepa-

Figure 5. A schematic Representation of Carbon Nanotube and Multi walled Carbon Nanotube (Zhu, Li, Zhaob, & Churchman, 2005)



rated from their dispersion for their re-use, are functionalized with various functional groups (e.g. hydroxyl, carboxyl, amines, etc.) to increase their water solubility and biocompatibility. To increase the absorption capacity of MWCNTs, it is oxidized with nitric acid, this creates reactive sites in either on tip of nanotube or either by creating defects site on the side wall of the tube, resulting to which a higher level of adsorption was achieved due to high reactivity. They are utilized for the removal of heavy metals like Cr^{3+}, Pb^{2+}, and Zn^{2+} (Savage, & Diallo, 2005), metalloids such as arsenic compounds, organics, biological impurities, and removing many kinds of organic and inorganic pollutants such as dioxin and volatile organic compounds.

Researchers are developing a range of nanoparticles to destroy or adsorb contaminants as part of *ex situ* or *in situ* processes. These particles include dendrimers, ferritin, metalloporphyrinogens and SAAMS (Self-Assembled Monolayers on Mesoporous Supports). Certain materials can be made with surface functional groups that serve as adsorbents for the scavenging of specific contaminants from waste streams.

SAMMS Particles

SAMMS particles include a nanoporous ceramic substrate with a functional group monolayer that is tailored to attach to the target contaminant. Covalent bonding of the functional molecules to the silica surface takes place so that the other end group binds to several contaminants. Researchers state that SAAMS particles maintain good thermal and chemical stability and can be readily restored or reused. Contaminants that can be successfully sorbed to SAAMS include mercury, radionuclides, arsenate, chromate, selenite and pertechnate (Figure 6).

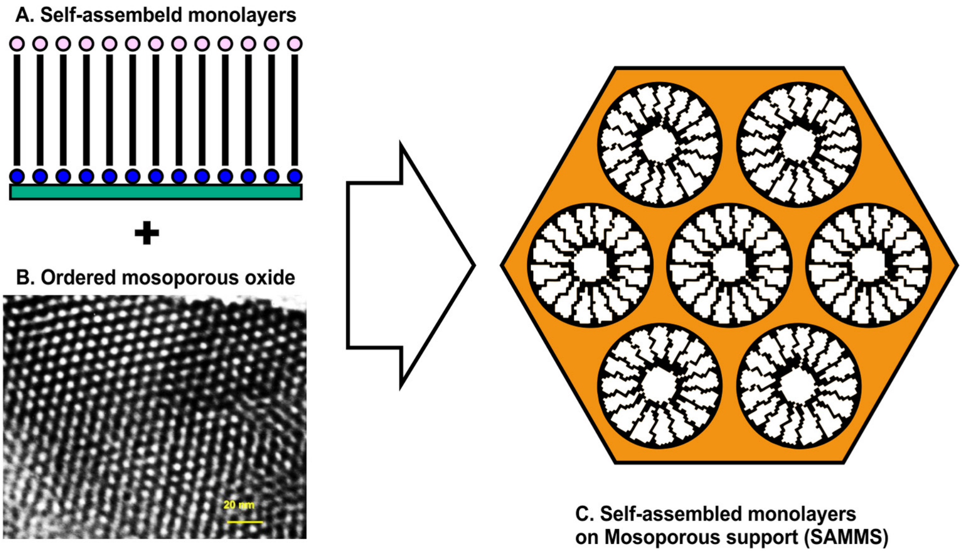
Photocatalytic Nanotubes

Nanotubes are engineered molecules that are most commonly made from carbon. They are highly electronegative, electrically insulating and polymerized easily. Titanium dioxide nanotubes are also available and these can be used as a photocatalytic degrader of chlorinated compounds. Research has shown that titanium dioxide nanotubes are effective at high temperatures - in one study, their use resulted in a 50% decrease in contaminant concentration in just 3 hours. (Figure 7)

Other nanomaterials wich have been used for environmental remediation include:

- **Ferritin:** An iron storage protein can minimize toxicity of contaminants such as technetium and chromium in groundwater and surface water to enable remediation.
- **Dendrimers:** Neatly organized, hyper-branched polymer molecules that have end groups, core and branches. FeO/FeS nanocomposites that are synthesized with dendrimers as templates can be used for the construction of permeable reactive barriers for remediation of ground water.

Figure 6. Self-assembled monolayers on mesoporous supports (Fryxell, Yuehe, Sandy, Jerome, Hing, 2005)



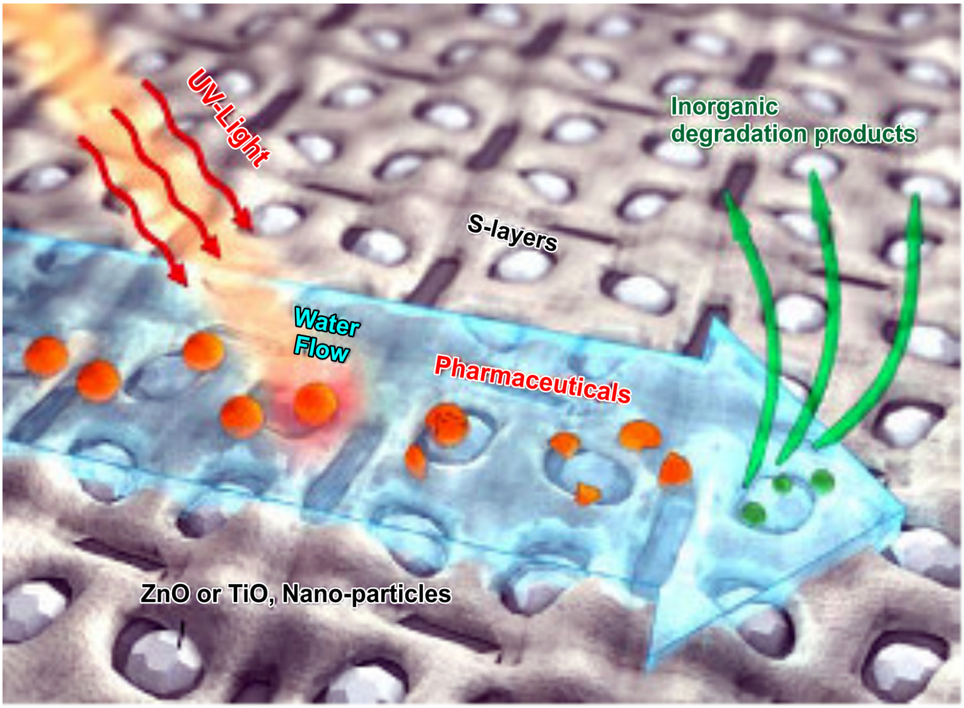


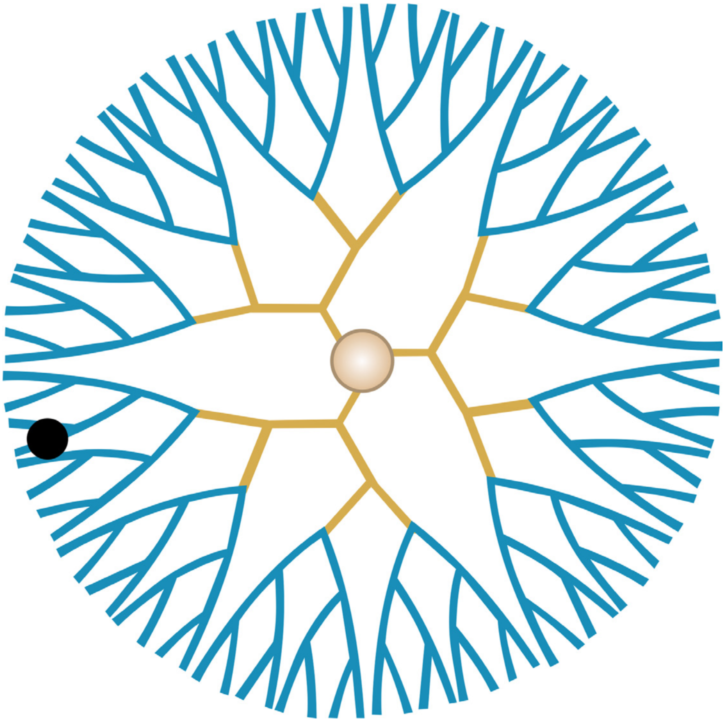
Figure 7. Photocatalytic nano particles can be used to degrade organic compounds and harmful waste substances like chlorinated chemicals. Image credit: EU ObservatoryNano.

- **Metalloporphyrinogens:** Metal complexes having naturally occurring organic porphyrin molecules. Biological metalloporphyrinogens are vitamin B_{12} and hemoglobin.

According to experiments, metalloporphyrins can reduce chlorinated hydrocarbons like PCE, TCE and carbon tetrachloride under anoxic conditions to remediate contaminated groundwater and soil.

In addition to groundwater remediation, nanotechnology holds promise in reducing the presence of NAPLs. Recently, a material using nanosized oxides (mostly calcium) was used *in situ* to clean up heating oil spills from underground oil tanks. Preliminary results from this redox-based technology suggest faster, cheaper methods and, ultimately, lower overall contaminant levels compared with previous remediation methods. Most of these sites have been in New Jersey, with cleanup conducted in consultation with the New Jersey Department of Environmental Protection (Continental Remediation LLC, 2009).

Figure 8. Dendrimers



BIOREMEDIATION

Bioremediation of harmful organic contaminants like carbazole and dibenzothiophene has been successfully reported by different groups using a variety of micro-organisms (Maeda, Nagashima, Widada, Iwata, & Omori, 2009) but their industrial application is limited by the lack of re-usability and difficulty in downstream processing, i.e. separation of cells from the solution. Also, the limited bioavailability of these compounds in water has led to lower rates of activity as compared to possible efficiency. Nanotechnology has played a role in microbial remediation. Increasing the solubility/bioavailability and subsequently the degradation rate, by far, has been the biggest challenge in bioremediation. In the present scenario, surfactant micelles are used to increase the solubility of the contaminant but these tend to interact with the liposome of microorganisms and also break down upon contact with soil and thus limiting the efficiency of bioremediation. Recent advances in nanotechnology have shown a promising step in this direction. Tungittiplakorn, Cohen, and Lion (2004) (Tungittiplakorn, Cohen, and Lion, 2004) have reported an increase in the solubilisation rate of model remediation compound Phenanthrene (PHEN) by using amphiphilic polyurethane (APU) nanoparticles. These particles, made of polyurethane acrylate anionmer (UAA) or poly (ethylene) glycol (PMUA) precursor chains, have hydrophobic interiors that show high affinity for PHEN. They enhance PAH desorption and mobility by forming a nanoparticle-suspension, which competes with NAPLs (Watlington, 2005). As opposed to surfactant, the affinity of the nanoparticles to hydrophobic contaminant can be increased by modifying the hydrophobic segment of the precursor chain and the mobility can be increased by controlling the charge density of the modified nanoparticles. Another advantage offered by nanoparticles in bioremediation, is in the form of Magnetite nanoparticles. Magnetite nanoparticles are formed by the co-precipitation of ferrous and ferric salts under inert conditions. This technology imparts great industrial applicability in terms of easier separation, re-usability, and cost-effectiveness. Li, Gao, Li, Xing, and Liu (2009) (Li, Gao, Li, Xing, & Liu, 2009) have reported the use of magnetite nanoparticles by coating them on dibenzothipohene-desulfurizing bacterial strain R. erthyropolis LSSE8-1 and P. delafiedelii and analyzing their biodesulfurization activity. The cells coated with ammonium oleate modified magnetite nanoparticles showed repeated biodesulfurization activity and could be collected on the surface of the flask by using an external magnet. The use of magnetite nanoparticles also showed increased desulfurization activity.

Nano Pollution and Health Concerns

It is believed that the current boom in nanotechnology will bring a lot of positive changes to the world. However, the increased levels of nanomaterials in waste which this will inevitably result in may give rise to an increase in “nano-pollution”, which is very difficult to detect or contain, and which has health consequences which are largely unknown.

One of the major concerns which must be addressed before nanomaterials begin to be used more extensively for water treatment and pollution remediation is their own effect on the environment. We need to understand how well we can control the materials, how effectively we can recover them, and what effect their use will have on the ecosystem.

POTENTIAL IMPLICATIONS

Fate and Transport

When released into the environment, manufactured nanoparticles aggregate to some degree and behave like natural nanomaterials. However, to be effective, nZVI needs to form stable dispersions in water so it can be delivered to water-saturated porous material in the contaminated area. Yet, its rapid aggregation limits its mobility (Phenrat, Saleh, Sirk, Tilton, Lowry, 2007). The rapid aggregation of the nanoscale Fe particles supports the need for polymer or other coatings to modify the nZVI surface in order to improve mobility (Phenrat, Saleh, Sirk, Tilton, Lowry, 2007).

Depending on the composition of ground-water and the hydrologic conditions, certain nanoscale colloids have the ability to travel unexpectedly large distances in the environment (Kersting, Efurd, Finnegan, Rokop. Smith, & Thompson, 1999 & Novikov, Kalmykov, Utsunomiya, Ewing, Horreard, Merkulov, et al. 2006). They could form stable nanoclusters in groundwater that are likely to be highly mobile, carrying with them surface-sorbed contaminants. These natural particles can carry materials between redox zones and facilitate or inhibit contaminant transport (Waite, Schafer, Fane, & Heuer, 1999).

The mobility of natural or synthetic nano-particles in the natural environment will strongly depend on whether the nanoparticles remain completely dispersed, aggregate and settle, or form mobile nanoclusters. Gilbert, Lu, and Kim (2007) suggested that many manufactured metal oxide and other inorganic nano-particles will exhibit cluster-forming behavior similar to that of natural nanoparticles. Despite numerous observations that nanoscale minerals represent an important fraction of the environmental colloids, the fundamental aggregation and transport properties of nanoparticles have not been extensively studied.

In addition to self-aggregation, nano-particles could associate with suspended solids or sediment, where they could bioaccumulate and enter the food chain or drinking water sources. These fate processes depend on both the characteristics of the particle and the characteristics of the environmental system (Boxall, Tiede, & Chaudhry, 2007).

The use of nanoparticles in environmental remediation will inevitably lead to the release of nanoparticles into the environment and subsequent ecosystems. To understand and quantify the potential risks, the mobility, bioavailability, toxicity, and persistence of manufactured nanoparticles need to be studied (Nowack, In: Krug, 2008). To pose a risk, nano-particles must be hazardous and have a route of exposure. Although aggregated and/or absorbed nanoparticles are usually less mobile, they still have the potential to be taken up by filter feeders and other sediment-dwelling organisms. The U.S. EPA has raised the possibility of biomagnification of nanoparticles; however, no data currently exist proving or disproving this hypothesis (Biswas, & Wu, 2005 & U.S. EPA, 2007). To be able to quantify the stability of nanoparticles in the environment, the stability of their suspensions and their tendency to aggregate and interact with other particles must first be determined (Mackay, Johns, Salatas, Bessinger, & Perri, 2006).

Potential Toxicity

Naturally occurring nanoscale Fe oxide particles with metals (such as copper) bound to their surface have been found many kilometers downstream from mining sites, indicating the ability of these colloidal nanoparticles to move and transport sorbed contaminants (Hochella, Moore, Putnis, Putnis, Kasama, & Eberl, 2005) These binding properties and processes may show size-dependent reactivity of crystalline Fe oxide nanoparticles, and each process might occur with different thermochemical and kinetic relationships as a function of size (Madden, Hochella, & Luxton, 2006). Thus, whereas the nanoparticles themselves may not possess toxic properties, the pollutants they could carry with them may. Fe nanomaterials may bind with and carry copper, which has a toxicity threshold for algae, flowering plants, fungi, and phytoplankton that is surpassed only by mercury and sometimes silver (Sposito, 1989).

Handy, Kammer, Lead, Hassellöv, Owen, and Crane (2008) suggested that despite the environment containing many natural particles at the nanoscale, manufactured nano-particles may act differently. These materials are designed to have specific surface properties and chemistries that are not likely to be found in natural particles. The properties of manufactured nanoparticles enhance novel physico-chemical and possibly toxicologic properties compared with natural particles. A range of ecotoxicologic effects of various manufactured nanomaterials has been reported, including effects on microbes, plants, invertebrates, and fish (Boxall, Tiede, Chaudhry, 2007). Laboratory studies using fish, *Daphnia*, copepods, and other organisms (Adams, Lyon, Alvarez, 2006, Fortner, Lyon, Sayes, Boyd, Falkner, Hotze, et al., 2005, Lovern, Strickler, Klaper, 2007 & Oberdörster, Zhu, Blickley, Green, Haasch, 2006) have shown that these organisms can take up some manufactured nanoparticles.

The factors and processes affecting eco-toxicity are complex, and the impact of manufactured nanoparticles on organisms is determined by a range of properties, including dissolution potential, aggregation potential, particle surface properties, the characteristics of the exposure environment, and the biochemical, physiological, and behavioral traits of the organism being exposed (Dhawan, Taurozzi, & Pandey, 2006).

Research on ultrafine particulates (< 100 nm in one dimension) has shown that as particle size decreases, potential for pulmonary toxicity tends to increase even if the material's larger form is inert. nZVI is typically between tens and hundreds of nanometers in size at the time of production. Under laboratory conditions, these particles tend to aggregate and produce clusters that can build up to the micrometer size. If this occurs, they will not take on the properties that apply to actual nano-sized particles and will behave similarly to larger environmental colloids (Keenan, & Sedlak, 2008).

Inhalation exposure to $Fe^0(s)$ nanoparticles could result in the release of Fe(III), followed by oxidative damage due to generation of Fe (IV) (Tratnyek, & Johnson, 2006). *In vitro* studies examining the response of the central nervous system to low concentrations of nano-Fe and nanomagnetite showed that these nanoparticles are taken up into cells and produce an oxidative stress response (Wiesner, Lowry, Alvarez, Dionysios, & Biswas, 2006). These studies indicate a potential for adverse health effects from exposure and uptake of Fe oxide nanoparticles into mammalian cells. The author's caution, however, that these tests were conducted at much higher dosages than would be encountered normally (Wiesner, Lowry, Alvarez, Dionysios, & Biswas, 2006).

In some cases, Fe oxide nanoparticles (a potential end product from redox reactions of nZVI) can be internalized by cells and cause cell death. The Low solubility of Fe oxide nano-particles enables them to persist in biological systems and could potentially induce long-term effects involving mutagenic influence on organisms (Auffan, Decome, Rose, Orsiere, Meo, & Briois, 2006). However, there are limited data on the interactions of Fe oxide nanoparticles with cells and the effect that coatings can have on cell adhesion, internalization, and interaction.

Mineral nanoparticles are common components of natural aqueous systems. Several natural inorganic and biologically mediated processes produce mineral nanoparticles, such as metal sulfides and metal oxides (Labrenz, Drusche, Thomsen-Ebert, Gilbert, Welch, Kemner, et al. 2000 & Villalobos, Toner, Bargar, Sposito, 2003). Nanoscale Fe (oxy) hydroxide phases is among the most common natural mineral nanoparticles formed by precipitation from solution after oxidation of aqueous ferrous Fe (Van der Zee, Roberts, Rancourt, Slomp, 2003). Although Fe is an essential element for growth in nearly all species, an abundance of free chelating Fe has been linked to DNA damage, lipid peroxidation, and oxidative protein damage *in vivo*.

Particle coating, surface treatments, surface excitation by ultraviolet radiation, and particle aggregation can modify the effects of particle size, suggesting that some nanoparticles could exert their toxic effects as aggregates or through the release of toxic chemicals (Nel, Xia, Mädler, Li, 2006). Although the aggregates are fractal-like, they may exhibit some of the properties of the discrete nanoparticles, including specific surface area and reactivity, particularly because these particles have been manufactured at the nanoscale in order to harness particular nanoscale properties.

Generally, little concern has been raised about the toxicity of nZVI because Fe oxides formed during remediation are already present in the form of rust and because the nano-Fe particles have not been found to produce radically new properties, compared with microscale-sized Fe particles (Li, Gao, Li, Xing, & Liu, 2009). Whether the addition of catalytic coatings changes these properties or presents another hazard has yet to be determined. Oberdörster, Zhu, Blickley, Green, and Haasch (2006) suggested that toxicity studies should not simply focus on human and wildlife, but should also examine benthic and soil flora and fauna, because they make up the basis of food chains. Biological systems did not evolve alongside the nanoparticles that are now being manufactured and released. Different reactions to nZVI may be found in some lower organisms.

The Royal Commission on Environmental Pollution (2008) summed up the current approach to potential implications from nanomaterials.

While there have been no significant events that would lead us to suppose that the contemporary introduction of novel materials is a source of environmental hazard, we are acutely aware of past instances where new chemicals and products, originally thought to be entirely benign, turned out to have very high environmental and public health costs.

CONCLUSION

Nanomaterials such as nanoparticles, nanofibers, and porous materials can function as catalysts and adsorbents, or be used to remove harmful gases, organic pollutants, contaminated chemicals and biological substances.

Nanomaterials have proved to be better than conventional techniques in environmental remediation due to their high reactivity and high surface area. These nanomaterials have properties that enable both chemical reduction and catalysis to mitigate the pollutants of concern. No groundwater is pumped out for above-ground treatment, and no soil is transported to other places for treatment and disposal. Nanoscale Fe particles are effective for the remediation and transformation of a variety of environmental contaminants. Because of the high cost and lengthy operating periods for pump-and-treat remedies, *in situ* groundwater treatment technologies are increasing. The number of actual applications of nZVI is increasing rapidly. Although the technology is likely a beneficial replacement of current practices for site remediation, potential risks are poorly understood. The factors and processes affecting ecotoxicity are complex, and knowledge of the potential impacts of manufactured nanoparticles in the environment on human health is still limited.

Nanoremediation has the potential to reduce the overall costs of cleaning up large-scale contaminated sites, reduce cleanup time, eliminate the need for treatment and disposal of contaminated dredged soil, and reduce some contaminant concentrations to near zero, and it can be done *in situ*. In order to prevent any potential adverse environmental impacts, proper evaluation, including full-scale ecosystem-wide studies, of these nanoparticles needs to be addressed before this technique is used on a mass scale.

The benefits of nanomaterials in environmental remediation can be summarized as follows:

- Increased surface area or sorption capacity.
- High reactivity.
- Readily tailored for application in several environments.
- Easy dispersability.

These technologies will hopefully open the door to more effective and less costly toxicant treatments. As can be seen, though, the success of these technologies is reliant on a better understanding of their potential health impacts. Success in the public eye is also dependent on maintaining a positive image for the entire field of nanotechnology. In the end, it likely will be the next few years that dictate the direction of nanotechnologies for environmental remediation.

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KEY TERMS AND DEFINITIONS

Bioremediation: It is a waste management technique that involves the use of organisms to remove or neutralize pollutants from a contaminated site.

Nanomedicine: The use of nanotechnology in the improvement of a contaminated site to prevent, minimize or mitigate damage to human health or the environment.

Nanoscale Zeolites: These are nano sized microporous, aluminosilicate minerals commonly used as commercial adsorbents.

Remediation: Remediation is the science of removal or reduction of pollutants from the environment using chemical or biological means.

Chapter 7

Applications of Nanotechnology in Cancer

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ABSTRACT

This chapter examines the importance of nanotechnology in cancer prevention, cure, and diagnosis. This chapter deals with the applications of nanomedicine in cancer and various strategies to target cancer cells by using nanotechnology such as gold nanoparticles, liposomes, nanodots, nanorods, etc. Nanotechnology is an interdisciplinary area with potential applications in fighting many diseases including cancer. Conventional drugs have poor cell specificity, solubility, and high toxicity. The continued development of cancer nanotechnology holds the promise for personalized oncology. For accurate and self-confirming cancer diagnosis, it is essential to combine dual-mode and multi-mode imaging functionalities within one nanoparticle system. Nanoparticles improve the solubility of poorly water-soluble drugs and prolong the half-life of drugs. Disadvantages of nanotechnology include the potential for mass poisoning. Understanding how nano-materials affect live cell functions, controlling such effects, and using them for disease therapeutics are now the principal aims and most challenging aspects of nanobiotechnology and nanomedicine.

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INTRODUCTION

Nanotechnology can be defined as the design, characterization, production and application of structures, devices and systems by controlling shape and size at a nanometer scale. Nanoparticles, according to the American Society for Testing and Materials (ASTM) standard definition, are particles with lengths that range from 1 to 100nm in two or three dimensions. Potential benefit of nanomaterial's are well recognized in the literature and some commentators argue that nanotechnology promises to far exceed the impact of the Industrial Revolution, projecting to become a $1 trillion market by 2015. In medicine, interest is in the use of nanoparticles to enhance drug delivery; in *in vitro* diagnostics, novel biomaterial design, bio-imaging, therapies and active implants.

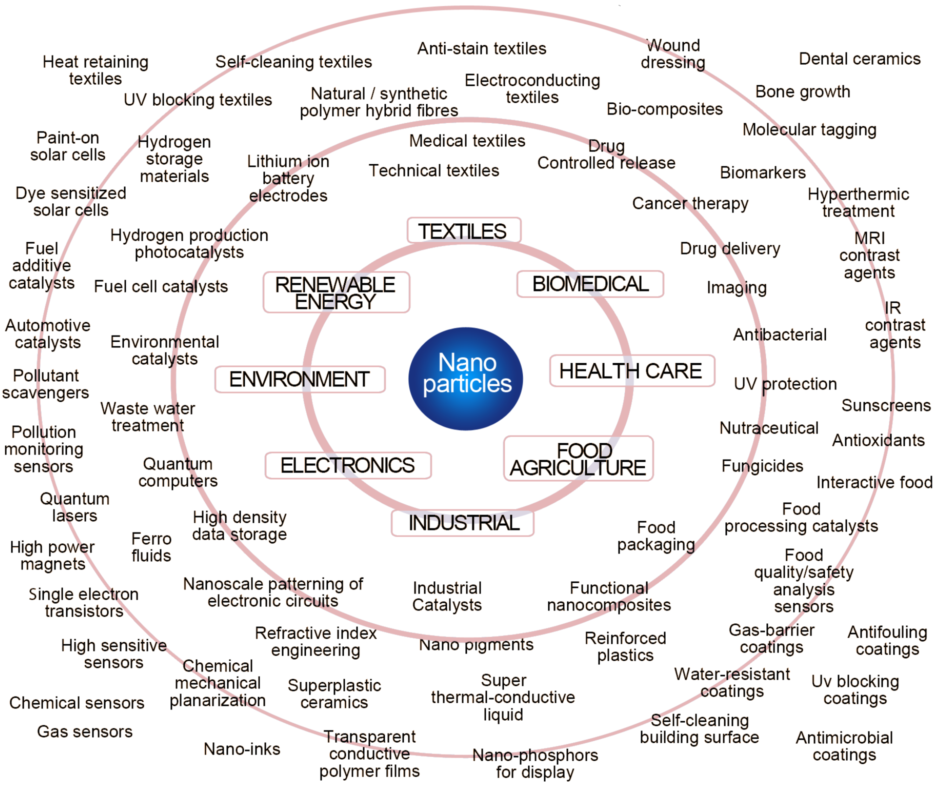
Nanotechnology is an interdisciplinary research field involving chemistry, engineering, biology and medicine. It has great potential for early detection, accurate diagnosis, and personalized treatment of cancer. Nanoparticles are typically smaller than several hundred nanometers in size, comparable to large biological molecules such as enzymes, receptors, and antibodies. With the size of about one hundred to ten thousand times smaller than human cells, these nanoparticles can offer unprecedented interactions with biomolecules both on the surface of and inside the cells, which may revolutionize cancer diagnosis and treatment.

Over the last decade, there have been many nanotechnology centers established worldwide. In the United States alone, more than six billion dollars have been invested in nanotechnology research and more than sixty centers, networks, and facilities, funded by various agencies, are in operation. After establishing an interdisciplinary nanotechnology workforce, it is expected that nanotechnology will mature into a clinically useful field in the near future. For *in vitro* and *ex vivo* applications, the advantages of state-of-the-art nano-devices (e.g., Nano-chips and Nano-sensors) over traditional assay methods are obvious.However, several barriers exist for *in vivo* applications in preclinical and potentially clinical use of nanotechnology, among which are the biocompatibility, *in vivo* kinetics, tumor targeting efficacy, acute and chronic toxicity, ability to escape the reticulo-endothelial system (RES), and cost-effectiveness (Cai and Chen 2007, 2008).

Nanotechnology and Cancer

It has been almost four decades since the "war on cancer" was declared. It is now generally believed that personalized medicine is the future for cancer patient management. Possessing unprecedented potential for early detection, accurate diagnosis, and personalized treatment of cancer, nanoparticles have been extensively studied over the last decade.

Figure 1. Applications of nanoparticles



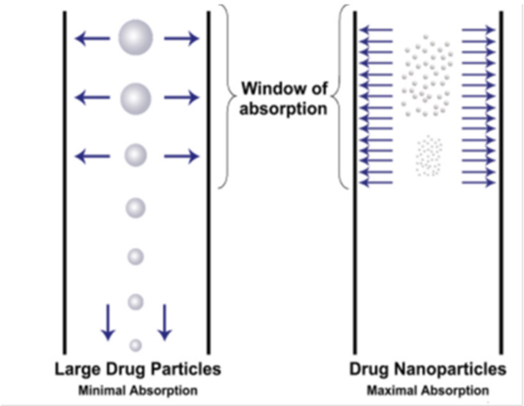
Nanomedicine involves utilization of nanotechnology for the benefit of human health and wellbeing. The use of nanotechnology in various sectors of therapeutics has revolutionized the field of medicine where nanoparticles of dimensions ranging between 1 - 100 nm are designed and used for diagnostics, therapeutics and as biomedical tools for research (Medina et al., 2007). Conventional drugs suffer from major limitations of adverse effects occurring as a result of non-specificity of drug action and lack of efficacy due to improper or ineffective dosage formulation (e.g., cancer chemotherapy and anti-diabetic agents). Designing of drugs with greater degree of cell specificity improves efficacy and minimizes adverse effects. One of the major challenges in drug delivery is to get the drug at the place it is needed in the body thereby avoiding potential side effects to non-diseased organs. This is especially challenging in cancer treatment where the tumor may be localized as distinct metastases in various organs. The non-restricted cytotoxicity of chemotherapeutics thus limits the full use of their therapeutic potential. Local drug delivery or drug targeting results in increased local drug concentrations and provides strategies for more specific therapy. Nanoparticles have specific particles as tools to enable these strategies. These include benefits such as their small size which allows penetration of cell membranes, binding and stabilization of proteins, and lysosomal escape after endocytosis. Various nanotechnology platforms like fullerenes, nanotubes, quantum dots, nanopores, dendrimers, liposomes, magnetic nano-probes and radio controlled nanoparticles are being developed.

The major factors influencing the treatment outcome in a patient are the efficacy and safety profile of the drug more so when used for cancer chemotherapy. Conventional drugs have poor cell specificity and high toxicity like bone marrow suppression, gastric erosion, hair loss, renal toxicity, cardiomyopathy, and several effects on other systems.

Nanoparticle formulation of wortmanin decreased toxicity, increased stability, solubility and effectiveness. Additionally, nanoparticle wortmanin can improve the efficacy of radiotherapy dramatically and is more effective than the most commonly utilized chemotherapeutics. Development of newer drug delivery systems based on nanotechnology methods is being tried for conditions like cancer, diabetes, fungal infections, viral infections and gene therapy. The main advantages of this modality of treatment are targeting of the drug and enhanced safety profile.

The recent successes of nanoparticle therapeutics have raised the interest of academic and industry investigators in the field of nanomedicine. There is an increasing momentum in the pace of discovery, which has resulted in the development of

Figure 2. The diagram demonstrates one of the primary issues associated with poorly water-soluble molecules whose bioavailability is dissolution-rate limited. On the left, large drug particles cannot adequately dissolve, which results in the inability to be absorbed. On the right, nanometer drug particles are rapidly dissolved during transit through the gut, thus maximizing absorption and improving bioavailability.



more complex nanoparticle systems over the past decade. These include increasing numbers of nanoscale vehicles like Liposomes, Niosomes, Microemulsions, Transfersomes, Lipidemulsions, Transfersomes, Solidlipidnanoparticles and Nanolipid carriers with distinct chemical, physical, and biological properties for a myriad of clinical indications (Farokhzad, 2006).

Photodynamic cancer therapy is based on the destruction of the cancer cells by laser generated atomic oxygen, which is cytotoxic. A greater quantity of a special dye that is used to generate the atomic oxygen is taken in by the cancer cells when compared with a healthy tissue. Hence, only the cancer cells are destroyed then exposed to a laser radiation. Unfortunately, the remaining dye molecules migrate to the skin and the eyes and make the patient very sensitive to the daylight exposure. This effect can last for up to six weeks. To avoid this side effect, the hydrophobic version of the dye molecule was enclosed inside a porous nanoparticle(Roy, 2003). The dye stayed trapped inside the Ormosil nanoparticle and did not spread to the other parts of the body. At the same time, its oxygen generating ability has not been affected and the pore size of about 1 nm freely allowed for the oxygen to diffuse out.

Nanotechnology heralds "a revolutionary time in oncology". The continued development of cancer nanotechnology holds the promise for personalized oncology in which genetic and protein biomarkers can be used to diagnose and treat cancer based on the molecular profile of each individual patient. Conventional strategies for cancer intervention include surgery, chemotherapy, and radiation therapy. Nanotechnology is being actively studied for treatment and diagnosis of several cancers (Chattopadhyay 2010; Huang 2006). The most well-studied nanoparticles include Gold nanoparticles (Huang et al., 2006), quantum dots (Cai et al., 2006, 2007b), carbon nanotubes (Liu et al., 2011), paramagnetic nanoparticles (Thorek et al., 2006), liposomes (Park et al., 2004) and many others (Ferrari, 2005; Grodzinski et al., 2006).

Liposomes

Liposomes discovered in mid 1960s were the original models of nanoscale drug delivery devices. They are spherical nanoparticles made of lipid bilayer membranes with an aqueous interior but can be unilamellar with a single lamella of membrane or multilamellar with multiple membranes.They can be used as effective drug delivery systems.

Cancer chemotherapeutic drugs and other toxic drugs like amphotericin and hamycin, when used as liposomal drugs produce much better efficacy and safety as compared to conventional preparations. These liposomes can be loaded with drugs either in the aqueous compartment or in the lipid membrane. Usually water soluble drugs are loaded in aqueous compartment and lipid soluble drugs are incorporated in the liposomal membrane (Gregoriadis et al., 1972). The major limitation of lipo-

Figure 3. Pictorial representation of different nanoparticles

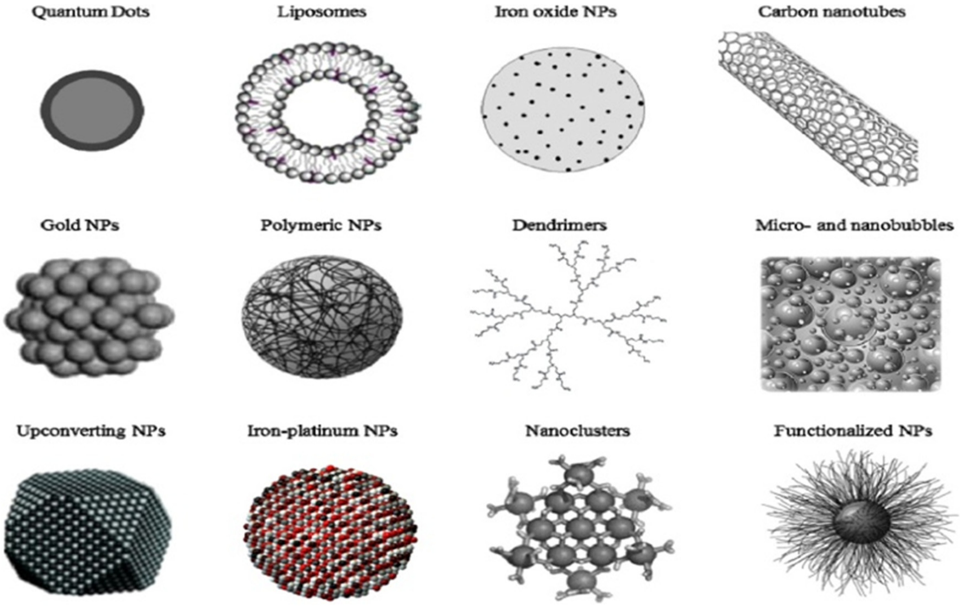
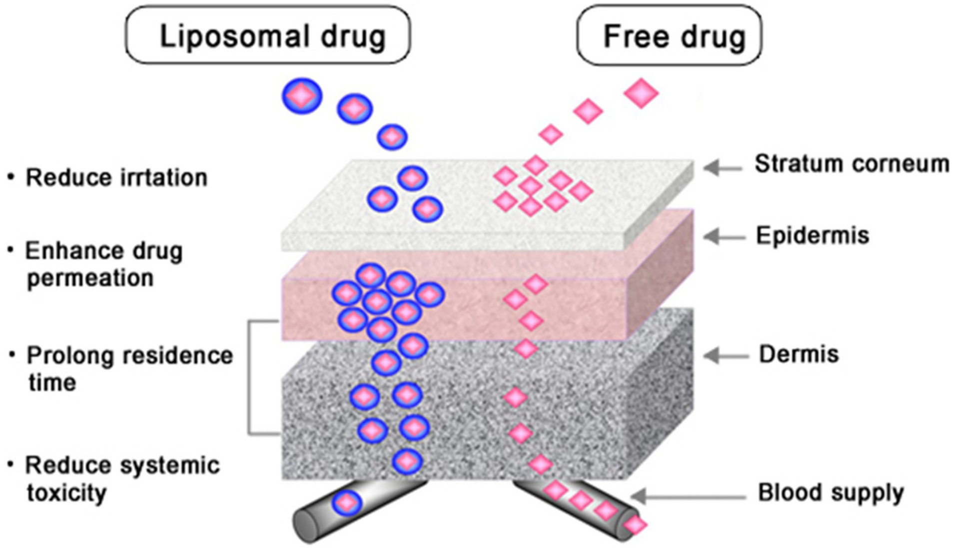


Figure 4. The diagram showing the comparison between the liposomal drug and free drug



some is its rapid degradation and clearance by the liver macrophages (McCormack et al., 1994), thus reducing the duration of action of the drug it carries. This can be reduced to a certain extent with the advent of stealth liposomes where the liposomes are coated with materials like polyoxyethylene (Illum, 1984) which prevents opsonisation of the liposome and their uptake by macrophages (Senior et al., 1991). Other ways of prolonging the circulation time of liposomes are incorporation of substances like cholesterol (Kirby, 1983),polyvinylpyrollidone polyacrylamide lipids (Torchilin, 1994) and high transition temperature phospholipids distearoylphosphatidylcholine

Gold Nanoparticles (GNPs)

In order to focus this Perspective, we highlight one chemical type of nanoparticle: gold. Bulk gold is well known to be "safe" and chemically inert, and gold-based compounds have been used in the clinic as anti-inflammatory agents to treat rheumatoid arthritis (Auranofin and Tauredon) (Finkelstein et al., 1976). Furthermore, radioactive gold microparticles have been effectively used in local radioisotope cancer therapy (Metz et al., 1982). Nanoscale gold particles show great potential as photothermal therapy agents and as imaging agents in living systems, In most of these imaging and therapeutic applications, the gold particles are ~5 nm or larger. At sizes larger than ~5 nm, the general assumption is that gold is chemically inert like the bulk. However, the chemical reactivity of gold particles for diameters less than 3 nm is most likely different than both organogold complexes (Turner et al. 2008) and larger gold nanoparticles (Tsoli et al., 2005). These properties are of clinical significance and contribute to the popularity of gold nanorods and other anisotropic shapes for biomedical therapeutic/imaging agents (Jain et al., 2008; Lal et al., 2008; Murphy et al., 2008b; Skrabalak et al., 2008).The strong light extinction (absorption and scattering) of gold nanorods has been employed in various biomedical imaging applications. For example, strong optical absorption of gold nanorods (at $\lambda = 757$ nm) was used to detect them in mouse tissue (4 cm depth) using an optoacoustic method (Eghtedari et al., 2007).

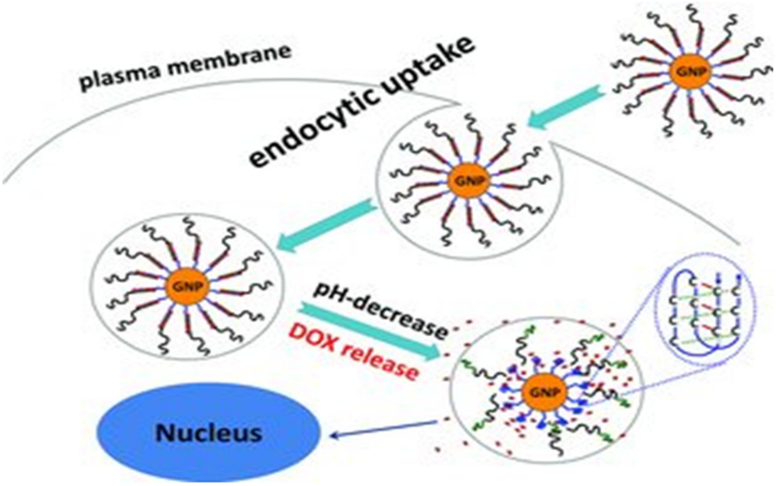
Common oxidation states of gold include +1 (Au (I) or aurous compounds) and +3 (Au (III) or auric compounds). GNPs, however, exist in a non-oxidized state (Au (0)). GNPs are not new; in the 19th century, Michael Faraday (1857) published the first scientific paper on GNP synthesis, describing the production of colloidal gold by the reduction of aurochloric acid by phosphorous. In the late 20th century, techniques including transmission electron microscopy (TEM) and atomic force microscopy (AFM) enabled direct imaging of GNPs, and control of properties such as size and surface coating was refined Common methods of GNP production include citrate reduction of Au (III) derivatives such as aurochloric acid

(HAuCl4) in water to Au (0) and the Brust–Schiffrin method, which uses two-phase synthesis and stabilization by thiols (Brust 1994). In recent years there has been an explosion in GNP research, with a rapid increase in GNP publications in diverse fields including imaging, bioengineering and molecular biology. It is probable that this relates to a similar increase in the broader field of nanotechnology, increased governmental awareness and funding, and rapid progress in chemical synthesis and molecular biology (Chen, 2008). There is intense interest in modifying existing drugs to improve pharmacokinetics, thereby reducing non-specific side effects and enabling higher dose delivery to target tissues. An important demonstration of the potential of multifunctional GNPs for drug delivery was the use of 5-nm GNPs as a delivery vehicle, covalently bound to Cetuximab, as an active targeting agent and Gemcitabine as a therapeutic payload in pancreatic cancer (Patra, 2010). The epidermal growth factor receptor (EGFR) is overexpressed in up to 60% of pancreatic cancers and the combination of cetuximab and gemcitabine has been investigated in Phase II trials of this disease (Kullmann 2009). Patra et al.,(2008) demonstrated that high intratumoural gold concentrations (4500 $\mu g\ g\text{-}^{21}$) could be achieved using this approach compared with 600 $\mu gg\text{-}^{21}$ with untargeted GNPs with minimal accumulation in the liver or kidney. The GNP–cetuximab– gemcitabine nano-complex was superior to any of the agents alone or in combination *in vitro* and *in vivo*. Low doses of complex gemcitabine (2$\mu g\ kg^{-1}$) led to 80% tumor growth inhibition in an orthotropic pancreatic cancer model compared with 30% inhibition using the non-conjugated agents in combination (Patra, 2008).

Gold nanoparticles (AuNPs) have gained attention in the last years due to the unique structural, electronic, magnetic, optical, and catalytic properties which have made them a very attractive material for biosensor systems and bioassays. The combination of biomolecules with AuNPs provides interesting tools for several biological components. Oligonucleotide functionalized AuNPs have become the basis for an increasing number of diagnostic applications that compete with molecular fluorophores in certain settings (Lytton-Jean et al., 2005). Due to their excellent biocompatibility, AuNPs are also finding increasing application as enzyme enhancers, (Ambrosi,2007). Nano scale building blocks, and immuno-histochemical probes (Ackerson, 2006; Stoeva, 2006).

Gold nanoparticles have been investigated in diverse areas such as *in vitro* assays, *in vitro* and *in vivo* imaging, cancer therapy, and drug delivery. Oligonucleotide-capped gold nanoparticles have been reported for polynucleotide or protein (such as p^{53}, a tumor suppressor gene) detection using various detection/characterization methods such as atomic force microscopy (AFM) (Han et al., 2000; Jin et al., 2007). Many paramagnetic nanoparticles have been used for magnetic resonance (MR) imaging, both preclinically and clinically (de Roos et al., 1988; Thorek et al., 2006). Recently, Au3Cu1 nanoshells were reported to be capable of enhancing the contract

Figure 5. Gold nanoparticles uptake



of blood vessels in vivo, which suggested their potential use in MR angiography as blood-pool agents (Su et al., 2007). However, due to the low sensitivity of MR imaging, a dose-dependent toxic effect of the Nanoshells was observed: 17% of the mice died at a dose of 20 mg/kg.

GNPs in Photothermal Therapy for the Destruction of Cancer Cells

Taking advantage of their unique properties, most studies of gold nanoparticle-based cancer therapy have used photothermal therapy for the destruction of cancer cells or tumor tissue, which may be potentially useful in the clinical setting. When irradiated with focused laser pulses of suitable wavelength, targeted gold nanospheres, nanorods, nanoshells, and nano-cages can kill bacteria (Zharov et al., 2006a) and cancer cells (Loo et al., 2005b; Huang et al., 2006a, 2006b, 2007c; Chen et al., 2007a; Tong et al., 2007). It was estimated that 70–80 °C was achieved through light absorption by the gold nanoparticles (Huang et al., 2006b) and up to 150 antibodies can be conjugated to a nano-shell through a bi-functional PEG linker (Lowery et al., 2006). One intriguing observation is that most of these studies targeted either EGFR or human epidermal growth factor receptor 2 (HER2), obviously due to the ready availability of monoclonal antibodies (already approved by the Food and Drug Administration (FDA) for cancer therapy), that recognize these two proteins. Since the absorbance wavelength (in the visible range) of small gold nanospheres is not optimal for *in vivo* applications, the assembly of gold nano-clusters on the cell membrane was investigated (Zharov et al., 2005). It was found that the formation of nano-clusters led to increased local absorption and red-shifting, compared to cells that did not have nano-clusters. Significant enhancement in laser-induced cancer cell killing was observed using anNear-infrared (NIR) laser. Gold nanoshells are sufficiently large (about 100–300 nm in diameter) to have surface plasmon resonance (SPR) peaks in the NIR region. In one pioneering study, human breast carcinoma cells incubated with gold nanoshells were found to undergo photo-thermally induced morbidity upon exposure to NIR light (Hirsch et al., 2003b). *In vivo* testing revealed that exposure to low dose NIR light in solid tumors treated with gold nanoshells resulted in significant average temperature increase, capable of inducing irreversible tissue damage, while the controls (not treated with nanoshells) exhibited much lower average temperature when exposed to NIR light and appeared undamaged (Hirsch et al., 2003b). In a recent report, it was suggested that 5000 gold nanoshells per prostate cancer cell was needed to achieve cell death (Stern et al., 2007). The cytotoxicity of gold nanoparticles has been correlated with a detailed study of their endocytic uptake using various microscopy tools such as atomic force microscopy (AFM), confocal-laser-scanning microscopy (CFLSM), and transmission electron microscopy (TEM). It has been suggested that Au(0) nanoparticles are not cytotoxic, reduce the production of reactive oxygen, nitrite species, and do not elicit secretion of proinflammatory cytokines TNF-alpha and IL1-beta, making them suitable candidates for nanomedicine. AFM measurements suggest that gold nanoparticles are internalized inside the cell via a mechanism involving pinocytosis, while CFLSM and TEM studies indicate their internalization in lysosomal bodies arranged in perinuclear fashion (Shukla*et al.,* 2005).Studies thus underline the noncytotoxic, nonimmunogenic, and biocompatible properties of gold nanoparticles with the potential for application in nanoimmunology, nanomedicine, and nanobiotechnology.

In another study, 93% of tumor necrosis and regression was observed in a high dose nano-shell (8.5 µl/g), treated group (Stern et al., 2008). Surprisingly, a slightly lower nano-shell dose (7.0 µl/g) only resulted in tumor growth arrest at 21 days but not tumor ablation. The reason why such a subtle difference in nano-shell dose could cause dramatically different therapeutic efficacy deserves careful investigation. It is worth noting that all these in vivo cancer therapy studies only involve passive tumor targeting but not specific molecular targeting. Passive tumor targeting is due to the non-specific c accumulation of the nanoshells in the tumor, termed “the enhanced permeability and retention (EPR) effect”, since the tumor vasculature is usually moreleaky than normal blood vessels and there is no lymphatic drainage in the tumor (Maeda et al., 2000). Gold nanoparticles have been shown to enhance the anti-proliferation and apoptosis of human hepatoma cells induced by Paclitaxel, a chemotherapeutic drug of radio sensitivity can be achieved due to the increased absorption of ionizing radiation by the gold nanoparticles, which in turn caused breaks in single- and double-stranded DNA (Zheng et al., 2008). Although it was proposed that targeting the DNA of cancer cells with gold nanoparticles may offer a novel approach that is generally applicable to external beam radiotherapy treatments, achieving DNA targeting in vivo is extremely difficult.

Gold Nanoparticle and Breast Cancer

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen. ROS form as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis.Breast cancer is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Cancers originating from ducts are known as ductal carcinomas, while those originating from lobules are known as lobular carcinomas. Breast cancer occurs in humans and other mammals. While the overwhelming majority of human cases are in women.Breast cancer is a commonly diagnosed cancer among women in the United States. It is estimated that 230,480 women were diagnosed with breast cancer and 39,520 women died in 2011 in the United States (Siegel, 2011). Designing a feasible targeted drug delivery system for cancer is important to improve patient compliance. This could be achieved by surface functionalized gold nanoparticles based drug delivery which has high affinity toward specific cancer cells than normal cells (Llevot, 2012; Dykman, 2012). Preparation of gold nanoparticles can be attained through diverse methods. Most of the nanoparticles synthesized by chemical methods involve toxic chemicals that may affect the environment in addition to human health. Hence, plant-based biological synthesis of gold nanoparticles is gaining importance due to its low cost, high reproducibility and eco-friendliness. Using plants for synthesis of AuNPs could be advantageous over other ecofriendly biological methods which involve elaborate process of purification (Iravani, 2011). PAuNPs have been used for many biomedical applications like thermal cancer therapy for destruction of cancer cells(Nam, 2009), radiofrequency therapy for destruction of cancer cells, therapy for angiogenesis (Kalishwaralal, 2011), drug delivery for cancer (Brown, 2010; Bhattacharyya, 2011; Eghtedari, 2009; Ganeshkumar,2012), breast cancer cell diagnosis (Lu, 2010; Hainfeld, 2011), hyperthermia therapy (Kennedy, 2011). Pomegranate peels are one of the most valuable by-products of the food industry, *Punicagranatum*, tamil name *maadulam pazham* peel extract has been reported to have antioxidant, antimicrobial activities and has high chemopreventive potential for skin, colon, prostate, lung cancer and also used as adjuvant therapy for human breast cancer (Syed, 2007).

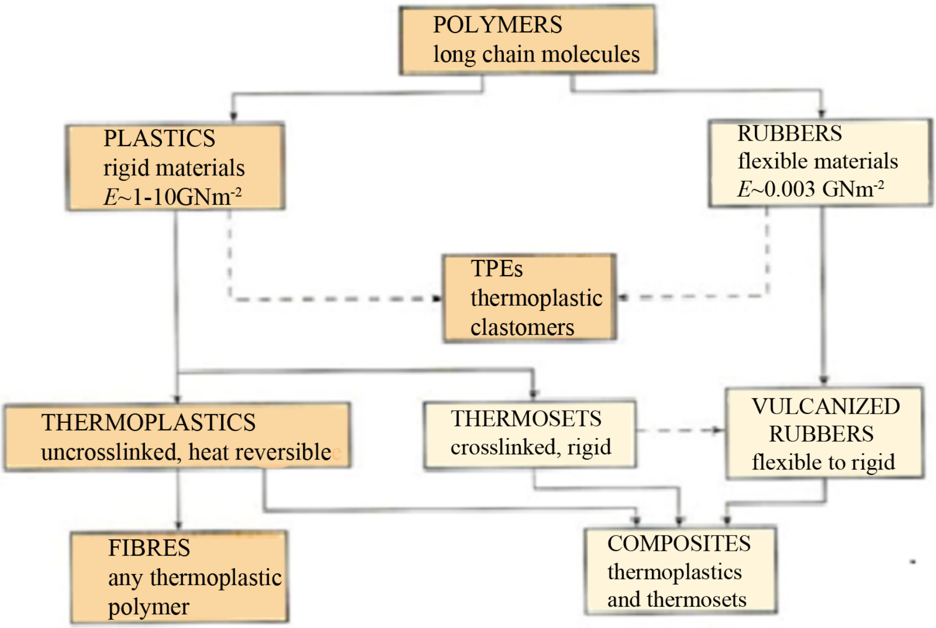
Reactive oxygen species (ROS), a specific type of oxygen-containing reactive molecules, play important roles in various cellular processes, and are known to be essential for cell proliferation at basal levels (Burdon, 1995). At sufficiently high concentrations, however, ROS could become cytotoxic, often entailing cellular necrosis or apoptosis (Fiers, 2000; Mat, 2008), an effect that is frequently utilized for various therapeutic applications. Radiation therapy (Coia, 1998), i.e. the use of ionizing radiation for treating local malignancies, could damage cells either directly, by ionizing DNA and other cellular molecules, or indirectly, through the production of high levels of ROS that lead to high cytotoxicity, it has been shown that the use of ROS scavengers could greatly reduce the drug's effect (Bragado, 2007;Ikeda, 1999). ROS also plays a key role in photodynamic therapy (PDT), where the activation of a photosensitizer by light initiates a chemical chain reaction which results in local ROS formation (Lee, 2008; Celli, 2010). In the last decade, several research groups have proposed the use of specifically targeted noble-metal nanoparticles irradiated by laser light as an effective therapeutic tool for treating various malignancies with minimum collateral damage to healthy tissue (Hirsch, 2003; O'Neal, 2004; El-Sayed, 2006; Huang, 2008). Gold nanoparticle-mediated photothermal therapy apply continuous wave (O'Neal, 2004;Terentyuk,2009; Krpeticc, 2010; Raji, 2011) and pulse laser irradiation to induce cellular damage either via extensive temperature rise or through rapid nanoparticle heating and the subsequent release of the energy in the form of small shock waves(Pustovalov, 2008;Huff, 2007; Minai, 2012;Volkov,2011).

Polymeric Nanoparticles

Polymeric nanoparticles have been extensively researched as delivery systems of different active components such as anticancer drugs, vitamins, proteins, peptides, and others (Chiellini, 2006; Rawat, 2006). The advantages are numerous. Polymeric nanoparticles protect the drug against degradation while releasing it in a controlled manner which translates into lower toxicity and less side effects. Also, drug targeting can be achieved by surface attachment of moieties of specific interaction with the target (i.e., proteins, peptides, folic acid, and lectins) (Agarwal, 2008; Zhao, 2008). Despite these advantages, polymeric nanoparticles, in and of themselves, do not provide any benefit in the treatment of disease, but rather, they act as carriers for the drug. Nanoparticles with inherent properties, such as antioxidant activity, could be useful in treating oxidative-stress related diseases such as atherosclerosis and cancer, in addition to playing their obvious role as vehicles for drug transport and delivery. Antioxidant nanoparticles with promising characteristics for the treatment of diseases related with oxidative damage have been built already. The current approach is mainly based on the entrapment of an antioxidant agent into the polymeric matrix to be protected and transported by the bloodstream. The antioxidant action is due to the release of the antioxidant agent entrapped in the polymeric matrix. In general, better antioxidant action is seen when the antioxidant is entrapped in a polymeric matrix relative to other modes of delivery.

Antioxidant nanoparticles with promising characteristics for the treatment of diseases related with oxidative damage have been built. For example, Superoxide dismutase(SOD)entrapped in poly(lactic-co-glycolic) acid (PLGA) nanoparticles were able to provide better protection to human neurons (100% cell survival for 6 h) compared to SOD in solution (25% cell survival) and pegylated SOD Polyethylene glycol (PEG-SOD) (40% cell survival) at a SOD dose of 100 U or higher (Reddy, 2008). Another study showed that entrapped melatonin in poly- (methacrylic acid-co-methyl methacrylate) nanoparticles had better antioxidant protection compared with melatonin in solution at doses of 1 mg/kg and 10 mg/kg (Schaffazick, 2008). The entrapment of catalase (an enzyme that dissociates hydrogen peroxide into water and oxygen) into poly(ethylene glycol (PEG) nano-carriers (spheres and filaments) by double emulsion was performed by Simone et al., (2009), with the purpose of promoting its resistance to proteases attack for an enhanced catalase activity. The catalase entrapped in nanoparticles was more resistant to proteases attack (Simone, 2009). Besides entrapping an antioxidant in polymeric nanoparticles, nanoparticle systems of intrinsic antioxidant properties could be built by virtue of

Figure 6. Classification polymeric nanoparticles



covalently linking an antioxidant to the nanoparticle or by attaching an antioxidant agent to inorganic nanoparticles (Williams et al., 2009), conjugated PEG with glutathione (scavenger of hydroxyl radicals, superoxide radicals, singlet oxygen) to form self-assembled nanoparticles and showed that the glutathionePEG nanoparticle protected the human brain neuroblastoma cells against oxidative damage at comparable levels with free glutathione (Williams et al., 2009). Another approach used. was to synthesize surface-functionalized gold nanoparticles with synthetic antioxidant Trolox (water soluble vitamin E analogue).

Nanoshells

Nanometer range spherical cores of particular semiconductor compounds surrounded by an ultra thin metal shell that is commonly made of gold or silver. This configuration gives the nanoshells highly tunable optical properties these nanoshells involve a quasiparticle called plasmon which is a collective excitation or quantum plasma oscillation where the electrons simultaneously oscillate with respect to all the ions. They have potential in biomedicine for diagnosis and therapy. This technology is being evaluated for cancer therapy, nanoshells which are tuned to absorb infrared rays when exposed from a source outside the body to demonstrate the thermo ablative property of nanoshells(Hirsch et al., 2003). The nanoshells when exposed to NIR region of the electromagnetic spectrum get heated and cause destruction of the tissue. This has been studied in both *in vitro* and *in vivo* experiments with HER 2 expressing SK-BR-3 human breast carcinoma cells. The control cells did not lose their viability even after treatment with nano-shells with non -specific anti IgG or PEG and NIR ablation (Lowery et al., 2006).

Quantum Dots

Quantum dots are small devices that contain a tiny droplet of free electrons. QDs are colloidal semiconductor nanocrystals ranging from 2 to 10 nm in diameter. QDs can be synthesized from various types of semiconductor materials via colloidal synthesis or electrochemistry. A quantum dot is a particle of matter so small that the addition or removal of an electron changes its properties in some useful way. All atom s are, of course, quantum dots, but multi-molecular combinations can have this characteristic. In nanotechnology, they are called quantum bits or qubits. Quantum dots typically have dimensions measured in nanometers, where one nanometer is 10^{-9} meter or a millionth of a millimeter. Applications for quantum dots in transistors, solar cells, LEDs, and diode lasers. Quantum dots as agents for medical imaging and as possible qubits in quantum computing Quantum dots are semiconductors whose electronic characteristics are closely related to the size and shape of the individual crystal. Size and band gap are inversely related in quantum dots. The biomolecule conjugation of the quantum dots can be modulated to target various biomarkers (Iga et al.,2006). Quantum dots can be used for biomedical purposes as a diagnostic as well as therapeutic tool. These can be tagged with biomolecules and used as highly sensitive probes. A study done on prostate cancer developed in nude mice has shown accumulation of quantum dots probe by enhanced permeability and retention as well as by antibody directed targeting (Gao, 2004). The quantum dots conjugated with polyethylene glycol (PEG) and antibody to prostate specific membrane antigen (PSMA) were accumulated and retained in the grafted tumour tissue in the mouse (Gao, 2004). Quantum dots can also be used for imaging of sentinel node in cancer patients for tumour staging and planning of therapy. This method can be adopted for various malignancies like melanoma, breast, lung and gastrointestinal tumours (Iga et al., 2006).

Nanotubes

A nanotube is a nanometer-scale tube-like structure. It may refer to Carbon nanotube, Silicon nanotube, Boron nitride nanotube, Inorganic nanotube, DNA nanotube and Membrane nanotub**e** - a tubular membrane connection between cells a sequence of nanoscale C60 atoms arranged in a long thin cylindrical structure. Nanotubes are extremely strong mechanically and very pure conductors of electric current. Applications of the nanotube in nanotechnology include resistors, capacitors, inductors, diodes and transistors.

Cell specificity can be achieved by conjugating antibodies to carbon nanotubes with fluorescent or radiolabelling (McDevitt et al., 2007). Entry of nanotubes into the cell may be mediated by endocytosis or by insertion through the cell membrane. Carbon nanotubes can be made more soluble by incorporation of carboxylic or ammonium groups to their structure and can be used for the transport of peptides, nucleic acids and other drug molecules. Indium-111 radionuclide labeled carbon nanotubes are being investigated for killing cancer cells selectively (Reilly et al., 2007).

Polymer–Drug Conjugates

Another extensively studied nanoparticle drug delivery platform currently in clinical practice is polymer–drug conjugates (Duncan et al., 2006). Small-molecule therapeutic agents, especially anticancer chemotherapeutic agents, usually have two unfavorable properties: short circulation half-life, which leads to frequent administrations, and non-site-specific targeting, resulting in undesired systemic side effects. The conjugation of small-molecule drugs to polymeric nano-carriers can improve the undesirable adverse effects. Polymer– drug conjugates not only prolong the *in vivo* circulation time from several minutes to several hours, but also reduce cellular uptake to the endocytic route. This enhances the passive delivery of drugs to tissues with leaky blood vessels, such as tumors and atherosclerotic plaques (Tanaka, 2004; Deguchi, 2006).

PEGylated Drugs

It can enhance the plasma stability and solubility of the drug while reducing its immunogenicity. Today, there are six examples of PEGylated drugs in clinical practice. For example, Adagen (PEG–adenosine deaminase) is used to treat immunodeficiency disease; Macugen (PEG–anti-vascular endothelial growth factor aptamer) is used to treat agerelated macular degeneration; Pegasys (PEG–a-interferon 2a) is used to treat hepatitis B and hepatitis C; and Oncaspar (PEG–L-asparaginase) is used to treat acute lymphoblastic leukemia. Besides PEG, other linear polymers such as polyglutamic acid, polysaccharide, and poly (allylamine hydrochloride) have also been harnessed as polymeric drug delivery carriers.

Other macromolecule–drug conjugates or adducts that have a hydrodynamic size of 5–200 nm have also been developed as drug carriers. One example is Abraxane, a 130-nm albumin-bound paclitaxel drug that was approved by the FDA in 2005 as a second-line treatment for patients with breast cancer (Harries, 2005).

N-(2-Hydroxypropyl) Methacrylamide (HPMA)

Another attractive polymer that has been employed to formulate polymer–drug conjugates is N-(2-hydroxypropyl) methacrylamide (HPMA). HPMA is a linear hydrophilic polymer with functionalizable side chains that can be activated to enable drug attachment or conjugation with targeting ligands. By conjugating small hydrophobic drugs such as paclitaxel to an HPMA polymer, drug water-solubility is highly improved. This makes drug formulation and patient administration easier. In addition, HPMA is biodegradable and non-immunogenic. Owing to these desirable attributes, a number of HPMA products have been developed and are currently in clinical trials. Examples include ProLindac (HPMA copolymer–diaminocyclohexane palatinate) in clinical phase II for treating recurrent ovarian cancer, FCE28069 (HMPA copolymer–doxorubicin-galactosamine) in phase II for hepatocellular carcinoma, and PNU166945 (HPMA copolymer–paclitaxel) in phase I to document its toxicity and pharmacokinetics for treating refractory solid tumors.

Nanomedicine and Clinical Trials

Nano-medical research remains relatively immature and the full clinical impact is not yet known. Many new nano-complexes are being developed for cancer therapy and there is a need to translate these products to clinical trials in a timely but safe manner. The Nanotechnology Characterisation Laboratory (NCL) was formed in 2004 by a formal collaboration between three US federal organizations: the National Cancer Institute, the US Food and Drug Administration and the National Institute of Standards and Technology (Stern 2010). It performs and standardizes the pre-clinical characterization of nano-materials intended for cancer therapeutics. The NCL will perform physicochemical *in vitro* and *in vivo* characterization and has tested over 180 nano-materials to date. The first GNP therapy to have reached early-phase clinical trials is CYT-6091, 27-nm citrate-coated GNPs bound with thiolated PEG and tumor necrosis factor-a (TNF-a) (Aurimmune; CytImmune Sciences, Rockville, MD), which has the dual effect of increasing tumor targeting and tumor toxicity (Libutti 2009). TNF-ais a multifunctional cytokine known to be both cytotoxic and immuno-modulatory. Previous clinical trials of TNF-α demonstrated dose-limiting toxicity of hypotension and nausea at concentrations of 225 μgm^{-2}, which limited more widespread clinical use (Schiller, 1991). Despite the rapid increase of GNP publications in recent years and an increasing number of *in vivo* studies investigating the uptake and distribution of GNPs, there remains a paucity of studies of *in vivo* radiosensitization with GNPs. These studies will be critical for successful translation of this approach to the clinic. 1.9 nm GNPs (Aurovist) in combination with 250 kVp radiations were shown to prolong survival in tumor bearing mice (Hainfeld, 2004). A study investigated 5-nm GNPs coated with gadolinium(Gd) in mice bearing MC7-L1 murine breast cancer cells (Hebert, 2008).

In the past decade, nanomedicine, owing to the unique advantages of nanoparticles over small molecules, has offered new strategies for cancer treatment. In clinical studies, some commercially available nano-medicines such as Doxil (100 nm) and Abraxane (130 nm) have been shown to significantly reduce the side effects of the delivered drug due to the long circulation time and altered bio-distribution of the particles. However, the therapeutic index increased to some extent because of limited drug delivery into the tumor tissue (Gradishar,2005; Torchilin, 2005). The tumor microenvironment is structurally heterogeneous, containing for example clusters of tumor cells, non-uniform leaky vasculature, and a dense interstitial structure. This environment hinders the effective delivery of nanoparticles into tumors, especially into regions distant from the vasculature (Minchinton, 2006; Mikhail, 2009) overcoming these physiological barriers are a major challenge for the field of nanoparticle research. Generally, the physical, chemical, and biological properties of nanoparticles affect the delivery capacity in different ways. Positively charged nanoparticles improve the delivery of payloads to the cells, whereas negatively charged nanoparticles diffuse more quickly, thereby delivering drugs into deep tissues (Kim,2010).It has been shown that nanorods penetrate tumors more rapidly than Nano spheres due to improved transportation through pores. Another study demonstrated significantly increased penetration (up to 100 nm) by collagenase-coated nanoparticles, owing to degradation of collagen in the extracellular matrix (Goodman, 2007). Decreasing the nanoparticle size may improve the delivery efficiency in tumor tissue (Kim, 2010; Cabral, 2011; Wong, 2011).

Gold and silver nanoparticles (2100 nm) coated with Herceptin (mAb) regulated membrane receptor internalization in monolayer cells (Jiang, 2008) In recent years, colloidal chemistry and nano-science have made great steps forward due to significant improvements in the controlled synthesis of nanostructures of different sizes for biomedical application However, the exact effects of ultrasmall nanoparticles on tumor penetration are still not well understood. It was shown that 2 nm AuNPs significantly improved the delivery of therapeutic peptides and targeted peptides into cancer cells. These ultra-small functional nanoparticles showed high efficacy for cancer treatment (Kumar, 2012). Therefore, smaller nanoparticles (those less than 10 nm) would have special advantages in terms of tumor penetration over larger nanoparticles. Colloidal gold nanoparticles have great potential to overcome delivery limitations because of their biocompatibility, low toxicity, small size, and tunable surface functionalities (Duncan, 2010). The first clinical trial of gold nanoparticle related nano-medicine, CYT-6091, is comprised of recombinant human tumor necrosis factor alpha (rhTNF) bound to the surface of PEGylated 27 nm colloidal gold nanoparticles (Paciotti, 2004) and a phase I clinical trial in patients with advanced stage solid cancers showed the accumulation of gold nanoparticle in tumor tissue (Libutti, 2010). In addition, gold nanoparticles have been identified as promising candidates for delivery of various payloads such as drugs(Zhao, 2010; Wang, 2007) proteins or peptides (Kumar, 2012;Shaw, 2012) and nucleic acids. Synthesis of gold nanoparticles can be controlled to obtain nanoparticles with a wide range of sizes (Kumar, 2012; Duncan, 2010). In a study small AuNPs that have tunable sizes from 2 to 15 nm with identical surface coatings and charge were systematically evaluated the size-dependent localization and penetration of 15 nm spherical gold nanoparticles in monolayer breast cancer cells, a MCF-7 tumor spheroid model, and *in vivo* tumor tissue in mice (Torchilin, 2005; Chauhan, 2011). *Ex vivo* multicellular models have become the most commonly used tools to evaluate drug or nanoparticle penetration into tumors. A breast tumor spheroid model system was established to compare the size-dependent effects and penetration behaviors of 215 nm spherical gold Nanoparticles.

Advantages and Disadvantages of Nano-Drugs

The use of materials in nanoscale provides unparalleled freedom to modify fundamental properties such as solubility, diffusivity, blood circulation half-life, drug release characteristics, and immunogenicity. In the last two decades, a number of nanoparticle-based therapeutic and diagnostic agents have been developed for the treatment of cancer, diabetes, pain, asthma, allergy, infections, and soon.

It improves the solubility of poorly water-soluble drugs, prolongs the half-life of drug systemic circulation by reducing immunogenicity, releases drugs at a sustained rate or in an environmentally responsive manner and thus lowers the frequency of administration, delivers drugs in a target manner to minimize systemic side effects, and delivers two or more drugs simultaneously for combination therapy to generate a synergistic effect and suppress drug resistance. As a result, a few pioneering nanoparticle-based therapeutic products have been introduced into the pharmaceutical market and numerous ensuing products are currently under clinical testing or are entering the pipeline.

Disadvantages of nanotechnology include the potential for mass poisoning over a period of time. While nano-science can produce all kinds of new and improved products, the particles that are created are so incredibly small that they may very well cause eventual health problems in the consumers that use them. Since almost everyone uses a product that has been touched by nanotechnology it is possible that the eventual health effects could be large scale. Mass poisoning could only happen if the coatings that nanotechnology has the potential to produce include poisonous micro-particles that can cross over into the brain. There is a barrier between the blood stream and the brain known as the blood—brain barrier. Coating all of our products with particles that are small enough to cross over this barrier runs the risk of creating a mass poisoning. Fortunately, the scientists that are able to study nanotechnology have already considered this possibility and there are very strict guidelines that will help detract from this potential risk.

Another potential problem with nanotechnology is the lack of our own knowledge. We know that we can create materials with nanotechnology but we still have to stop and understand the impact of the creation of these products will have on the nanoscale. If we change the structure of material on the nano level without understanding the potential impact on the nanoscale, we risk creating a whole world of materials that have atoms that actually do not fit together cohesively. There are some potential disadvantages of nanotechnology that fall in the realm of both the practical and the ethical. If nanotechnology can help the human body recover from illness or injury then it is quite possible that nanotechnology can create an altered human state. We could potentially be able to create a human race that is engineered and altered to become hyper—intelligent and super strong. The serious complications with such issues include the idea that the scientific technology would only be available to those who can afford it. That would mean there would be an underclass of people; the people we are now. Should nanotechnology actually be able to procure an honest and true molecular manufacturing machine for every household how would the world's economy survive? What would we do with all those jobs that are lost in the manufacturing fields and how would we calculate monetary concerns when it comes to this type of on demand manufacturing?

There is a host of potential weaponry that could be produced on a molecular level. For any scientist, the potential to engineer diseases and create lethal weaponry that can't even be seen is an ethical quagmire. Even more distressing is whether or not other countries that have nanotechnology capabilities will create these weapons. While it sounds as though the disadvantages of nanotechnology will be the end of the world, this is not really the case. With all the good any science can do, there is always the capability of engineering evil potential. There is a system of checks and balances in place to help prevent the mishandling of scientific research and capabilities.

FUTURE PERSPECTIVES IN NANOMEDICINE AND CONCLUSION

Understanding how nano-materials affect live cell functions, controlling such effects, and using them for disease therapeutics are now the principal aims and most challenging aspects of nano-biotechnology and nanomedicine. Gold nanoparticles (AuNPs), nanorods, and nanoshells with unique properties have been shown to be of potential use in anticancer drug delivery systems and photothermal cancer treatment agents (El-Sayed,2001**;** Daniel, 2004;Hirsch 2003). Although such applications have shown promising potential in cancer treatment, the fundamental interactions and effects of nano-materials in living systems for the most part still remain unknown. To address these fundamentals, many studies to assess the effect of introducing AuNPs into the cytoplasm of the cell have been done, (Jiang, 2008) yet little is known about the effect of AuNPs at the nucleus of the cell. The cell nucleus functions to maintain all processes that occur within the cell, and any disruptions within the nucleus would subsequently affect the cell's DNA, thereby disturbing the highly regulated cell cycle. Here we report the use of nuclear targeting of AuNPs to selectively disturb the division of cancer cells by the observation of cytokinesis arrest. Cytokinesis arrest was observed by AuNP dark-field imaging of live cells in real time, which showed binucleate cell formation at late stages of mitosis, leading to the failure of complete cell division. Confocal microscopy, flow cytometry gave evidence that DNA damage, programmed cell death (apoptosis), respectively, accompany the observed cytokinesis arrest (Bin Kang et al., 2010).

Over the past decade, molecular imaging (MI) has provided the possibility of obtaining *in vitro* and *in vivo* physiological and pathological information with high sensitivity and specificity (Weissleder, 2008). The modalities of MI include optical imaging, (van Schooneveld, 2008) computed tomography (CT) imaging, (Guo, 2010) magnetic resonance (MR) imaging, Karfeld-Sulzer, 2010) position emission tomography, (Schindler, 2010) and single photon emission computed tomography (Bhushan, 2008). As two of the important MI technologies, CT and MR afford better resolution than other imaging modalities. They will have more advantages when appropriate MI probes are used. Recent advances in nanotechnology show that multifunctional nanomaterial's can be used as MI probes, which are able to not only carry targeting molecules and drugs to perform targeted diagnosis and therapeutics, (Barreto,2007) but also afford different imaging modalities dependent on the composition of the materials (Louie, 2010). For accurate and self-confirming cancer diagnosis, it is essential to combine dual-mode and multi-mode imaging functionalities within one nanoparticle (NP) system, which can avoid putting additional stress on the body's blood clearance capability via administration of multiple doses of agents.

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KEY TERMS AND DEFINITIONS

Cancer: A broad group of diseases involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, which may invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream.

Gold Nanoparticles: These are commonly produced in a liquid by reducing chloroauric acid. After dissolving the acid, the solution is rapidly mixed along with a reducing agent. This process then causes Au^{3+} ions to be reduced to neutral gold atoms.

Liposomes: They are artificially-prepared spherical vesicle composed of a lipid bilayer. The liposome can be used as a vehicle for administration of nutrients and pharmaceutical drugs.

Nanoshells: Ananoshell, or rather a nanoshellplasmon, is a type of spherical nanoparticle consisting of a dielectric core which is covered by a thin metallic shell (usually gold). These nanoshells involve a quasiparticle called plasmon which is a collective excitation or quantum plasma oscillation where the electrons simultaneously oscillate with respect to all the ions.

Nanotechnology: It is the manipulation of matter on an atomic, molecular, and supramolecular scale. The earliest, widespread description of nanotechnologyreferred to the particular technological goal of precisely manipulating atoms and molecules for fabrication of macroscale products, also now referred to as molecular nanotechnology. A more generalized description of nanotechnology was subsequently established by the National Nanotechnology Initiative, which defines nanotechnology as the manipulation of matter with at least one dimension sized from 1 to 100 nanometers.

Nanotubes: A nanotube is a nanometer-scale tube-like structure. It may refer to:Carbon nanotube, Silicon nanotube, Boron nitride nanotube, Inorganic nanotube, DNA nanotube, Membrane nanotube - a tubular membrane connection between cells.

Photodynamic Therapy: The therapy photosensitizer is excited with specific band light. This activation brings the sensitizer to an excited state where it then releases vibrational energy (heat), which is what kills the targeted cells.

Photothermal Therapy: It refers to efforts to use electromagnetic radiation (most often in infrared wavelengths) for the treatment of various medical conditions, including cancer.

Quantum Dots: A quantum dot is a nanocrystal made of semiconductor materials that are small enough to exhibit quantum mechanical properties. Specifically, its exactions are confined in all three spatial dimensions.

Chapter 8

Nanotechnology in the Food Industry

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ABSTRACT

This chapter addresses the potential application of nanotechnology in various areas of the food industry. Nanotechnology is having an impact on several aspects of the food industry, from product development to packaging processes. Nanotechnology is capable of solving the very complex set of engineering and scientific challenges in the food processing industries. This chapter focuses on exploring the role of nanotechnology in enhancing food stability at the various stages of processing. Research has highlighted the prospective role of nanotechnology use in the food sector, including nanoencapsulation, nanopackaging, nanoemulsions, nanonutraceuticals, and nanoadditives. Industries are developing nanomaterials that will make a difference not only in the taste of food but also in food safety and the health benefits that food delivers. While proposed applications of nanotechnologies are wide and varied, developments are met with some caution as progress may be stifled by lack of governance and potential risks.

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INTRODUCTION

Nanotechnology offers much promise to food science. Food nanotechnology includes a range of potential applications, including alterations to the properties of foods (e.g., nano-additives and nano-ingredients), improvements to the delivery, quality, and safety of food; and the development of enhanced food packaging (i.e., food contact materials). For example, scientists are creating food packages that contain nano-sized particles devised to warn consumers that a food product is unsafe to eat, and are inventing nanoencapsulated materials that can distribute nutrients to human cells. The food industry has been researching how nanoscience can be used to improve food since 1999, and there are signs that the research and development of food nanotechnologies is likely to grow quickly in the coming years. Nanotechnology is expected to influence numerous areas of food science in ways that will benefit both the food industry and consumers. For example, nanotechnology is being used to improve the quality and safety of food. Nano sensors are being developed that can detect and signal the presence of spoilage microorganisms, and potentially even differentiate the presence of pathogenic from benign microorganisms. Nanotechnology is also being used to create healthier foods that can deliver nutrients and medications to different parts of the human body and can alleviate allergenic.

The food and beverage sector is a global multi trillion dollar industry. The major food industries and companies are consistently looking for ways to improve production efficiency, food safety and food characteristics. Extensive research and development projects are ongoing with the ultimate goal of gaining competitive advantage and market share. For an industry where competition is intense and innovation is vital, nanotechnologies have emerged as a potential aid to advances in the production of improved quality food with functionalised properties. Advances in areas such as electronics, computing, data storage, communication and the growing use of integrated devices are likely to indirectly impact the food industry in the areas of food safety, authenticity and waste reduction.

Nanotechnologies involve the manipulation of matter at a very small scale generally between 1 and 100 nanometres. They exploit novel properties and functions that occur in matter at this scale. Nanomaterials and nanoparticles may include any of the following nano forms: nanoparticles, nanotubes, fullerenes, nanofibres, nanowhiskers, nanosheets. A nanoparticle is defined as a discrete entity that has three dimensions of the order of 100 nm or less. A nanomaterial is defined as an “insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nanometres. Nanotubes have a cylindrical lattice arrangement of material; fullerenes have a spherical molecular arrangement; and nanofibres have a length to diameter ratio of at least and are in the nano range. Nanowhiskers are fine fibres in the nano range; they are 5-20 nm in cross-section with lengths of several micrometres. Nanosheets are an arrangement of material where only one dimension is in the nano range. Many of these different nano forms are either in use or under investigation for use within the food industry.

Many common elements and compounds behave differently at the molecular and atomic scales of nanotechnology than they do at larger particle sizes. When discussing properties which change with decreasing size, it is important to distinguish between properties that change smoothly over a series of size reductions and properties that change abruptly below a certain critical size. The abrupt change of properties below a certain size is the key novelty of nanotechnologies. This critical size depends on the property in question and on the material, hence the difficulty with defining an upper size range. Although there are many benefits of these technologies there is also concern over potential negative effects. In the case of particulate nanomaterials coming into contact with the human body by design or by accident, for example, the reduction in particle size associated with nanotechnologies potentially reduces the effectiveness of barriers to the penetration of foreign materials into the human body and to their movement within the body. There is growing concern that the use of nanomaterials in the food industry could result in particulate nanomaterials gaining access to tissues in the human body, resulting in accumulation of toxic contaminants and therefore adversely affecting human health. Many new consumer products containing nanoparticles have been launched to the market and are beginning to impact on the food associated industries. Nanotechnologies are set to impact on the food industry at all stages of production from primary production at farming level, due to advances in pesticide efficacy and delivery (novel formulations and better crop adherence), to processing where emulsion creation and encapsulation have progressed to the nanoscale.

The area of food packaging has seen much innovation in barrier improvement with the use of various nanoscale fillers and this has also resulted in reduced effects of targeted accelerating factors of spoilage and contamination. Intelligent packaging is the new generation of packaging, many of which are in the late development stages, which incorporates sensors and sometimes nanosensors. They can communicate information about the food to the consumer or react to the information and change conditions within the packaging to delay spoilage/ contamination.

The present chapter discusses the several aspects on role of nanotechnology in food industry. The chapter addresses the comprehensive information of current developments in nanotechnology as it applies to food and food related systems, focusing specially on applications which are most likely to enjoy consumer acceptance and regulatory attention in the immediate future. The chapter focus on exploring the current technological innovations role in enhancing food and nutritional availability more at the post-harvest and food processing stages. In addition to covering the technical aspects, the current health implications of the technology are also discussed.

BACKGROUND

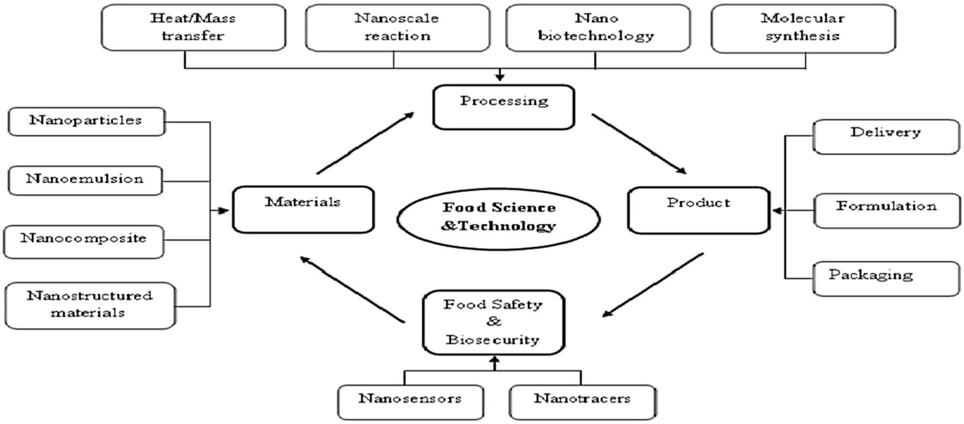
Types of Nanomaterials and Nanostructures

The novel properties of nanomaterials offer many new opportunities for the food industry. Different types of functional nanostructures can be used as building blocks to create novel structures and introduce new functionalities into foods. These include: nanoliposomes, nanoemulsions, nanoparticles and nanofibers. According to the currently available information, nanomaterials used in food applications include both inorganic and organic substances. Engineered nanomaterials (ENMs) which are likely to be found in nanofood products fall into three main categories: inorganic, surface functionalized materials, and organic engineered nanomaterials.

Inorganic nanomaterials for application in food, food additives, food packaging or storage include ENMs of transition metals, such as silver and iron; alkaline earth metals, such as calcium and magnesium; and non-metals, such as selenium and silicates. Other ENMs that can potentially be used in food applications include titanium dioxide. Food packaging is the major area of application of metal (oxide) ENMs. Nanosilver is finding a growing use in a number of consumer products, including food and health food, water, and food contact surfaces and packaging materials. Indeed, the use of nanosilver as an antimicrobial, antiodorant, and a (proclaimed) health supplement has already surpassed all other ENMs currently in use in different sectors. Amorphous nanosilica is known to be used in food contact surfaces and food packaging applications. Nanoselenium is being marketed as an additive to a green tea product, with a number of (proclaimed) health benefits resulting from enhanced uptake of selenium. Nano-iron is available as a health supplement and is used in the treatment of contaminated water, where it is claimed to decontaminate water by breaking down organic pollutants and killing microbial pathogens. A soluble nanomaterial under development is nanosalt, which will enable consumers to cut down their salt intake, since a small amount will cover a larger area of the food surface. Cola-tasting nanomilk and fat-reduced nanomayonnaise are just two of the nanotechnology-based food products in the from Wageningen University in Holland.

The application of nanotechnology in food science and technology is given in Figure 1. Nanotechnology would even be used to manufacture ‘smart’ packaging to dramatically extend the shelf life of food and enable it to be transported even further. Smart’ packaging (containing nanosensors and antimicrobial activators)

Figure 1. Application of nanotechnology in food science and technology



is being developed that will be capable of detecting food spoilage and releasing nanoantimicrobes to extend food shelf life, enabling supermarkets to keep food for even greater periods before its sale. Nanosensors, embedded into food products as tiny chips invisible to the human eye, would also act as electronic barcodes.

Surface functionalized nanomaterials add certain types of functionality to the matrix, such as antimicrobial activity or a preservative action through absorption of oxygen. For food packaging materials, functionalized ENMs are used to bind with the polymer matrix to offer mechanical strength or a barrier against movement of gases, volatile components (such as flavors) or moisture. Compared to inert nanomaterials, they are more likely to react with different food components, or become bound to food matrices, and hence may not be available for migration from packaging materials, or translocation to other organs outside the gastro intestinal tract. The nanoclay mineral is mainly montmorillonite (also termed as bentonite), which is natural clay obtained from volcanic ash/rocks. Nanoclay has a natural nanoscaled layer structure and is organically modified to bind to polymer matrices. The use of functionalized nanoclays in food packaging can help to develop materials with enhanced gas-barrier properties.

Organic nanomaterials (many of them naturally-occurring substances) are used (or have been developed for use) in food/feed products for their increased uptake and absorption, and improved bioavailability of vitamins, antioxidants in the body, compared to conventional bulk equivalents. A wide range of materials are available in this category, for example food additives (eg, benzoic acid, citric acid, ascorbic acid) and supplements (eg, vitamins A and E, isoflavones, beta-carotene, lutein, omega-3 fatty acids, and coenzyme-Q10). An example of an organic nanomaterial is the tomato lycopene. A synthetic nanosized form of lycopene has been produced and found as equivalent sources of lycopene compared to natural lycopene. Proteins, fat and sugar molecules, as well as neutraceuticals consisting of food additives derived from plants, are examples of organic nanomaterials.

Nanotechnology analysts estimated that between 150–600 nanofoods and 400–500 nano food packaging applications are already on the market. Nanotechnology has also opened the way for the introduction of other functionalities, such as antimicrobial activity in biodegradable materials. For instance, the preservative benzoic acid has been bonded to a magnesium–aluminium hydrotalcite and the complex has been blended with polycaprolactone to slow down the release of the antimicrobial molecule. Other developments include the use of certain enzymes with antimicrobial activity that could be covalently immobilized on to amino- or carboxyl-plasma-activated bio-oriented polypropylene films via suitable coupling agents.

Applications of Nanotechnology in Food Industry

Nanotechnology has been touted as the next revolution in many industries, including food processing and packaging. The applications of nano-based technology in food industry may include nanoparticulate delivery systems (e.g. micelles, liposomes, nanoemulsion, biopolymeric nanoparticles, and cubosomes), packaging, food safety and biosecurity (e.g. nanosensors), and nanotoxicity.

Nanoencapsulation

Nanoencapsulation is defined as a technology to pack substances in miniature making use of techniques such as nanocomposite, nanoemulsification and provides final product functionality that includes controlled release of the core. The protection of bioactive compounds, such as vitamins, antioxidants, proteins, and lipids as well as carbohydrates may be achieved using this technique for the production of functional foods with enhanced functionality and stability. The different techniques developed for the production of nanocapsules have been reported along with examples of their application. Scientists have developed a novel patented technology that has the ability to nanoencapsulate a multitude of bioactive and active ingredients in nutraceutical products.

These nanocapsules were found to break down and were absorbed as common foods after they have delivered their active ingredients. The recent innovation in encapsulation and controlled release technologies, as well as a design principle of novel food delivery systems has been reported. Nanoencapsulation can make significant savings for formulators, as it can reduce the amount of active ingredients needed. Researchers examined the encapsulation and controlled release of active food ingredients using nanotechnological approaches. Octenyl succinic anhydrideε-polylysine has the potential to become bifunctional molecules that can be used as either surfactants or emulsifiers in the encapsulation of nutraceuticals or drugs or as antimicrobial agents. Hydrophobically modified starch formed micelles encapsulated curcumin.

Lipid-based nanoencapsulation systems enhance the performance of antioxidants by improving their solubility and bioavailability, *in vitro* and *in vivo* stability, and preventing their unwanted interactions with other food components. The main lipid-based nanoencapsulation systems that can be used for the protection and delivery of foods and nutraceuticals are nanoliposomes, nanocochleates, and archaeosomes. Nanoliposome technology presents exciting opportunities for food technologists in areas such as encapsulation and controlled release of food materials, as well as the enhanced bioavailability, stability, and shelf-life of sensitive ingredients. Coenzyme Q10 nanoliposomes were produced with the desired encapsulation quality and stability. Colloidosomes are minute capsules made of particles one tenth the size of a human cell and assemble themselves into a hollow shell. Molecules of any substance can be placed inside this shell. Scientists believe that fat blockers, medicine, and vitamins could be placed into the colloidosomes. A method was proposed to form water-soluble nanoparticles with entrapped β-carotene of controlled functionality. Scientists formulated beta-carotene within a nanostructured lipid carrier that allows the normally hydrophobic beta-carotene to be easily dispersed and stabilized in beverages.

Nanoencapsulation technologies have the potential to meet food industry challenges concerning the effective delivery of health functional ingredients and controlled release of flavor compounds. Zein, the prolamine in corn endosperm binds and enrobes lipids, keeping them from deteriorative changes. Further, zein has been shown to adsorb fatty acids and produce periodic structures, most interestingly, nanoscale layers of cooperatively assembled fatty acid and zein sheets. Soy lecithin is the main structural ingredient in the formation of aqueous nanodispersions that carry high loads of water-insoluble actives. These actives include water-insoluble nutraceuticals, fat-soluble vitamins, and flavors. The encapsulated actives disperse easily into water-based products, showing improved stability and increased bioavailability. A separate study has shown a seven-fold increase in intestinal cell uptake of CoQ10 in nanodispersions versus traditional powder formulations.

Nanocochleates are nanocoiled particles that wrap around micronutrients and have the ability to stabilize and protect an extended range of micronutrients and the potential to increase the nutritional value of processed foods. Nanocochleates consists of a purified soy based phospholipid that contains at least about 75% by weight of lipid that can be phosphotidyl serine, dioleoylphosphatidylserine, phosphatidic acid, phosphatidylinositol, phosphatidyl glycerol and/or a mixture of one or more of these lipids with other lipids. Additionally or alternatively, the lipid can include phosphatidylcholine, phosphatidylethanolamine, diphosphotidylglycerol, dioleoyl phosphatidic acid, distearoyl phosphatidylserine, dimyristoyl phosphatidylserine, and dipalmitoyl phosphatidylgycerol.

Nanoencapsulation is desirable to develop designer probiotic bacterial preparations that could be delivered to certain parts of the gastro-intestinal tract where they interact with specific receptors. These nanoencapsulated designer probiotic bacterial preparations may act as *de novo* vaccines, with the capability of modulating immune responses. Biopolymer assemblies stabilized by various types of noncovalent forces have recently shown considerable progress.

A starch-like nanoparticle can help stop lipids from oxidizing and therefore improve the stability of oil-in-water emulsions. The health benefits of curcumin, the natural pigment that gives the spice turmeric its yellow colour, could be enhanced by encapsulation in nanoemulsions. The health promotion properties of polyphenols have attracted a lot of attention in recent years. Nanoemulsions could improve stability and oral bioavailability of epigallocatechin gallate and curcumin. A stearin-rich milk fraction was used, alone or in combination with α-tocopherol, for the preparation of oil-in-water sodium caseinate-stabilized nanoemulsions. Immobilization of α-tocopherol in fat droplets, composed by high melting temperature milk fat triglycerides, provided protection against degradation.

Nanocomposites in Food Packaging

Nanotechnology has the potential to generate new food packaging. Nanocomposites can improve mechanical strength; reduce weight; increase heat resistance; and improve barrier against oxygen, carbon dioxide, ultraviolet radiation, moisture, and volatiles of food package materials. Fine nanoparticulates (100 nm or less) are incorporated into plastics to improve the properties over those of conventional counterparts. Polymer nanocomposites are thermoplastic polymers that have nanoscale inclusions, 2%–8% by weight. Nanoscale inclusions consist of nanoclays, carbon nanoparticles, nanoscale metals and oxides, and polymeric resins. Nanocomposites are characterized by extremely high surface-to-volume ratio, making them highly reactive in comparison to their macroscale counterparts, and thus presenting fundamentally different properties.

Moreover, nanocomposites could also be characterized by an antimicrobial activity. Packaging containing nanosensors are coming to food stores to give information of enzymes produced in the breakdown of food molecules making them unsafe for human consumption. The packages could also be used to let air and other enzymes out but not in, thus increasing shelf life, as well as the reduction of man-made preservatives in our foods. Another important potential application of nanoparticles in food packaging is the degradation of ripening gas, such as ethylene. In view of the above, the idea to insert active nanoparticles into polymer matrices could bring the twofold advantage to improve the performance of food packaging material and to impart it an additional functionality (antimicrobial, antioxidant, scavenger), thus promoting the prolongation of the shelf life of the packaged product. Researchers reported the challenges of using nanotechnology to create low-cost packaging that assists in functionality, weight, and ease of processing. The new hybrid plastic, comprising polyamide and layered silicate barriers, makes it much more difficult for oxygen to pass through to the packaged goods than does conventional films made of polyamide. Durethan, is a nanocomposite film enriched with an enormous number of silicate nanoparticles that reduce entry of oxygen and other gases and the exit of moisture, thus preventing food from spoiling.

Natural biopolymer-based nanocomposite packaging materials with bio-functional properties have a huge potential for application in the active food packaging industry. Recent advances in the preparation of natural biopolymer-based films and their nanocomposites, and their potential use in packaging applications were reported. The other improvements in nanotechnology for food packaging include carbon nanotubes that can be used in food packaging to improve its mechanical properties. It has been recently discovered that they might exhibit powerful antimicrobial effects. For example, *Escherichia coli* bacteria died on immediate direct contact with aggregates of carbon nanotubes.

Polymer-clay nanocomposite has emerged as a novel food packaging material due to benefits, such as enhanced mechanical, thermal, and barrier properties. Scientists have discussed the potential use of these polymer composites as novel food packaging materials with emphasis on preparation, characterization, properties, recent developments and future prospects. More flexible packaging methods will provide the consumers with fresher and customized products. Nanowheels, nanofibers and nanotubes are being investigated as a means to improve the properties of food packages. Nanotechnology has the potential to influence the packaging sector by delaying oxidation and controlling moisture migration, microbial growth, respiration rates, and volatile flavors and aromas. A methodology used to produce polymer nanocomposites with low-cost fibrous materials similar to expensive carbon nanotubes exhibiting optimized dispersion, interfacial bonding, and attractive physical and other properties has been reported. Chitosan- based nanocomposite films, especially silver-containing ones, showed a promising range of antimicrobial activity. PEG coating nanoparticles loaded with garlic essential oil could be used to control the store-product pests. Phytoglycogen octenyl succinate nanoparticles with ε-polylysine significantly increased the shelf life of the product. Here, the nanoparticle created a stronger defense against oxygen, free radical and metal ions that cause lipid oxidation. Researchers are using silicate nanoparticles to provide a barrier to gasses (for example oxygen), or moisture in a plastic film used for packaging. This could reduce the possibly of food spoiling or drying out.

Smart packaging responds to environmental conditions or repairs it or alert a consumer to contamination and/or the presence of pathogens. The nanoparticles are dispersed throughout the plastic and are able to block oxygen, carbon dioxide and moisture from reaching fresh meats or other foods. The nanoclay also makes the plastic lighter, stronger and more heat resistant. Researchers have developed the intelligent packaging that will release a preservative if the food within begins to spoil. This "release on command" preservative packaging operates by using a bio switch developed through nanotechnology. 'Smart' food packaging will warn when oxygen has got inside, or if food is going off. Such packaging is already in use in brewing and dairy production and consists of nanofilters that can filter out micro-organisms and even viruses. In lab experiments, the color has been removed from beetroot juice, leaving the flavor; and red wine turned into white. Lactose can now be filtered from milk, and replaced with another sugar – making all milk suitable for the lactose-intolerant. Nano-capsules delivered chemicals in rapeseed cooking oil, will stop cholesterol entering the bloodstream. Nano packaging with self cleaning abilities or nanoscale filters will allow the removal of all bacteria from milk or water without boiling. In the area of nanolaminated coatings on the bioavailability of encapsulated lipids, bioactive lipophilic or fat-liking compounds could be incorporated into foods or beverages, which may increase the ingredient's stability, palatability, desirability, and bioactivity. Functionalized nanostructured materials are finding applications in many sectors of the food industry, including novel nanosensors, new packaging materials with improved mechanical and barrier properties, and efficient and targeted nutrient delivery systems. An improved understanding of the benefits and the risks of the technology, based on sound scientific data, will help gain the acceptance of nanotechnology by the food industry. New horizons for nanotechnology in food science may be achieved by further research on nanoscale structures and methods to control interactions between single molecules. Advances in processes for producing nanostructured materials coupled with appropriate formulation strategies have enabled the production and stabilization of nanoparticles that have potential applications in the food and related industries. The food processing industry should ensure consumer confidence and acceptance of nanofoods. Scientists are not yet certain how various nanomaterials will behave when they cross membranes, such as the blood–brain barrier, or when they are inhaled during production. The safety of a given compound in a food should not automatically apply to a nanoversion of the compound, due to possible novel properties and characteristics.

Nanotechnology Derived Food Ingredients

Organic constituents that are naturally present in foods such as protein, carbohydrate and fat can vary in size from large polymers to simpler molecules in the nano range. Organic nanomaterials can be synthesised for specific purposes such as the encapsulation of nutrients to increase bioavailability, enhance taste, texture and consistency of foodstuffs or mask an undesirable taste or odour. Functionalities of such nanomaterials (e.g., particle size, size distribution, potential agglomeration and surface charge) can be affected by the biological matrix in which they are held such as the composition of a food. The science of the production of nano-derived food ingredients is still in its infancy; nevertheless, it shows much promise with the prospect of improving product functionality without compromising product quality or safety.

Nanoemulsions

The use of nanoemulsions is an example of how a nanotechnology can be applied to an existing process which can prove beneficial for the food industry. The small droplet size gives nanoemulsions unique rheological and textural properties which render them transparent and pleasant to the touch; both of these unique features can be desirable in the food industry and the cosmetics industry. Using nanoemulsions in food products can facilitate the use of less fat without a compromise in creaminess, thus offering the consumer a healthier option. Products of this type include low fat nanostructured mayonnaise, spreads and ice creams. A 2.5% fat ice cream is commercially available worldwide from a recognised premium ice cream brand which claims to have no flavour defects due to the low fat content, however no nanotechnology claim is made by the product. More choice of such low fat ice cream is available in the United States where many brands have introduced them. As the size of the droplets in an emulsion is reduced, the less likely the emulsion will break down and separate. In this way nanoemulsification may reduce the need for certain stabilisers in a product. Nanoemulsions look set to play a future role in revolutionising the production of spreads and mayonnaise.

Nanoemulsions have been developed for use in the decontamination of food packaging equipment and in the packaging of food. A typical example is a nano-micelle-based product claimed to contain natural glycerin. It removes pesticide residues from fruits and vegetables, as well as the oil/dirt from cutlery. Nanoemulsions have recently received a lot of attention from the food industry due to their high clarity. These enable the addition of nanoemulsified bioactives and flavors to a beverage without a change in product appearance. Nanoemulsions are effective against a variety of food pathogens, including Gram-negative bacteria. They can be used for surface decontamination of food processing plants and for reduction of surface contamination of chicken skin. The growth of *Salmonella typhimurium* colonies has been eliminated by treatment with nanoemulsion. Based on the physicochemical properties of the microencapsulated fish oil, sugar beet pectin must be considered as an alternative to milk proteins and gum arabic for the encapsulation of functional food ingredients. The nanoemulsions showed great promise for use in beverage and other applications. Various types of nanoemulsion, including single-layer, double-layers and triple-layers nanoemulsions, could be produced, depending on the polyelectrolytes, such as alginate and chitosan. Solid lipid nanoparticles are formed by controlled crystallization of food nanoemulsions and have been reported for delivery of bioactives, such as lycopene and carotenoids. The major advantages of solid lipid nanoparticles include large-scale production without the use of organic solvents, high concentration of functional compounds in the system, long term stability, and the ability to be spray dried into powder form.

Nanonutraceuticals

Nutraceutical compounds such as bioactive proteins are used in functional foods to impart a health benefit to consumers in addition to the nutrition that the food itself offers. Nanomaterials can be used as bioactives in functional foods. Reducing the particle size of bioactives may improve the availability, delivery properties and solubility of the bioactives and thus their biological activity because the biological activity of a substance depends on its ability to be transferred across intestinal membranes into the blood. In addition, nanotechnologies can be utilised to improve the stability of such micronutrients during processing, storage and distribution. Commercial success in this area has been achieved by Omega-3 fatty acids, and certain beneficial probiotic bacteria species, lycopene, Vitamin D2 and beta-Carotene have demonstrated potential commercial success in research studies. Maintaining nutraceuticals in a stable state throughout the production process is invariably challenging. The prospect of the production of nutraceuticals at the nanoscale, which will have increased stability throughout the processing chain, will be of significant interest to food processors trying to maximise nutrient content and hence will ultimately be of benefit to consumers.

Natural Nanostructures in Food

Whilst nanotechnologies offer exciting opportunities for the development of new tastes and textures through the development of nanostructures, emulsions and micelles in foodstuffs, it is known that our food already contains certain natural nanostructures. The three basic food constituents are proteins, carbohydrates and fats. Many food proteins and carbohydrate starches exist naturally in the nanoscale and simple triglyceride lipids are about 2 nm long. Food substances are also metabolised in the body at a nanoscale. Although proteins, carbohydrates and lipids are each digested in the gastrointestinal tract (GIT) in a different way, a common factor is that they are all broken down to nanostructures before assimilation. It has, therefore, been argued that our body is already used to dealing with nanostructures in the GIT, and that foods processed at the nanoscale would simply be more readily digestible, absorbed and bioavailable in the body. However, it remains to be seen whether nanoscale processing of food materials might produce structures that are different from those that occur naturally.

Nanofood Additives

A key application area of nanotechnology for food processing is the development of certain nano-structured (also termed as nano-textured) foodstuffs, such as spreads, mayonnaises, creams, yoghurts and ice creams. The nano-structuring of food materials has been claimed for new tastes, improved textures, consistency and stability of emulsions, compared to equivalent conventionally processed products. A typical product of this technology could be in the form of a low-fat nano-textured product that is as ‘creamy’ as the full-fat alternative, and hence would offer a ‘healthy’ option to the consumer.

One such example under R&D is that of a mayonnaise which is composed of nanomicelles that contain nanodroplets of water inside. The mayonnaise would offer taste and texture attributes similar to the full-fat equivalent, but with a substantial reduction in the amount of fat intake by the consumer. Another area of application involves the use of nano-sized or nano-encapsulated food additives. This type of application is expected to exploit a much larger segment of the (health) food sector, encompassing colours, preservatives, flavourings and supplements. The main advantage is said to be a better dispersability of water-insoluble additives in foodstuffs without the use of additional fat or surfactants, and enhanced tastes and flavours due to enlarged surface area of nano-sized additives over conventional forms. A range of consumer products containing nano-sized additives is already available in the supplements, nutraceuticals and (health)food sectors. These include minerals, antimicrobials, vitamins, antioxidants, etc. Virtually all of these products also claim enhanced absorption and bioavailability in the body compared to their conventional equivalents.

Nano-encapsulation is the technological extension of micro-encapsulation that has been used by the industry for (health) food ingredients and additives for many years. Nano-encapsulation offers benefits that are similar to, but better than, microencapsulation, in terms of preserving the ingredients and additives during processing and storage, masking unpleasant tastes and flavours, controlling the release of additives, as well as enhanced uptake of the encapsulated nutrients and supplements.

Following food packaging, nano-encapsulation is currently the largest area of nanotechnology applications in the (heath) food sector. Nano-encapsulation in the form of nanomicelles, liposomes or protein-based carrier systems has been used to develop delivery systems for additives and supplements in food and beverage products. A growing number of (health) food and nutraceutical products based on nanocarrier technology are already available on the market. These include a number of food additives and supplements. Other products containing nano-antimicrobials and nano-antioxidants, etc., are also commercially available. The concept of nanodelivery systems seems to have originated from research on targeted delivery of drugs and therapeutics. However, the use of similar technology in foodstuffs is interesting in the sense that whilst it can offer increased absorption, uptake and bioavailability, it also has the potential to alter tissue distribution of the substances in the body. For example, certain water-soluble compounds can be rendered fat dispersible through nanocarrier technology. Vice versa, fat-dispersible compounds can be rendered water dispersible. It is hoped that these nanocarriers are completely broken down and their contents are released in the GI tract. As such, the encapsulated compounds will not be any different from their conventional equivalents. However, if a nanocarrier system is capable of delivering the encapsulated substance to the bloodstream, its absorption, tissue distribution and bioavailability may be drastically different from the conventional forms. This raises the concern that some nanocarriers may act as a ‘Trojan Horse’ and facilitate translocation of the encapsulated substances or other foreign materials to unintended parts of the body.

Analytical Food Nanotechnology

Detection and characterization of nano delivery systems is an essential part of understanding the benefits, as well as the potential toxicity of these systems in food. A detailed description of food nano delivery systems based on lipids, proteins, and/or polysaccharides, and the current analytical techniques used for the identification and characterization of these delivery systems in food products has been reported. The analytical approaches have been subdivided into three groups; separation techniques, imaging techniques, and characterization techniques. The recent progress made in analytical nanotechnology, as applied to the food industry and to food analysis; with particular emphasis on nanosensing have been reported. The electronic nose is a device that uses an array of chemical sensors tied to a data-processing system that mimics the way a nose works. A new strategy for feature selection has been introduced to Microsoft-based electronic nose applications. Its fine performance has been demonstrated using two Microsoft e-nose databases. Detection of fruit odors using an electronic nose has been reported. Methods have been reported to estimate chemical and physical properties of pears from the electronic nose signal. The electronic nose could also be a useful and innovative tool to monitor strawberry aroma changes during osmotic dehydration. A typical nanosensor 'electronic nose' can be used for quality control of milk during industrial processing. Nanotechnology-based electronic nose applications include: monitoring and control (for example, direct measuring of specific stages of a process, such as baking); more accurate volatiles measurement than measuring temperature and the time taken currently in baking to monitor product quality, quality assurance (eg, timely warning in a refrigerated environment on whether a ham is no longer safe to eat). Nanosensors are integrated in food packaging to show if the food product is still fit for human consumption. Nanosensors have been developed for food safety and quality control in the European project GOODFOOD (2004–2007) and Nanosieves can be used for filtration of beer or of milk for cheese production. Nanofiber of microbial cellulose produced by fermentation was also studied to develop novel nanostructured materials.

Detection and characterization of nano delivery systems are an essential part of understanding the benefits, as well as the potential toxicity of these systems, in food. Scientists showed that for a sufficient characterization, the nano delivery systems need to be separated from the food matrix, for which high-performance liquid chromatography or field flow fractionation are the most promising techniques. Subsequently, online photon correlation spectroscopy and mass spectrometry proved a convenient combination of techniques to characterize a wide variety of nano delivery systems. The detection and characteristics of engineered nanoparticles in food has been reported. A rapid and cost-effective method has been reported that simultaneously detects three food-borne pathogenic bacteria, *Salmonella typhimurium, Shigella flexneri, and E. coli* O157:H7, via an approach that combines magnetic microparticles for the enrichment and antibody-conjugated semiconductor quantum dots as fluorescence markers. Nanosensors can detect allergen proteins to prevent adverse reactions to foods, such as peanuts, tree nuts, and gluten.

Polymeric Nanoparticles

Polymeric nanoparticles for controlled release and targeted delivery of functional compounds have been reported. They are made using polymers and surfactants and include alginic acid, polylactic-co-glycolic acid, and chitosan. Further, scientists reported data on polymeric nanoparticles, including vitamin E, itraconazole (an antimicrobial), and beta-carotene as a colorant. Biopolymer nanoparticles are highly bioactive solid particles with diameters of 100 nm or less. Weiss and his colleagues have demonstrated that the particles can also serve as carriers of antimicrobial components, with niacin-containing biopolymeric nanoparticles exhibiting much more potent activity against *E. coli* O157:H7 than particles without nicin. The discovery of antimicrobial properties of nanozinc oxide and nanomagnesium oxide at the University of Leeds may provide more affordable materials for such applications in food packaging. Recently, nanoscale processing has been used to make new solids tate forms of food materials, such as cereals. Compared to conventional materials, these materials have new physicochemical properties, such as altered solubility, cohesiveness, stability, and reactivity.

Potential Risk of Food Nanotechnology

With these potential benefits of any technology some risks will also come. On one hand, while nanoscale components already occur naturally in many foods, the food nanotechnologies may pose direct risks to human health. Recent research shows that inhaled nanoparticles can accumulate in the lungs and cause chronic diseases due to their small scale.

Food-related nanotechnologies may also pose indirect threats to human health. For example, food could be contaminated by the use of nano-sized pesticides and nanoparticles could migrate into food from nano-packaging. There is also the possibility that nanoparticles could bioconcentrate in the environment and alter the food chain.

Many food substances or ingredients have nanostructures in nature and are present at micro- or nanometer in size. Food proteins, which are globular particles between 10s and 100s of nanometers in size, are true nanoparticles. Linear polysaccharides with one-dimensional nanostructures are less than 1 nm in thickness, and starch polysaccharides having small 3-D crystalline nanostructures are only 10s of nanometers in thickness. In the food industry, many attempts have been made to manufacture micro- or nanosize food materials by the top-down (e.g. grinding down) or bottom-up (e.g. aggregation of substances) approaches. In general, physicochemical properties including particle size and size distribution, agglomeration state, shape, crystal structure, chemical composition, surface area, surface chemistry, surface charge, and porosity may all be important for understanding the toxic effects of nanomaterials. However, it remains to be determined whether the unique physicochemical properties of nanomaterials will introduce new mechanisms of injury and result in unpredictable harmful effects.

Nanotechnology opens up a whole universe of new possibilities for the food industry (e.g. food packaging), but the entry of manufactured nanoparticles into food chain may result in an accumulation of the toxic contaminant in foods and adversely affect human health. There are questions if the food materials of nanometer sized (or up to a few micron) should be categorized as new or unnatural materials while compared with their larger forms. Although the nanomaterials might be toxic and cause harmful effects beyond the expectation, research efforts have also revealed that the ways of making nanomaterials and processing may not necessarily produce products with harmful effects: for instance, the toxicity of certain substance (e.g. selenium) might be significantly reduced while its particle size was decreased to nanoscale. It was also reported that pure carbon nanotubes administered to the trachea of mice might cause death; whereas, doping carbon nanotubes with nitrogen reduced their toxicity and the risk of death, paving the way for the use of the technology in food packaging. On the basis of a ‘‘Precautionary Principle’’, more investigations on the toxicity of nanoparticles contacting with food products, however, should be performed to dispel the doubts. In spite of the fact that most of the existing nanotoxicity studies are generally focusing on nonfood materials or consumer products, those relevant research findings can still be useful hints for understanding the potential toxicity of the nanotechnology-based food materials.

CONCLUSION

Nanotechnology has the potential to improve foods, making them tastier, healthier, and more nutritious, to generate new food products, new food packaging, and storage. However, many of the applications are currently at an elementary stage, and most are aimed at high-value products, at least in the short term. Successful applications of nanotechnology to foods are limited. Nanotechnology can be used to enhance food flavor and texture, to reduce fat content, or to encapsulate nutrients, such as vitamins, to ensure they do not degrade during a product’s shelf life. In addition to this, nanomaterials can be used to make packaging that keeps the product inside fresher for longer period. Intelligent food packaging, incorporating nanosensors, could even provide consumers with information on the state of the food inside. Food packages are embedded with nanoparticles that alert consumers when a product is no longer safe to eat. Sensors can warn before the food goes rotten or can inform us the exact nutritional status contained in the contents. In fact, nanotechnology is going to change the fabrication of the entire packaging industry.

As with many new technologies, being enthusiastic in the rush to market, nanotechnologies may distract from the importance of the investigation of possible health and environmental implications. The scientific community must learn from previous introductions of new technologies, being particularly sensitive in the food area. For example, genetically modified foods were not well received by consumers because there was a perceived risk associated with them. Thorough risk assessment of nanotechnologies in the food sector should provide a sound foundation on which commercial products can be launched with confidence, or withdrawn to protect consumers and the environment from potential hazards.

Food nanotechnology advances offers important challenges for both government and industry. The food processing industry must ensure consumer confidence and acceptance of nanofoods. Regulatory bodies, such as FDA, should author guidance with respect to the criteria to be followed in evaluating the safety of food, food packaging, and supplement uses of nanomaterials with novel properties. It is important to note that nanofoods originate in the laboratory, hence are not the same thing as conventional nanofoods. There has been insufficient scientific exploration of naturally occurring nanosystems and the benefits they provide. Thus, it is very difficult to make broad generalizations as to whether nanotechnology is good or bad. However, nanotechnology food packaging was assessed as less problematic than nanotechnology foods. Moreover, nanofoods are not labelled as such, and consumers who wish to avoid these food products are not being given this option. Thus, mandatory testing of nanomodified foods is desirable before they are allowed on the market. New approaches and standardized test procedures to study the impact of nanoparticles on living cells are urgently needed for the evaluation of potential hazards relating to human exposure to nanoparticles. It is widely expected that nanotechnology- derived food products will be available increasingly to consumers worldwide in the coming years.

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KEY TERMS AND DEFINITIONS

Liposome: Phospholipid bilayer vesicle formed from an aqueous suspension of phospholipid molecules.

Microencapsulation: Nanoencapsulation is the coating of various substances within another material at sizes on the nano scale.

Nanocomposites: Polymer/inorganic nanocomposites are composed of two or more physically distinct components with one or more average dimensions smaller than 100nm.

Nanoemulsions: Non-toxic lipid droplets a few hundred nanometers in diameter and made from surfactants approved for human consumption These emulsions are easily produced in large quantities by mixing a water-immiscible oil phase into an aqueous phase with a high-stress, mechanical extrusion process that is available worldwide. Nano-emulsions consist of fine oil-in-water dispersions, having droplets covering the size range of 100-600 nm.

Nanofilters: One opportunity for nanoscale filters is for the separation of molecules, such as proteins or DNA, for research in genomics.

Nanomaterials: materials in which one of the dimensions of the constituent objects is under 100 nm.

Nanoprobe: Nanoscale machines used to diagnose, image, report on, and treat disease within the body.

Nanosensor: A device for sensing radiation, forces, chemicals, or biological agents, in which some portion of a device operates at the nanoscale.

Nanotube: Hollow, cylindrical structures, with a diameter usually less than 5 nanometers. They are often but not necessarily, composed of carbon, and having remarkable strength and electrical properties.

Nutraceuticals: Components/nutrients isolated or purified from foods which have health benefits besides their actual function of providing nutrition and are therefore used to prevent the occurrence of a disease or are used in its treatment.

Polymer: A polymer is a large molecule or macromolecule, composed of many repeated subunits, known as monomers.

Quantum Dots: Nonocrystals or nanoparticles. Refer to confined electrons. Electrons in them occupy discrete states as in the case of atoms and therefore, quantum dots are referred to as artificial atoms.

Chapter 9

Nanosuspensions in Nanobiomedicine

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ABSTRACT

The tremendous success in developing new nanomaterials and fostering technological innovation arises from the focus on interdisciplinary research and collaboration between physical and medical scientists. The concept of nano-medicine is one of the most important and exciting ideas ever generated by the applications of nanoscience. One of the most challenging tasks in the pharmaceutical industry is the formulation of poorly soluble drugs. The implication of conventional techniques for improving the solubility has gained limited success. Nanoparticles facilitate formulation with improved solubility and efficacy mainly through nanosuspension approach. Techniques such as media milling, high-pressure homogenization, and use of microemulsion have been used for production of nanosuspensions for a novel delivery system. Moreover, they are manoeuvred to patient-acceptable dosage forms like tablets, capsules, and lyophilized powder products. Nanosuspension technology has also been studied for active and passive targeted drug delivery systems, which the chapter highlights on various formulational perspectives and applications as a biomedicine delivery system.

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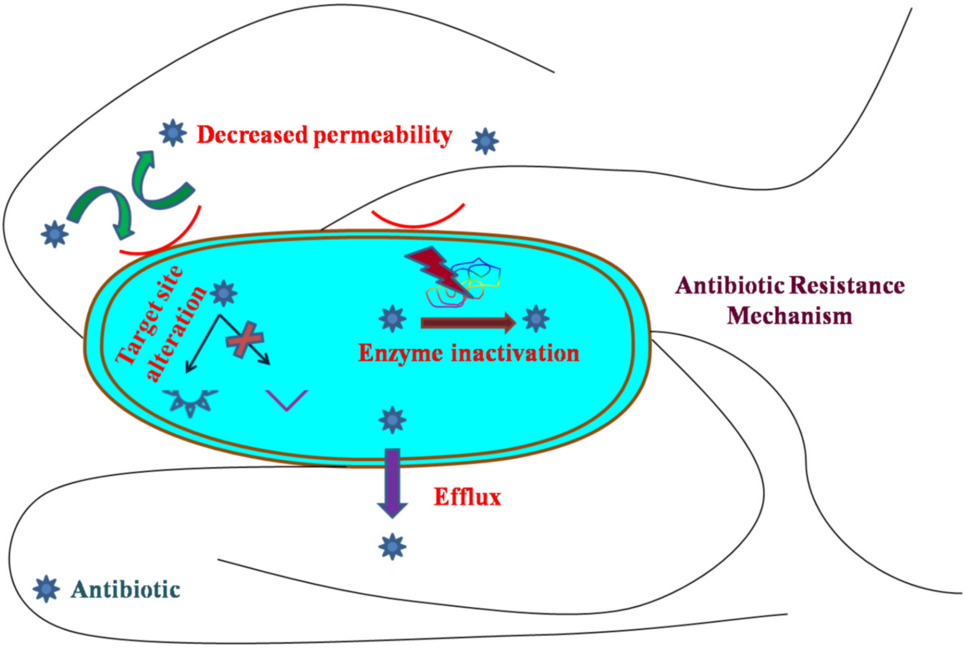
INTRODUCTION

In recent years various technological advances have led to unprecedented improvements in lifestyle, productivity and life span. Moreover there has been a significant burden on global economies and public health as shown by the increases in the outbreak of emerging and re-emerging infectious diseases. Transmission of infectious pathogens to the community has caused outbreaks such as influenza (*A*/*H1N*1 – Swine flu), Dengue fever, Diarrhoea *(Escherichia coli),* Cholera *(Vibrio cholera)* etc throughout the world. Societal changes resulting from mass urbanization (with the mechanisation of agricultural practices and industrialization) and population explosion along with poor water supply and environmental hygiene are the main reasons for the increase in outbreak of infectious pathogens. These events have led to the widespread use of illicit intravenous drugs, which in turn has contributed to the spread of serious blood-borne pathogens like human immunodeficiency virus (HIV) and hepatitis viruses (HBV), and to increased incidence of sub-acute bacterial endocarditis (Hawkey 2008).

The impact of technology on biomedical and clinical practice is among the most valuable changes that have occurred during the twentieth century, notably in the area of prevention and treatment of infectious diseases. The introduction of antibiotics, penicillin (Flemming, 1929) as an antimicrobial agent has pioneered the era of chemotherapy by bringing down the mortality rate with a breakthrough in medicinal field. The different classes of antibiotics that followed served as broad range *wonder drugs* inhibiting the growth of infectious agents by disrupting cell wall synthesis, interfering with DNA replication and protein synthesis (Finberg et al 2004). Furthermore, inappropriate antibiotic usage and inability to produce new antibiotics have introduced extreme selection pressure on bacterial survival. However, the difficulty in identifying the newly proposed crucial bacterial targets by the antibiotics has culminated in the emergence of resistance in the context of antibiotic-mediated stress, an important criterion in bacterial evolution and pathogenesis. The resistance phenomena have several potential mechanisms such as (a) spontaneous / induced mutation, (b) horizontal DNA transfer and (c) alteration of bacterial surface (Figure 1). In addition, bacteria themselves produce a number of antimicrobial products, the most common being the peptide antibiotics. The best studied are the colicins produced by a gram negative bacterium *E. coli* (Riley and Wertz 2002).

The emergence of antibacterial resistance has prompted restrictions on antibacterial use in developed countries like the United Kingdom in 1970 (Swann report 1969), and banning the use of antibacterials as growth-promotional agents by the European Union since 2003. According to US centers for Disease control and Prevention in Atlanta, Georgia drug misuse plays a key factor in the emergence of

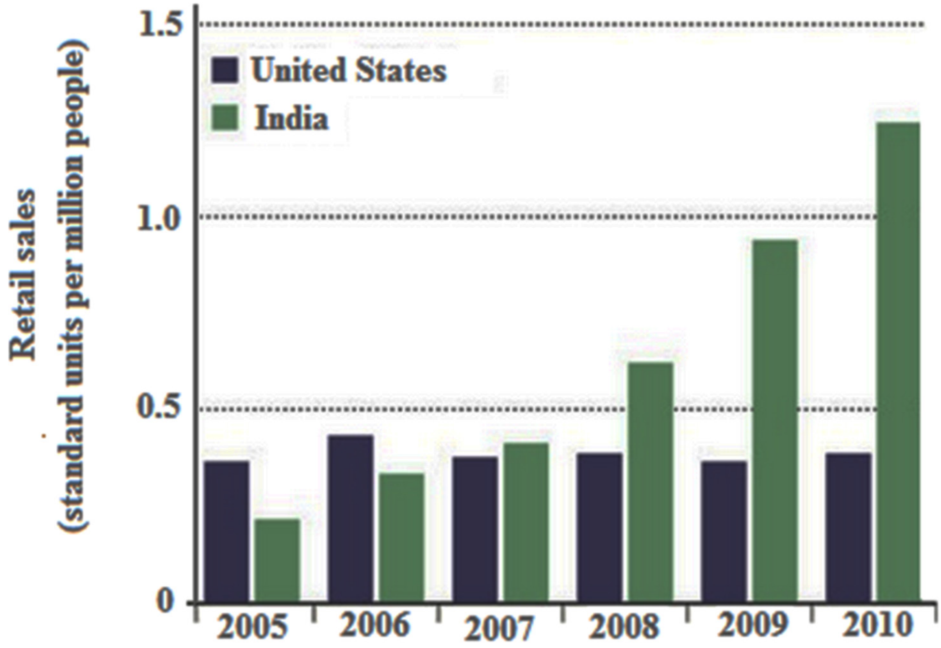
Figure 1. The antibacterial resistance pattern exhibited by a bacterium



antibiotic resistance. A survey published earlier this year by the Center for Disease Dynamics, Economics and Policy, found that in developing countries sales of carbapenems ("last resort") increased by nearly six times between 2005 and 2010 (Figure 2). It is noteworthy to mention that due to limited / poor basic medical facilities, nearly 70% of 1.2 billion rural Indian citizens rely entirely on local pharmacists rather than a Physician and have access to drugs of their sort. The fact that antibiotics have revolutionised medical care in the 20th century has been toppled up by the emergence of superbugs winning the battle against the medical profession. According to reports from Infectious Disease Society of America (IDSA), the containment of emerging superbugs especially the Gram negative bacilli pose a major threat. As a matter of fact, since 2009 only 2 new antibiotics were approved in US and the numbers approved for marketing continues to decline where only few antibiotics were identified in phase 2 or phase 3 trials to contain *E. coli, Salmonella, Shigella* and Enterobacteriaceae members (Boucher et al, 2013).

The increase in bacterial strains that are resistant to conventional antibacterial therapies has prompted the development of bacterial disease treatment strategies which are alternatives to conventional antibacterials. One strategy to address bacterial drug resistance is the discovery and application of compounds that modify resistance to common antibacterials. For example, some resistance-modifying agents

Figure 2. Sales scenario of carbapenem antibiotics in the United States and India



may inhibit multidrug resistance mechanisms, such as drug efflux from the cell, thus increasing the susceptibility of bacteria to an antibacterial. Further, phage therapy (Mattery, M 2008), bacteriocins, chelation (Jones 1977), vaccines, biotherapy (Nacar et al 2008), Probiotics (Ljungh et al 2009), Silver (Morones-Ramirez et al, 2013), host defense peptides, antimicrobial coatings – copper alloy surfaces (Samuel 2012) and targeting the trans-translational pathway (Keiler et al 2013) remain some of the strategies in combating the drug resistant microflora.

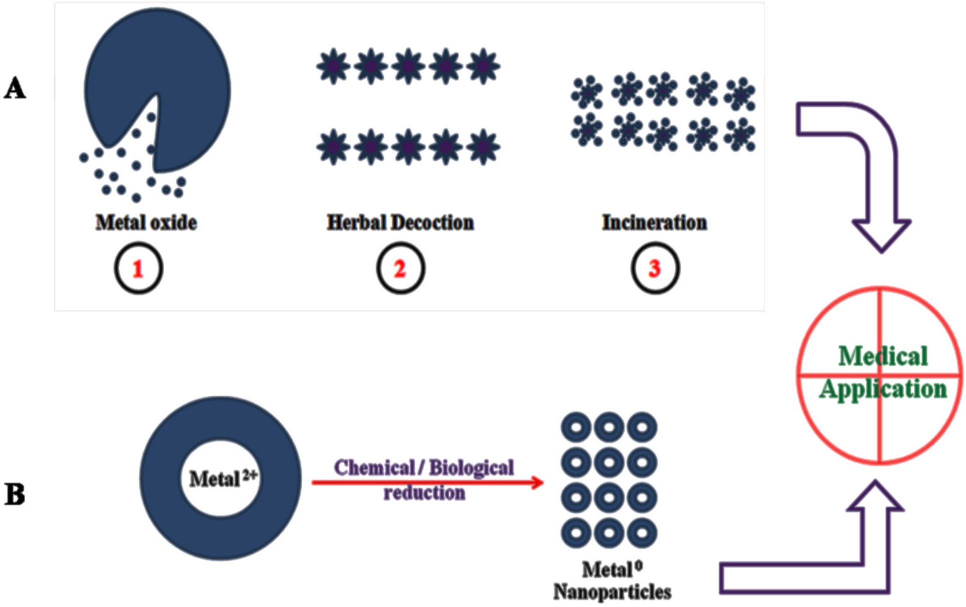
'Bhasmas' one of the ancient and unique ayurvedic metallic / mineral preparations prevailing since Charak Samhita worked similar to the nanoparticles of modern nanotechnology with the concept of reduction in particle size. The common properties like immune-modulation and anti-aging quality (rasayana) and targeted drug delivery (yogavahi) were observed in all bhasmas that are comparable to the novel medical strategies of modern era (Sanjeetha Paul et al. 2011) (Figure 3). In pharmaceutics, nanoparticles are typically defined as a discrete internal phase consisting of an active pharmaceutical ingredient having physical dimensions, less than 1 micron in an external phase. The use of nanoparticles as a drug-delivery approach for various difficult-to-formulate reagents is an age old practice (Poste et al., 1976;

Poste and Kirsh, 1983; Davis et al., 1987; Douglas et al., 1987; Papahadjopoulos, 1988) wherein they can be designed to form *de novo* when exposed to appropriate biological fluid (Shott, 1995).

Nanosuspensions consist of the pure poorly water-soluble drug without any matrix material suspended in dispersion. For a successful formulation, entire range of parameters like solubility, stability, compatibility and photostability need to be considered. Alongside, the switching over to nanosuspensions confers following advantages: enhanced solubility and bioavailability, suitability for hydrophilic drugs, higher drug loading, dose reduction, enhancement of physical and chemical stability and possible passive drug targeting (Vishal R Patel et al. 2011) those of which breach the barriers and resolve issues related to solubility and bioavailiablity.

The current chapter describes the insights about nanosuspensions and also the methods of preparation, merits & demerits, characterization and evaluation parameters. A nanosuspension not only solves the problems of poor solubility and bioavailability but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy.

Figure 3. (A) showing different steps involved in 'Bhasmikarana' converting the zero valent metal to oxide with high medicinal value (1) and mixing it with herbal decoction (2) thereby turning into ashes by incineration (3); (B) shows the metal oxide being reduced by any chemical or biological reducing agent converting it into a zero valent metal nanoparticles



NANOBIOMATERIALS

Nanostructures

Nanoparticles are gaining scientific interest as they effectively bridge the gap between bulk materials and atomic or molecular structures. A bulk material exhibits a constant physical properties regardless of its size, whereas at the nano-scale level size-dependent properties could be observed: quantum confinement in semiconductor particles, surface plasmon resonance in some metal particles (Ag, Au, Zn) and superparamagnetism (Nanocrystals, quantum dots) in magnetic materials.

- **Nanotubes:** Buckminsterfullerene or bucky balls, single layer of carbon atoms arranged in a cylinder with 1 – 2 nm in diameter and 1mm in length.
- **Nanowires:** Small conducting or semiconducting nanoparticles with a single crystal structure with a large aspect ratio.
- **Quantum Dots:** The number of atoms in a quantum dot range from 1000 to 100,000, makes it neither an extended solid structure nor a single molecular entity.
- **Other Nanoparticles:** It includes a wide range of primarily spherical or aggregated dendritic forms of nanoparticles.

Nanoparticles can be synthesised using variety of methods in order to optimise specific properties of the materials. The properties include, but are not limited, to size (diameter, length, volume) & distribution, symmetry, surface properties, surface coating, purity, ease of manipulation, yield and suitability for scaling up. Nanoparticles used in commercial or deliberate purpose employ methods that are divided into four main groups. These are gas phase processes including flame pyrolysis, high temperature evaporation and plasma synthesis, vapour deposition synthesis, colloidal or liquid phase methods in which chemical reactions in solvents lead to the formation of colloids and mechanical processes including grinding, milling and alloying.

Nanotechnology and Biological Bridge

Most preparations of the building blocks of nanotechnology involve hazardous chemicals, low material conversions, high energy requirements, and difficult, wasteful purifications; thus, there are multiple opportunities to develop greener processes for the manufacture of these materials. Many of the green chemistry principles apply readily to the synthesis or production of nanoscale materials. Green chemistry provides a number of advantages in process development and manufacturing as well as product design. As a result, researchers in the field of nanoparticle synthesis and assembly are focussing their attention on biological systems.

With the bioremediation of toxic metals using bacteria (Stephen and Maenaughton 1999) or yeasts (Mehra and Winge 1991), detoxification often occurs via reduction of the metal ions or formation of metal sulfides. Such microorganisms may then be used as possible nanofactories. Gold particles of nanoscale dimensions can, indeed, be readily precipitated within bacterial cells by incubation of the cells with Au^{2+} ions (Fortin and Beveridge 2000). *Pseudomonas stutzeri*, isolated from a silver mine, when placed in concentrated aqueous solution of $AgNO_3$ formed silver nanoparticles of well-defined size and distinct morphology within the periplasmic space of the bacteria (Klaus-Joerger et al. 2001). See Table 1.

Nanosuspensions: Scope

An important challenge that is being faced by the pharmaceutical industry is the poor solubility of drugs which is now considered to be an area of prime importance in the field of biomedical research. There are about 40% new molecular entities (NMEs) synthesized with advanced drug discovery tools incorporated with combinatorial

Table 1. Bio-nanofactories in the synthesis of various metal nanoparticles

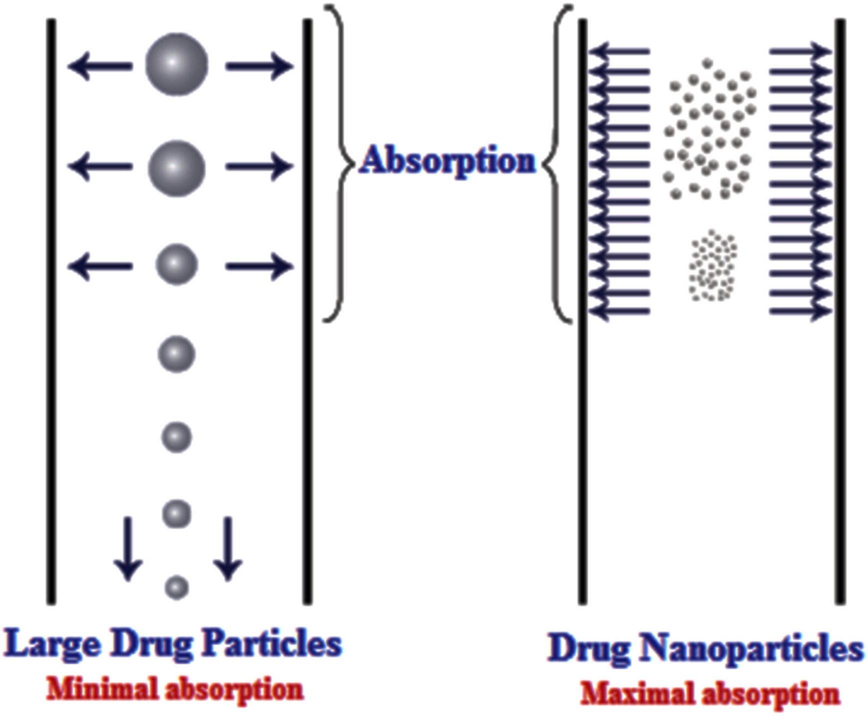
Biotic Counterpart	Nanoparticles	Size	Extracellular / Intracellular	Reference
Magnetotactic bacteria	Magnetic (Fe3O4) Greigite (Fe3S4)			Roh et al (2001)
Pseudomonas stutzeri	Ag	Upto 200 nm		Jeorger et al. (2000)
Ps. aeruginosa	Au	15 – 30 nm	Extracellular	Husseiny et al (2007)
Desulphovibrio desulfuricans	Palladium			Yong et al. (2002)
Thermomonospora sp.	Au	8 nm	Extracellular	Ahmad et al. (2003b)
Plectonema boryanum UTEX 485	Octahedral Au platlets	6 µm to 10 nm	At the cell wall	Lengke et al. (2006)
Schizosaccharomyces pombe	CdS	20 Ǻ	Intracellular	Dameron et al. (1989)
Fusarium oxysporum	Zirconia Barium titanate	3 – 11 nm 4 – 5 nm	Extracellular	Bansal et al. (2004; 2006)
Tamarind leaf extract	Au nanotriangles	20 – 40 nm	Extracellular	Ankamwar et al. (2005b)

chemistry even suffer from solubility and bioavailability related issues (Lipinski 2002). Despite bacterial resistance, tight junctional epithelial cells, transporters and enzymatic barriers also reduce the absorption of drugs. In order to make both ends meet, advanced disinfectant nanomaterials have been proposed as a prime source of prophylaxis. The techniques for solubility enhancement have some limitations for which nanotechnology can be used to resolve the problems associated with these conventional approaches for solubility and bioavailability enhancement (Figure 4).

METHODS OF NANOSUSPENSION PREPARATION

There are two methods for preparation of nanosuspensions. The conventional methods of precipitation (Hydrosols) are called ‘Bottom Up technology’. In Bottom Up Technology the drug is dissolved in a solvent, which is then added to non-solvent to precipitate the crystals. The basic advantage of precipitation technique is the use of simple and low cost equipments. The basic challenge of this technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled

Figure 4. Absorption rate of drug molecules at nanoscale level (Chaubal 2004)



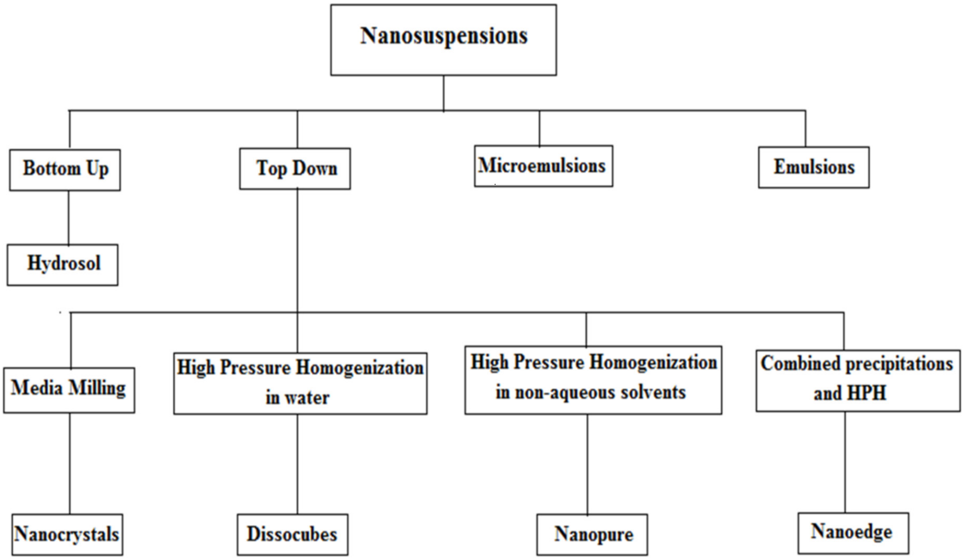
by addition of surfactant to avoid formation of microparticles. The limitation of this precipitation technique is that the drug needs to be soluble in atleast one solvent and this solvent needs to be miscible with nonsolvent. Moreover precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media (Muller et al 2000).

The 'Top Down Technologies' are the disintegration methods and are preferred over the precipitation methods. The 'Top Down Technologies' include Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege) (Chowdary et al 2005; Cornelia et al 2006). Few other techniques used for preparing nanosuspensions are emulsion as templates, microemulsion as templates etc (Patravale et al 2004) (Figure 5).

Media Milling (Nanocrystals or Nanosystems)

The method is first developed and reported by Liversidge et.al. (1992). The nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug and stabilizer is rotated at a very high shear rate under controlled temperatures for several days (at least 2-7 days). The milling medium is composed of glass, Zirconium oxide or highly cross-linked polystyrene

Figure 5. Flow chart representing different methods of preparation of nanosuspensions



resin. The high energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particles.

Homogenization in Water (Dissocubes)

R. H. Muller developed Dissocubes technology in 1999. The instrument can be operated at pressure varying from 100 – 1500 bars (2800 –21300psi) and up to 2000 bars with volume capacity of 40ml (for laboratory scale). For preparation of nano suspension, we have to start with the micronized drug particle size less than 25μm to prevent blocking of homogenization gap hence it is essential to prepare a presuspension of the micronized drug in a surfactant solution using high speed stirrer (Cornelia et al 2006).

Homogenisation in Nonaqueous Media (Nanopure)

The drugs that are chemically labile can be processed in such nonaqueous media or water-miscible liquids like polyethyleneglycol-400 (PEG), PEG1000 etc. The homogenization can be done at room temperature, 0^{o} C and below freezing point (-20^{o} C).

Combined Precipitation and Homogenization (Nanoedge)

The precipitated drug nanoparticles have tendency to continue crystal growth to the size of microcrystals. They need to be processed with high-energy forces (Homogenisation). They are completely amorphous, partially amorphous or completely crystalline which create problems in long term stability as well as in bioavailability, so the precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step.

NANOSUSPENSIONS AND PROPERTIES

Physical Long-Term Stability

Dispersed systems show physical instability due to Ostwald ripening which is responsible for crystal growth to form microparticles. Ostwald ripening is defined as the tendency for a particle dispersion to grow in diameter over time; by a process in which the smaller particles dissolve because of their higher solubility, with subsequent crystallization onto larger particles to form microparticles. Ostwald ripening is caused due to the difference in dissolution velocity/ saturation solubility of small and large particles.

In nanosuspensions all particles are of uniform size hence there is little difference between saturation solubility of drug particles. The difference in the concentration of the saturated solutions around a small and large particle leads to the diffusion of dissolved drug from the outer area of the large particles. As a result the solution around large particles is supersaturated leading to the drug crystallization and growth of the large crystals or microparticles. Ostwald ripening is totally absent in nanosuspensions due to uniform particle size, which is also responsible for long-term physical stability of nanosuspensions.

Increase in Saturation Solubility and Dissolution Velocity of Drug

Dissolution of drug is increased due to increase in the surface area of the drug particles from micrometers to the nanometer size. According to Noyes-Whitney equation (equation no.1) dissolution velocity increase due to increase in the surface area from micron size to particles of nanometer size.

$$Dx/dt = [(D \text{ x } A/ h] [Cs\text{-}X/V]$$

where D is diffusion coefficient, A is surface area of particle, dx/dt is the dissolution velocity, V is volume of dissolution medium and X is the concentration in surrounding liquid.

According to the Prandtl equation, for small particles the diffusional distance h decreases with decreasing particle size. The decrease in h increases Cs (saturation solubility) and leads to an increase in gradient (Cs-Cx)/h and thus to an increase in the dissolution velocity. According to Ostwald-Freunddlich equation decrease in particle size below 1µm increases the intrinsic solubility or saturation solubility (Patravale et al 2004; Muller et al 2000).

Internal Structure of Nanosuspensions

The high-energy input during disintegration process causes structural changes inside the drug particles. When the drug particles are exposed to high-pressure homogenisation particles are transformed from crystalline state to amorphous state. The change in state depends upon the hardness of drug, number of homogenisation cycles chemical nature of drug and power density applied by homogeniser.

CHARACTERIZATION OF NANOSUSPENSIONS

The essential characterization parameters for nanosuspensions are as follows. Mean particle size and particle size distribution. The mean particle size and the width of particle size distribution are important characterization parameters as they govern the saturation solubility, dissolution velocity, physical stability and even biological performance of nanosuspensions. It has been indicated by Muller & Peters (1998) that saturation solubility and dissolution velocity show considerable variation with the changing particle size of the drug.

1. **Photon Correlation Spectroscopy (PCS) (Muller & Muller 1984):** Can be used for rapid and accurate determination of the mean particle diameter of nanosuspensions. Moreover, PCS can even be used for determining the width of the particle size distribution (polydispersity index, PI). The PI is an important parameter that governs the physical stability of nanosuspensions and should be as low as possible for the long-term stability of nanosuspensions. A PI value of 0.1–0.25 indicates a fairly narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution. Although PCS is a versatile technique, because of its low measuring range (3nm to 3 μm) it becomes difficult to determine the possibility of contamination of the nanosuspension by microparticulate drugs (having particle size greater than 3 μm). Hence, in addition to PCS analysis, laser diffractometry (LD) analysis of nanosuspensions should be carried out in order to detect as well as quantify the drug microparticles that might have been generated during the production process.
2. **Laser Diffractometry:** Yields a volume size distribution and can be used to measure particles ranging from 0.05 – 80 μm and in certain instruments particle sizes up to 2000 μm can be measured. The typical LD characterization includes determination of diameter 50% LD (50) and diameter 99% LD (99) values, which indicate that either 50 or 99% of the particles are below the indicated size. The LD analysis becomes critical for nanosuspensions that are meant for parenteral and pulmonary delivery. Even if the nanosuspension contains a small number of particles greater than 5–6 μm, there could be a possibility of capillary blockade or emboli formation, as the size of the smallest blood capillary is 5–6 μm.
3. **Crystalline State and Particle Morphology:** Assessment of the crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing. Additionally, when nanosuspensions are prepared, drug particles in an amorphous state are likely to be generated. Hence, it is essential to

investigate the extent of amorphous drug nanoparticles generated during the production of nanosuspensions. The changes in the physical state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis (Muller & Bohm 1998; Muller & Grau 1998) and can be supplemented by differential scanning calorimetry (Shanthakumar et al 2004). In order to get an actual idea of particle morphology, scanning electron microscopy is preferred (Muller & Bohm 1998).

4. **Particle Charge (Zeta Potential):** Determination of the zeta potential of a nanosuspension is essential as it gives an idea about the physical stability of the nanosuspension. The zeta potential of a nanosuspension is governed by both the stabilizer and the drug itself. In order to obtain a nanosuspension exhibiting good stability, for an electrostatically stabilized nanosuspension a minimum zeta potential of ±30mV is required whereas in the case of a combined electrostatic and steric stabilization, a minimum zeta potential of ±20mV is desirable (Muller & Jacobs 2002b).
5. **Saturation Solubility and Dissolution Velocity:** The determination of the saturation solubility and dissolution velocity is very important as these two parameters together help to anticipate any change in the *in vivo* performance (blood profiles, plasma peaks and bioavailability) of the drug. As nanosuspensions are known to improve the saturation solubility of the drug, the determination of the saturation solubility rather than an increase in saturation solubility remains an important investigational parameter. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can be achieved over conventional formulations, especially when designing the sustained-release dosage forms based on nanoparticulate drugs. The dissolution velocity of drug nanosuspensions in various physiological buffers should be determined according to methods reported in the pharmacopoeia.
6. ***In-Vivo* Biological Performance:** The establishment of an *in-vitro/in-vivo* correlation and the monitoring of the *in-vivo* performance of the drug is an essential part of the study, irrespective of the route and the delivery system employed. It is of the utmost importance in the case of intravenously injected nanosuspensions since the Nanosuspensions: a promising drug delivery strategy *in vivo* behaviour of the drug depends on the organ distribution, which in turn depends on its surface properties, such as surface hydrophobicity and interactions with plasma proteins (Blunk et al 1993, 1996; Luck et al 1997a,b). In fact, the qualitative and quantitative composition of the protein absorption pattern observed after the intravenous injection of nanoparticles is recognized as the essential factor for organ distribution (Muller 1989; Blunk et al 1993, 1996; Luck et al 1997a,b). Hence, suitable techniques have to be used in order to evaluate the surface properties and protein interactions to get an idea of in-

vivo behaviour. Techniques such as hydrophobic interaction chromatography can be used to determine surface hydrophobicity (Wallis & Muller 1993), whereas 2-D PAGE (Blunk et al 1993) can be employed for the quantitative and qualitative measurement of protein adsorption after intravenous injection of drug nanosuspensions in animals.

NANOTECHNOLOGY IN MEDICINE: NANOMEDICINE

Applying nanotechnology for treatment, diagnosis, monitoring, and control of diseases has been referred to as "nanomedicine". Although the application of nanotechnology to medicine appears to be a relatively recent trend, the basic nanotechnology approaches for medical application date back several decades. The first example of lipid vesicles which later became known as liposomes were described in 1965 (Bangham et al); the first controlled release polymer system of macromolecules was described in 1976 (Langer et al); the first long circulating stealth polymeric nanoparticle was described in 1994 (Gref et al); the first quantum dot bioconjugate was described in 1998 (Bruchez et al); and the first nanowire nanosensor dates back to 2001 (Cui et al). Recent Studies on new targeted nanoparticle contrast agents for early characterization of atherosclerosis and cardiovascular pathology at the cellular and molecular levels that might represent the next frontier for combining imaging and rational drug delivery to facilitate personalized medicine (Wickline et al 2002) (Table 2).

Nanotechnology-based highly efficient markers and precise, quantitative detection devices for early diagnosis and for therapy monitoring will have a wide influence in patient management, in improving patient's quality of life and in lowering mortality rates, in diseases like cancer and Alzheimer's disease.

Table 2. Different categories of Nanoparticles and their applications

Nanostructures	Material	Applications
Nanotubes	Carbon (fullerenes)	Synthetic muscles, Body armor, Nanotube membrane filters, Scaffolds (Haddon et al; Sholl et al 2006;
Nanowires	Metals, semiconductors, oxides, sulphides, nitrides	Real time sensing of biomarker proteins for cancer, Diagnosis of myocardial infarction (Elnathan et al)
Nanocrystals, quantum dots	Insulators, semiconductors, metals, magnetic materials	Fluorescent probes for cellular imaging – Real time tracking
Other nanoparticles	Ceramic oxides, metals	Gene delivery and Tissue engineering

Multi-Functional Nanoparticles

Biodegradable chitosan nanoparticles encapsulating quantum dots were prepared by D. K. Chatterjee and Y. Zhang, with suitable surface modification to immobilize both tumor targeting agent and chemokine on their surfaces. The interactions between immune cells and tumor cells were visualized using optical microscope. Use of Quantum dots in the treatment of cancer is a great advancement in this area. Quantum dots glow when exposed to UV light. When injected they seep into cancer tumour. The surgeon can see the glowing tumour. Nanotechnology could be very helpful in regenerating the injured nerves. During the last decade, however, developments in the areas of surface microscopy, silicon fabrication, biochemistry, physical chemistry, and computational engineering have converged to provide remarkable capabilities for understanding, fabricating and manipulating structures at the atomic level. The rapid evolution of this new science and the opportunities for its application promise that nanotechnology will become one of the dominant technologies of the 21st century.

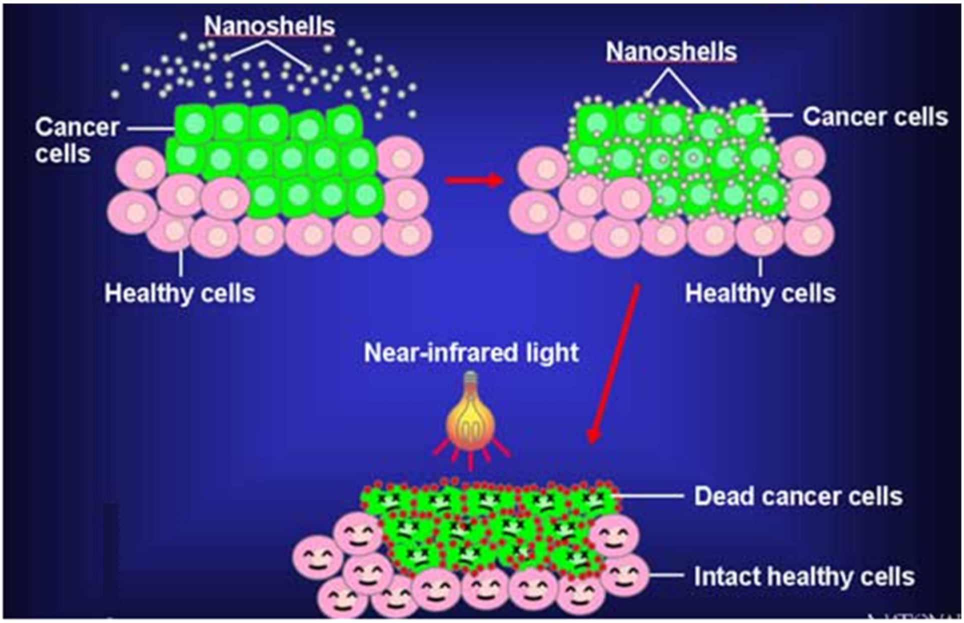
Nanoshells

Nanoshells are miniscule beads coated with gold. By manipulating the thickness of the layers making up the nanoshells, scientists can design these beads to absorb specific wavelengths of light. The most useful nanoshells are those that absorb near-infrared light, which can easily penetrate several centimeters of human tissue. The absorption of light by the nanoshells creates an intense heat that is lethal to cells. Researchers can already link nanoshells to antibodies that recognize cancer cells. Scientists envision letting these nanoshells seek out their cancerous targets, then applying near-infrared light. In laboratory cultures, the heat generated by the light-absorbing nanoshells has successfully killed tumor cells while leaving neighboring cells intact (Figure 6).

Dendrimers

Dendrimers are man-made molecules about the size of an average protein, and have a branching shape. They are used to facilitate drug delivery as they behave as a potent diagnostic tool. The shape gives them vast amounts of surface area to which therapeutic agents or other biologically active molecules can be attached. A single dendrimer can carry a molecule that recognizes cancer cells, a therapeutic agent to kill those cells, and a molecule that recognizes the signals of cell death. It has been manipulated in such a way that they release their contents only in the

Figure 6. Nanoshells as cancer therapy. (Courtesy: National Cancer Institute at the National Institutes of Health http://www.cancer.gov/cancertopics/understandingcancer/nanodevices).



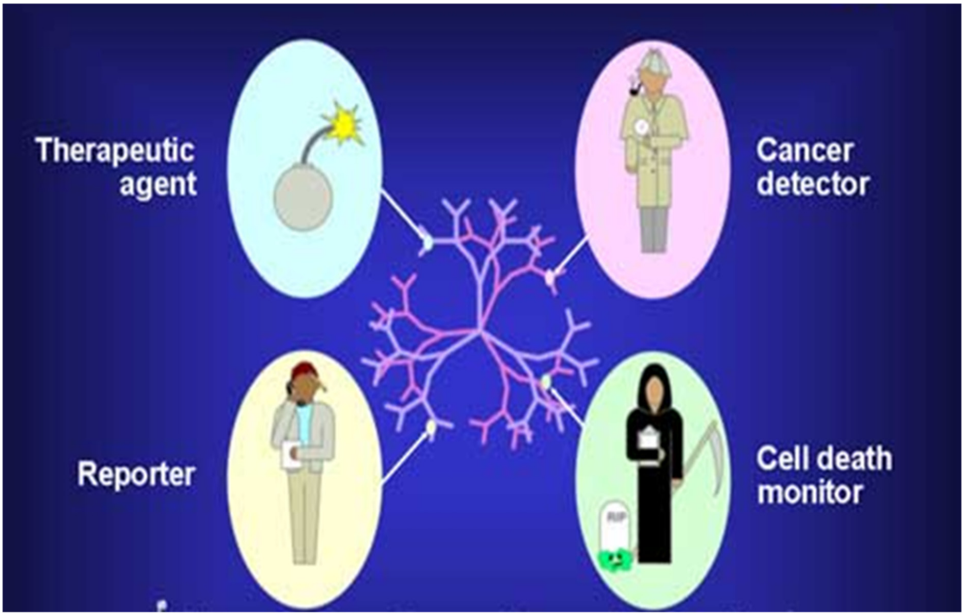
presence of certain trigger molecules associated with cancer. Following drug release, the dendrimers may also report back whether they are successfully killing their targets (Figure 7).

Early Detection of Alzheimer's Disease

Brain represents one of the most complex systems in biomedicine. With an improved understanding of brain functioning, better diagnosis and treatment for neurodegenerative diseases like Alzheimer's is offered by nanotechnology. Presently, the prevailing problem is early detection for effective treatment of the disease. An ideal diagnostic tool for Alzheimer's disease (AD) must have specificity & sensitivity more than 80% for its early diagnosis & excluding other causes. Since the neurodegeneration process begins well before AD becomes symptomatic the potential for early detection is another important characteristic of an ideal diagnostic tool.

Nanotechnology can be the basis of new tools for very early detection of AD. Nanotechnology in the diagnosis of AD came into light after two articles were published in February 2005. The two detection approaches proposed are the Bio-barcode assay (BCA) & Localized surface plasmon resonance (LSPR) technology.

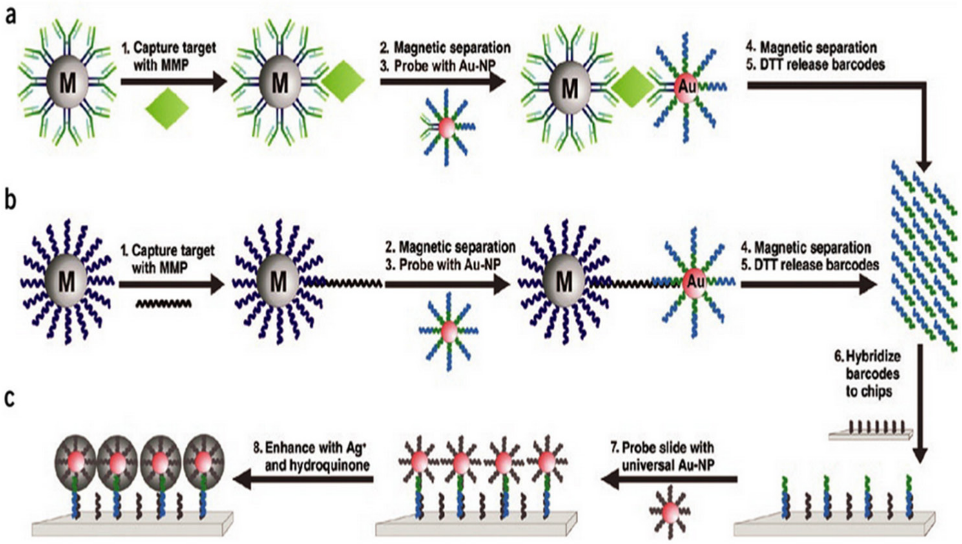
Figure 7. Dendrimers in cancer therapy. (Courtesy: National Cancer Institute at the National Institutes of Health http://www.cancer.gov/cancertopics/understandingcancer/nanodevices).



Bio-Barcode Assay

One of the recently developed bio-barcode assay used for the detection of nucleic acid and protein targets without PCR showing high sensitivity for both nucleic acid and protein targets. Two types of particles are used in the assay: (i) a magnetic microparticle with recognition elements for the target of interest and (ii) a gold nanoparticle (Au-NP) with a second recognition agent (which can form a sandwich around the target in conjunction with the magnetic particle) and hundreds of thiolated single-strand oligonucleotide barcodes. After reaction with the analyte, a magnetic field is used to localize and collect the sandwich structures, and a DTT solution at elevated temperature is used to release the barcode strands. The barcode strands can be identified on a microarray via scanometric detection or *in situ* if the barcodes carry with them a detectable marker (Figure 8).

Figure 8. Schematic representation of protein and nucleic acid detection using bio-barcode assay (Hill et al. 2006)



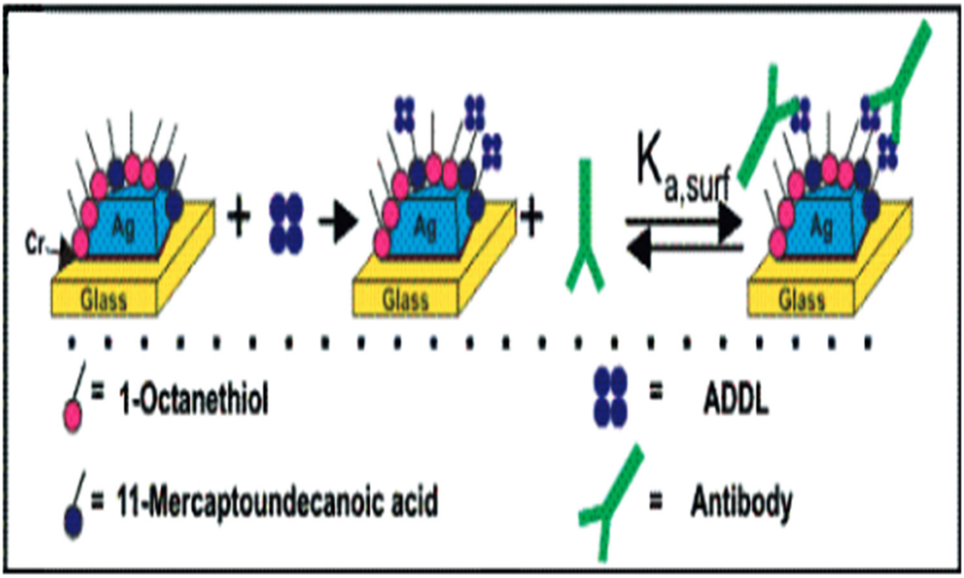
Localized Surface Plasmon Resonance (LSPR) Technology (Heas et al. 2004)

Surface-confined Ag nanoparticles are synthesized using Nanosphere lithography (NSL). Nanoparticle adhesion to the glass substrate is promoted using a 0.4 nm Cr layer. The nanoparticles are incubated in a 3:1 1-octane-thiol / 11-mercaptoundecanoic acid solution to form a self assembled monolayer. Then the samples are incubated in 100 mM 1-ethyl-3-[3-dimethyl-aminopropyl] carbodiimide hydrochloride / 100 nM amyloid-derived diffusible ligands (ADDL) solution. Finally, incubating the ADDL-coated nanoparticles to varying concentrations of antibody completes an anti-ADDL immunoassay. By varying the concentration of anti-ADDL antibody, a surface confined binding constant of 3.0×10^7 M^{-1} for the interaction of ADDLs and anti-ADDLs measured (Figure 9).

Nanosuspensions in Drug Delivery

Nanosuspensions are also advantageous in achieving quick onset of action for drugs that are completely but slowly absorbed. A study involving a comparison of the pharmacokinetic profiles of a drug in the form of nanosuspension, suspension

Figure 9. Design of LSPR sensor based on optical properties of Ag nanoparticle (Heas et al., 2004)



and tablet forms revealed that the time required to achieve C_{max} was reduced by approximately 50% for the nanosuspension compared to the suspension and tablet. Additionally, the nanosuspension resulted in 2.5 to 4.5 fold increase with improved dose proportionality, reduced variability and increased bioavailability.

Oral Drug Delivery

The oral route is the most preferred route for drug delivery. The efficacy or performance of the orally administered drug generally depends on its solubility and absorption through the gastrointestinal tract. When a drug candidate exhibits poor aqueous solubility or rate limited absorption, it is believed to possess low and/or highly variable oral bioavailability. In such cases, the drug candidate would have to be administered in a larger excess than actually required in order to achieve a therapeutically active concentration, thus making the therapy costly. This could very well be appreciated in case of antibiotics such as atovaquone and bupravaquone.

Nanosizing and Nanosuspensions of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability. The adhesiveness of the drug nanosuspension, increased surface area (due to reduction in particle size by 10–50-fold), increased saturation solubility, leading to an increased concentration gradient between the gastrointestinal tract lumen and blood, and increased dissolution velocity. This enhancement in bioavailability will lead to a subsequent reduction in drug dose, rendering the therapy cost-effective and undue drug dumping in the body.

Parenteral Drug Delivery

The parenteral route is an invasive route and the administration of drugs is critical and often associated with safety issues and biological problems such as allergies and thrombophlebitis (thrombus - blood clot; phlebitis - vein inflammation). Despite all these limitations, the parenteral route still retains its value with special advantages, such as quick onset of action in case of emergency, reduction in dose of the drug and the ability to target the drug quickly to the desired site of action, especially in the case of severe infections. This route is also employed as an alternative to oral administration in case of poor absorption. For administration by the parenteral route, the drug either has to be solubilized or have particle/globule size below 5 μm to avoid the capillary blockade.

The current approaches for parenteral delivery include salt formation, solubilization using co-solvents, micellar solutions (Kim et al 2001), complexation with cyclodextrins and recently liposomes (Dupont 2002). However, there are limitations on the use of these approaches because of limitations on their solubilization capacity and parenteral acceptability. In this regard, liposomes are much more tolerable and versatile in terms of parenteral delivery. However, they often suffer from problems such as physical instability, high manufacturing cost and difficulties in scale-up.

Nanosuspensions appear to be a unique approach to solving the problems mentioned above. From the formulation perspective, nanosuspensions meet almost all the requirements of an ideal drug delivery system for the parenteral route. The nanosized drug particles and absence of any harsh solvents or any toxic ingredient makes the nanosuspensions bypass the limitations leading to improved therapeutic performance. A therapeutic efficacy of paclitaxel nanosuspension against Taxol on mammary 16-C murine tumour model revealed the superiority of paclitaxel nanosuspension over Taxol in reducing the median tumour burden (Merisko-Liversidge et al 2003).

Ocular Drug Delivery

Nanosuspensions support the drugs that exhibit poor solubility in lachrymal fluids. Even though delivery approaches such as suspensions and ointments have been recommended, the therapeutic performance of the water-soluble drugs depends on the intrinsic solubility of the drug in lachrymal fluids. Thus, the intrinsic dissolution rate of the drug in lachrymal fluid (constant inflow and outflow) governs its release and ocular bioavailability. However, nanosuspensions, by their inherent ability to improve the saturation solubility of the drug, represent an ideal approach for ocular delivery of hydrophobic drugs. Moreover, the nanoparticulate nature of the drug allows its prolonged residence in the cul-de-sac, giving sustained release of the drug. To achieve sustained release of the drug for a stipulated time period, nanosuspensions can be incorporated in a suitable hydrogel base or mucoadhesive base or even in ocular inserts. An approach that has recently been investigated to achieve the desired duration of action of the drug is the formulation of polymeric nanosuspensions loaded with the drug. The bioerodible as well as water soluble/permeable polymers possessing ocular tolerability (Pignatello et al 2002a) could be used to sustain the release of the medication. The polymeric nanosuspensions of flurbiprofen and ibuprofen have been successfully formulated using acrylate polymers such as Eudragit RS 100 and Eudragit RL 100 (Bucolo et al 2002; Pignatello et al 2002b,c).

Pulmonary Drug Delivery

Nanosuspensions compete with the poor soluble drugs delivered as dry powders or as suspension aerosols via pulmonary secretions. The suspension drugs are initially jet milled to achieve particle sizes of microns. As a result, there is a limited diffusion and dissolution of the drug, rapid clearance from the lungs because of ciliary movements, less residence time and deposition of the drug thereby affecting the bioavailability.

The nanoparticulate nature of the drug allows the rapid diffusion and dissolution of the drug at the site of action. At the same time, the increased adhesiveness of the drug to mucosal surfaces (Ponchel et al 1997) offers a prolonged residence time for the drug at the absorption site. This ability of nanosuspensions to offer quick onset of action initially and then controlled release of the active moiety is highly beneficial and is required by most pulmonary diseases. Nanosuspensions could be used in all available types of nebulizer. However, the extent of influence exerted by the nebulizer type as well as the nebulization process on the particle size of nanosuspensions should be ascertained. Budesonide, a poorly water-soluble corticosteroid, has been successfully formulated as a nanosuspension for pulmonary delivery (Muller & Jacobs 2002b).

Targeted Drug Delivery

The need to target specific sites remains one of the major challenges in the drug delivery system. Nanoparticulate systems have shown tremendous potential in targeted drug delivery, especially to the brain (Schroeder et al 1998; Kreuter 2001).

Successful targeting of the peptide dalargin to the brain by employing surface modified polyisobutyl cyanoacrylate nanoparticles has been a major achievement in targeted delivery (Kreuter et al 1997).

The shift and drift strategy exhibited by the nanosuspensions makes them a potent candidate for targeted delivery as their surface properties and *in-vivo* behaviour can easily be altered. Natural targeting of macrophages by nanosuspensions has been achieved but could pose an obstacle when macrophages are not the desired targets. Hence, in order to bypass the phagocytic uptake of the drug, its surface properties need to be altered, as in the case of stealth liposomes (Gregoriades 1995; Allen 1997; Lasic et al 1997; Papisov 1998; Woodle 1998; Vyas et al 2000).

The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems.

Example 1: *Cryptosporidium parvum*, the organism responsible for cryptosporidiosis was targeted by using surface-modified mucoadhesive nanosuspensions of bupravaquone (Kayser 2001; Muller & Jacobs 2002a). Mucoadhesive bupravaquone nanosuspensions, because of their prolonged residence at the infection site, revealed a 10-fold reduction in the infectivity score of *Cryptosporidium parvum* as compared to the bupravaquone nanosuspensions without mucoadhesive polymers.

Example 2: Similarly, conditions such as pulmonary aspergillosis can easily be targeted by using suitable drug candidates, such as amphotericin B, in the form of pulmonary nanosuspensions instead of using stealth liposomes (Kohno et al 1997). With the advent of polymeric nanosuspensions loaded with drug, it should be possible to target sites, such as the colon, or bacteria, such as *Helicobacter pyroli*, by suitable modifications in the formulation strategy. Overall, nanosuspensions have indicated a good potential in targeted drug delivery.

Pharmacological and Toxicological Aspects

1. **Inhalation:** Exposure to fine particulate dusts leads to pulmonary diseases. The idea that any poorly soluble particles administered in sufficient quantities to the lung can cause an inflammatory reaction has arisen following the demonstration of rat lung overload (Mauderly et al 1994). An important challenge in particle toxicology is to define the quantity that produces inflammation i.e. define the effective dose. Since the late 1980's, toxicological evidence has been emerging indicating that the health effects associated with inhaling ultrafine particles may not be closely associated with particle mass. Early studies with PTFE (polytetrafluoroethylene) particles around 20 nm in diameter showed

> that airborne concentrations of a supposedly inert insoluble material lower than 50μg m^{-3} could be fatal to rats (Johnston et al., 2000). Since then, many studies have indicated that the toxicity of insoluble materials increases with decreasing particle size, on a mass for mass basis (Faux et al., 2003).

Traditionally the dose of particle administered to the lung, e.g. in an instillation or inhalation situation, is measured in mass. A number of recent studies indicate that the inflammatory response depends on the surface area of particles deposited in the proximal alveolar region of the lungs (Tran et al., 2000; Faux et al., 2003). Thus, particle surface area is a better metric than mass for relating the particle dose to the inflammatory reaction. The precise mechanisms by which these materials exhibit higher levels of toxicity, at smaller particle sizes, have yet to be elucidated, although it is now understood that oxidative stress plays an important role in initiating the chain of events, at the molecular and cellular level, leading to the observed health effects. This was demonstrated in a recent study in which in vitro experiments with a 12 range of poorly soluble particles were conducted (Faux et al., 2003). The data generated by this study were able to demonstrate a relationship between the surface area dose and inflammatory response *in vitro* and the earlier *in vivo* results. This discovery has important practical and theoretical implications.

At the theoretical level, it has highlighted the role of the epithelial cells in the proximal alveolar region, their interaction with the deposited particles and the ensuing molecular events leading to inflammation. At the practical level, it has offered a new approach to interpreting *in vitro* data, a cost effective way of screening new materials for toxicity and an alternative way to animal testing. But particles also exist in a wide range of surface reactivity. Upon deposition in the pulmonary region, such reactivity exerts an oxidative stress on the cells via contact between particle/cell surface area. Consequently, both highly reactive particles with a low surface area and low toxicity particles with a high surface area can exert the same oxidative stress level on the cells they come into contact with. When this inhaled dose reaches a critical level, an inflammatory response occurs. For low toxicity dusts, inflammation will diminish with the cessation of exposure, while for high toxicity dusts, inflammation will persist (Tran et al., 2000). Persistent inflammation is likely to lead to diseases such as fibrosis and cancer. Thus it is important to control inflammation. This can be done by (i) determining the critical dose of particles that initiates inflammation and (ii) setting up exposure limits, according to the relevant metric, so that such a dose cannot be reached within a lifetime exposure scenario. Regulations for the control of airborne particle pollution in the workplaces are currently mass based and vary between particulate types (HSE, 2002b). A proper description of the metric of the particle dose would provide a coherent and consistent body of knowledge on particle toxicity and would, in turn, facilitate a coherent and rational policy for regulating dust exposure in the workplace. Thus, it is apparent that measuring exposures against mass alone is not sufficient. Of the three primary exposure metrics (mass, surface area, and number), there is compelling evidence to suggest that occupational nanoparticle aerosols should be monitored in terms of surface area.

The concentration of nanoparticles might be very small in terms of mass, quite large in terms of surface area and huge in terms of particle number. However, the estimate of surface area does depend on the measurement technique used. Depending on how much detail of the surface is inspected, the measurement can increase significantly. For example, if a prune is seen as approximately a sphere then it has approximately the surface of a smooth sphere of the same diameter; but if the surface of the wrinkles is included then its surface area becomes notably larger. Similarly, with techniques that use adsorption of gas molecules on to the surface of the particle to measure the surface, the smaller the gas molecule chosen, the more it can enter the wrinkles on the particle surface. Nitrogen as the gas molecule for adsorption and measurement of surface area may be a good choice, but other gases (or other surface measurement techniques) are worth considering.

Biologically relevant surface area is likely to be that accessible to biologically relevant molecules in the body. So far, we have assessed the risk of pulmonary disease from inhaled particles. However, it has also been suggested that due to their small diameter, nanoparticles are capable of penetrating epithelial cells, entering the bloodstream from the lungs (Gilmour et al., 2004), and even translocating to the brain via the olfactory nerves (Oberdorster et al., 2004). The ability of inhaled nanoparticles to disperse beyond the lungs suggests that the health effects of nanoparticles may not be confined to the lungs. Also, nanoparticles cleared by macrophages via the mucociliary escalator, can be swallowed and therefore available for transfer to other body organs via the gastro-intestinal compartment. There is also some evidence that smaller particles can be transferred more readily than their larger counterparts across the intestinal wall (Behrens et al., 2002). Little is currently known about the health effects of nanoparticles on the liver and kidneys as well as the correct metric for describing the nanoparticle dose in these organs. Another area which merits further research is the transfer of nanoparticles across the placental barrier.

Exposure to nanoparticles during the critical window of foetal development may lead to developmental damage in the offspring. While a strong case may be made for using aerosol surface area as a dose metric, this may not be universally so. For example, for fibrous aerosols such as asbestos and glass fibre, the currently accepted best approach is to count fibres (i.e. the metric is particle number). Some types of nanoparticle could be considered fibres. Carbon nanotubes for example have high aspect ratios and are durable. They can be manufactured with lengths well within the range conventionally considered to be a fibre (although their diameters are much smaller than we could detect with current standard counting methods which are based on optical microscopy). In any case, it is also necessary to consider characterising exposures against aerosol mass and number concentration until further information and improved methods are available. For each of these exposure metrics, but particularly in the case of mass concentration, size-selective sampling need to be employed to ensure only particles within the relevant size range.

2. **Dermal Exposure:** The importance of dermal exposure to hazardous substances continues to increase. The UK HSE estimate that there are around 85,000 cases of work related skin disease at any one time, with people employed as bricklayers, laboratory technicians and hairdressers being at particular risk (Hodgson et al; 1993). Substances which are considered to be potentially harmful include pesticides such as methyl parathion and solvents such as carbon tetrachloride. Harmful effects arising from skin exposure may either occur locally within the skin or alternatively the substance may be absorbed through the skin and disseminated via the bloodstream, possibly causing systemic effects. Because of this there have been considerable efforts made to develop quantitative methods for monitoring skin exposure.

All of these techniques essentially measure the mass of material deposited onto the skin, either per body part or per unit area of skin exposed. Difficulties in this area are compounded by a multitude of measuring methods which are not easily comparable. The development of a conceptual model of dermal exposure has been beneficial in clarifying some of these issues (Schneider et al; 2000). Systemic effects in particular are unlikely to depend only on the mass on the skin but are more likely to be related to uptake through the skin. Uptake is the flux through the skin and will depend on the concentration through the skin, the area exposed and the duration of exposure. Because of this some authors have suggested that uptake is a more appropriate metric than mass (Robertson and Cherrie, 1995).

A recent review of dermal exposure issues concluded that there was no evidence to indicate that specific health problems are currently arising from dermal penetration of ultrafine particles (HSE, 2000). However, the review conceded that dermal absorption of ultrafine particles (nanoparticles) has not been well investigated and suggested that ultrafine particles may penetrate into hair follicles where constituents of the particles could dissolve in the aqueous conditions and enter the skin. Direct penetration of the skin has been reported by Tinkle et al (2003) for particles with a diameter of 1000 nm, much larger than nanoparticles. It is reasonable to postulate that nanoparticles are more likely to penetrate, but this has not yet been demonstrated. Several pharmaceutical companies are believed to be working on dermal penetration of nanoparticles as a drug delivery route. Any metric proposed to assess dermal exposure to nanoparticles should be biologically relevant and should relate to health effects. Further work including workplace studies and *in vitro* assessment of penetration is required. Based on the current level of knowledge, measurement approaches should include assessment of mass, particle number, concentration, area exposed and duration of exposure.

3. **Ingestion Exposure:** In occupational settings very little work has been done up to now on ingestion exposure. Lead is one of the few materials where the ingestion route has received some attention. Lead paint removal activity can produce high ingestion exposures via hand-mouth contact and food contamination in certain workplaces. A recent study has shown that workers involved in the supply and removal of scaffolding can have particularly high blood lead levels as a result of hand contamination and subsequent ingestion (Sen et al; 2002). No work was identified in relation to ingestion exposure of nanoparticles. Metrics to assess ingestion exposure to nanoparticles should be biologically relevant and (probably) in the first instance should be measures of mass uptake.

In conclusion, scientific evidence, so far, has demonstrated that particle surface area and surface reactivity is likely to be the metric of choice to describe the inflammatory reaction to deposited particles in the proximal alveolar region of the lung. For nanoparticles, their potential dispersal to other organs as well as the possibility of exposure by other routes such as dermal or ingestion mean that possible health risks beyond the lung cannot be ruled out. Further research to generate vital data on the possible mode action of nanoparticles in the extra-pulmonary system is needed in order to assess realistically the health risks to nanoparticle exposure.

CONCLUSION AND SUMMARY

Nanosuspensions appear to be a unique and yet commercially viable approach to combating problems such as poor bioavailability that are associated with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. Production techniques such as media milling and high-pressure homogenization have been successfully employed for large-scale production of nanosuspensions. The advances in production methodologies using emulsions or microemulsions as templates have provided still simpler approaches for production but with limitations. Further investigation in this regard is still essential. Attractive features, such as increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification and ease of post-production processing, have widened the applications of nanosuspensions for various routes. The applications of nanosuspensions in parenteral and oral routes have been very well investigated and applications in pulmonary and ocular delivery have been realized. However, their applications in buccal, nasal and topical delivery are still awaiting exploration. The development of stealth nanosuspensions laced with functionalized surface coatings capable of eliciting passive or active targeting as per the requirement can be regarded as the future step in the nanosuspension research.

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KEY TERMS AND DEFINITIONS

Alzheimer's Disease: Alzheimer's disease is a neurological disorder in which the death of brain cells causes memory loss and cognitive decline. A neurodegenerative type of dementia, the disease starts mild and gets progressively worse.

Atovaquone: It is a chemical compound belonging to the class of naphthoquinones with anti-pneumocystic activity.

Bhasmikarana: It is a process of reducing to ashes or calcinations. It is a method employed to convert a metal to its oxide form for a more medicinal application.

Bioadhesive: A property of natural polymeric materials to act as an adhesive or in simple terms any synthetic material designed to adhere to biological tissues.

Bioavailability: It is the measurement of rate and extent to which the administered drug reaches the systemic circulation. It is also one of the essential tools in pharmacokinetics.

Horizontal Gene Transfer: It refers to the transfer of genes between organisms in contrast to the transfer from parent to offspring (vertical). It is considered to be an important factor in the evolution and antibiotic resistance.

Micro-Emulsion: Dispersion made of water, oil and surfactant(s) i.e. an isotropic an thermodyamically stable system with dispersed domain diameter varying approximately from 1 to 100nm, usually 10 to 50nm.

Nanosuspensions: They are defined as a biphasic system consisting of any pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particles is less than 1μm.

Phage Therapy: It is defined as the therapeutic use of bacteriophages (virus infecting bacteria) to treat pathogenic bacterial infections. They are more specific in their mode of action compared to antibiotics.

PTFE (Polytetrafluoroethylene): It is a synthetic hydrophobic fluoropolymer used as a lubricant, coating material and a graft material in surgical interventions.

Sustained Release: It is the process of releasing any drug for a predetermined rate and maintaining a constant drug concentration for a specific period of time at minimal side effects.

Targeted Drug Delivery: A method of delivering the drug in such a way that increases the dose in some parts of the body relative to others. It is also an effective and a protective drug interaction strategy against diseased tissue.

Tumor: A condition resulting from the abnormal growth or division of cells forming a mass of tissues (Neoplasm).

Chapter 10

A Review of Various Nanostructures to Enhance the Efficiency of Solar–Photon–Conversions

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ABSTRACT

The problem of dwindling energy can be attributed to the rapidly increasing world-wide energy demand, leading to an urgent need for alternative energy-harvesting technologies to sustain the economic growth by maintaining our appetite for energy. Among them, solar-energy-harvesting is most promising, and the huge demand for clean, cost-effective, and cost-efficient energy can be met by solar energy. The large-scale solar energy utilization has not become practical because of the high cost and inadequate efficiencies of the current solar-energy-conversions. Nanotechnology

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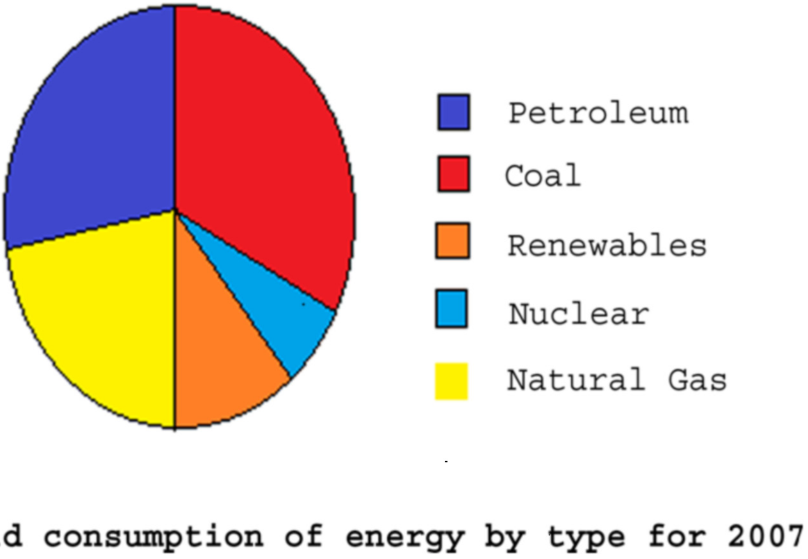
offers tools to develop cost-effective and cost-efficient technologies for solar-energy conversions. Nanostructures, such as nanowires, nanopillars, nanodomes, nanorods, quatumdots, nanoparticles, etc., facilitate photon absorption, electron transport, and electron collection properties of the solar-energy-conversion devices. This review specifically summarizes the contribution of the nanotechnology to photovoltaics, dye-sensitive solar cells, quantum-dot-sensitized solar cells, and solar hydrogen production devices.

INTRODUCTION

Energy supply is arguably one of the most important challenges that the whole world is facing today and a big concern in future. We heavily rely on the fossil fuels for this energy demand, which, being non-renewable energy sources will lead to quick depletion of these resources. As the population is increasing at a faster rate, so is the energy consumption as shown in Figure 1a. The ever increasing energy demand, of which ~ 65% is currently fulfilled by coal and petroleum (Figure 1b) has disturbed the life on all fronts (economically and technically, ecology and health, present and future). These resources are harmful to the atmosphere as their consumption not

Figure 1. It clearly demonstrates that petroleum, coal and natural gas are the most utilized fuels over renewables



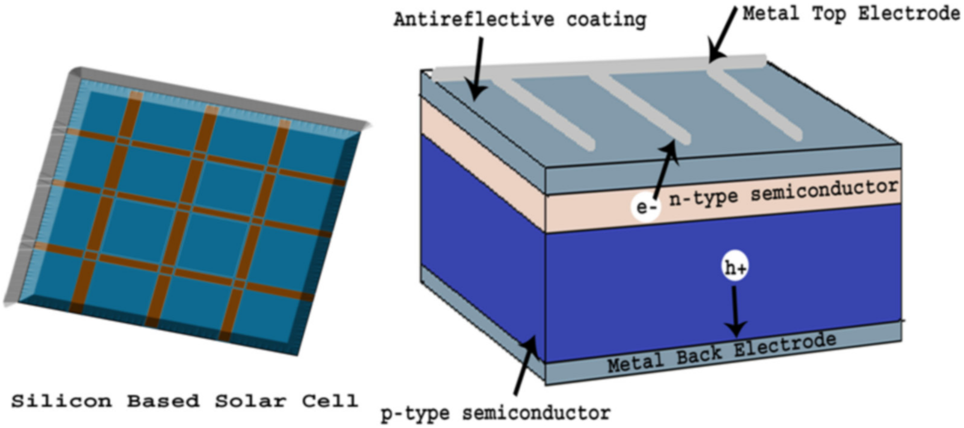
only provides energy but also releases green house gases into the atmosphere leading to global warming and other harmful effects on living beings (Service, 2005).

Contrarily, renewable energy sources such as solar, wind, geothermal, tidal are actively investigated as alternatives for both energy demand fulfillment and clean energy production. Among all the alternatives, solar energy is the most easily available and abundant source of energy. Besides, being the clean source of energy and available at almost every part of the earth, the total energy that the whole population of the world will consume in sixteen years at present rates of utilization is not more than the energy that earth's surface receives each day. Considering these factors, we can pin our hopes onto this source of energy for our better present and sustainable future.

Even though, solar-energy harvesting is attractive and promising to tackle the global energy problem and environmental pollution, harvesting solar energy in a low cost and high efficient way is not easy. The energy density of solar energy is far lower than the fossil fuels and also that sun light intensity is different at different places and at different times adds to the difficulty of harvesting solar energy.

Furthermore, storing this sort of energy is difficult as it cannot be stored in chemical bonds as in case of fossil fuels, which accounts to why solar energy utilization is as low as ~0.0015% of the total energy used today (Crabtree, 2007). The major hindrance to the large scale use of solar conversion devices such as photovoltaics, dye sensitive solar cells, quantum-dot- sensitized solar cells and solar hydrogen production etc, is their high cost and low efficiencies. Sunlight to electricity conversion has the highest theoretical efficiency and flexibility and hence there is a great potential to explore free and clean solar-energy in the form of electricity by techniques such as photovoltaics(PV's) (Fan, 2011), photo-electrochemical cells

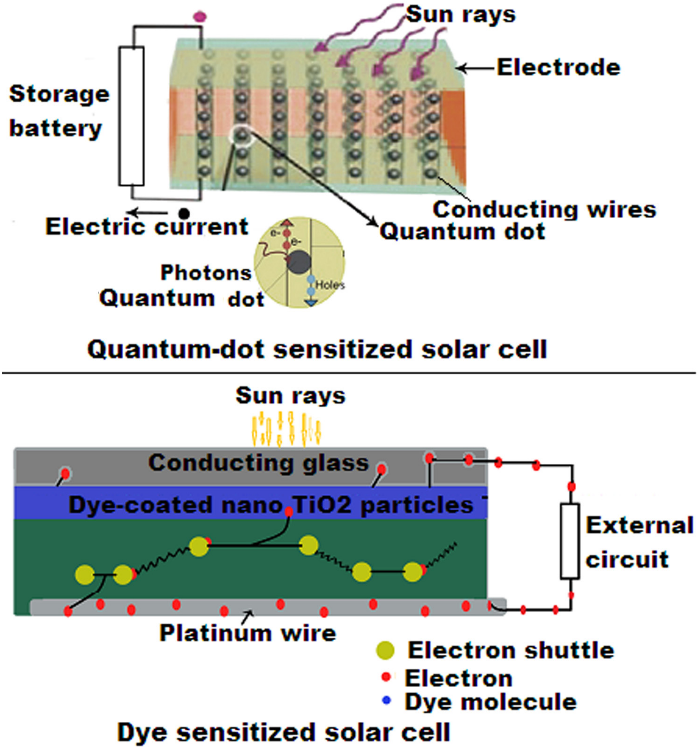
Figure 2. Conventional solar cells



(PEC's), electricity-storing solar hydrogen and quantum dot sensitized solar cells (QDSC). Single crystal based commercial solar cells, so called first generation solar cells have the efficiencies of ~18% (Crabtree, 2007; Lewis, 2005). These suffer from high cost of manufacturing and installation. The second generation polycrystalline semiconductor thin film solar cells ($CuInGaSe_2$) even though reduce the price significantly but the challenge to make their efficiency more practical for commercial application is still not overcome. The third generation solar cells (dye sensitive solar cells) (DSSC) (Bach, 1998), based on cheap dye and titanium dioxide ($TiO_{2)}$ semiconductor offer a typical of ~11% efficiency (Gratzel, 2001; Crabtree, 2007) and cells based on even cheaper dye are 2-5% efficient; bulk hetero-junction cells (Yu, 1995; Rowell, 2006; Huynh, 2002) and organic solar cells (Lagemaat, 2006) promise inexpensive and large scale solar conversion while as solar hydrogen production offers an efficiency of ~11% but out of the total commercial hydrogen production, only ~5% comes from the renewable sources of energy, mostly through water electrolysis (Ni, 2007) while as 70-80% of the total hydrogen production comes from steam reforming of natural gas (Service RF, 2004).

To develop new cost-effective and cost-efficient based industries, nanotechnology plays the role of a light house. Nanotechnology makes it possible to tune or manipulate atoms and molecules so as to design and control the properties of nanomaterials so that innovations needed to harvest incident solar photon with greater efficiency and economical stability (Green, 2004; Lewis, 2005) can be fulfilled. Nanostructured materials such as nanowires (Garnett, 2010; Yuhas, 2009), nanopillars (Fan, 2009; Cho, 2011), nanocone (Zhu, 2009), quantum dots and nanoparticles (Gerisher, 1986; Vogel, 1990; Kohtani, 1993; Vogel, 1994; Plass, 2002; Liu, 1993; Zaban, 1998) show extraordinary optical and electronic properties and hence make it possible to reduce the processing cost and increase the energy conversion efficiency in photovoltaics (Ning, 2011). The dominant advantage of the nanomaterials is the reduction of the active material for energy harvesting as compared to the entire wafer required for the bulk silicon based first generation photovoltaics (Garnett, 2008; Tsakalakos, 2007), leading to reduced cost of manufacture while the efficiency is not compromised. It has been also demonstrated that the facile synthesis of the nanomaterials, compared with the epitaxial growth of second generation solar cells reduces their processing costs (Lewis, 2007). Dye sensitized solar cells fabricated using several semiconductor nanoparticles (Corma, 2004; Singh RS, 2004; Singh VP, 2004; Mathew, 2000; Neale, 2007; Katoh R, 2007; Rodriguez I, 2007) and with different architectures such as nanotubes, photonic sponges (Ramiro-Manzano, 2007; Rodriguez, 2005), considerably increase their efficiencies through benefits such as direct path for charge transport and large surface area for harvesting light. The use of quantum dots in the quantum dot sensitized solar cells (QDSSC's) provides the ability of optical absorption tunning through selection of semiconductor material and particle size (Kehan, 2009). Single wall carbon nanotubes, decorated with quantum dots, as photo-anodes in QDSSC's generate photo current with unusually high efficiencies (Robel, 2006; Sheeney, 2005). Furthermore, in case of solar hydrogen production, the use of one dimensional nanomaterials with smaller band gaps are considered attractive for the anode materials of the solar hydrogen production devices (Chakrapani, 2009; Aryal, 2010; Hensel, 2010; Yu, 2005). Similarly, double sided zinc oxide nanorod arrays have been reported to yield an efficiency of nearly 45% (Wang, 2010) and the Vanadium dioxide (VO_2) when synthesized as nanorods, yields an photon efficiency of 38.7% (Wang, 2008). This paper reviews the recent progress in the above mentioned areas through the contribution of nanotechnology for a more sustainable use of energy. Specifically, the assemblies of nanomaterials in various active device structures in photovoltaics, dye-sensitive solar cells, Quantum-dot-sensitized solar cells and Solar hydrogen production are addressed as these are the most attractive in reducing the material and the processing costs and simultaneously improve the efficiency due to their unique optical and electronic properties (Ford, 2009, Takei, 2010).

Figure 3. Quantum dot sensitized solar cell. Adapted from Elena Serrano (2009).



NANOSTRUCTURED PHOTOVOLTAICS

Though solar energy being free and abundant in nature, still PV technology produces only about 0.04% of the total world's energy supply (IEA 2007). PV solar cells are devices which directly convert solar energy into electrical energy by means of photovoltaic effect. The big share in the PV market is shared by silicon based solar cells (First generation solar cells), which account for 86% of total global solar market. The reason that these PV cells only share about 0.04% of the total world's energy supply is that these suffer from certain limitations: (a) First, the sunlight comprises of different energy photons and hence conventional PV cells, which suffer from band gap flexibility and interchangeability utilize only some part of the incident energy for electricity generation and the rest is wasted as heat (b) Second, photon consumption only takes place at the exposed effective surface area of the PV cells and hence most of the bulk PV cell remains inactive, besides providing inadequate optical path. (c) Third, the electron-hole pairs, created at the site of production have high probability of recombination because of slow carrier collection and further suffer from drawbacks of surface reflectivity, "hot-carrier" creation, etc (Tisdale, 2010; Elena, 2009).

To overcome these drawbacks, nanomaterials have been engineered with tunable band gaps by controlling their dimensions (Huynh, 2002). On the other hand, since the dimensions of nanoparticles are lesser than 100 nm and hence are transparent to incident light so, for complete absorption, nanoparticles need to be mixed with larger dimension particles so as to scatter light effectively (Zhang, 2008). Furthermore, one dimensional nanomaterials have lengths upto 100 nm to tens of microns and hence scatter light effectively (Tan, 2006). Experiments have also shown that Zinc Oxide (ZnO) nanorod arrays act as effective anti-reflection coating in a broad band range of 400-1200 nm (Lee, 2008), while similar effects have been also observed in silicon (Garnett, 2010) so that most of the incident energy is utilized by the cell for better incident photon conversion efficiency (IPCE). Nanotubes have also shown high absorbance because of multiple reflections, once a photon is trapped inside nanotubes (Zhu, 2007). Nanostructures such as nanopillars (Fan et al 2011, Cho et al 2011), nanocone (Zhu, 2009; Jia, 2010) etc, improve significantly both photon absorption as well as carrier-collection efficiencies. Photon management, which comes to nanomaterials, reduces transportation losses due to shortened carrier-collection lengths and also for manufacturing-cost reduction, by reducing film thickness, expands the range; improve the throughput and quality of materials (Jia, 2010). Thus, it has been found that nanostructures have a tremendous impact on the performance of photovoltaics as discussed below:

Theoretically, it has been calculated that nanowire arrays have a higher absorbance in the high frequency range. Nanowire (NW) arrays reflect less amount of incident light due to their periodic structure. This structure not only absorbs photons directly incident on it but also the photons which scatter among its structure (Hu, 2007). Furthermore, the absorbance can be tailored by tunning the NW filling factor in the low frequency range to get higher absorbance. Effective photon absorption nanostructures are the tapered silicon nanowire arrays (Jung, 2010) and the dual diameter germanium nanopillars (bowling-bottle like structure) (Fan, 2010), in which the low filling factor (diameter = 60 nm) nanopilllar (NPL) array absorbs better in the high frequency region (λ=300-600 nm) whereas the higher filling factor (Diameter =130 nm) nanopillar array absorbs better in the low frequency region (λ=600-900 nm). This way the low and high filling factors are combined to design a dual diameter nanopillar array, which results in the higher absorbance of up-to 99% in the broadband range of 300-900 nm.

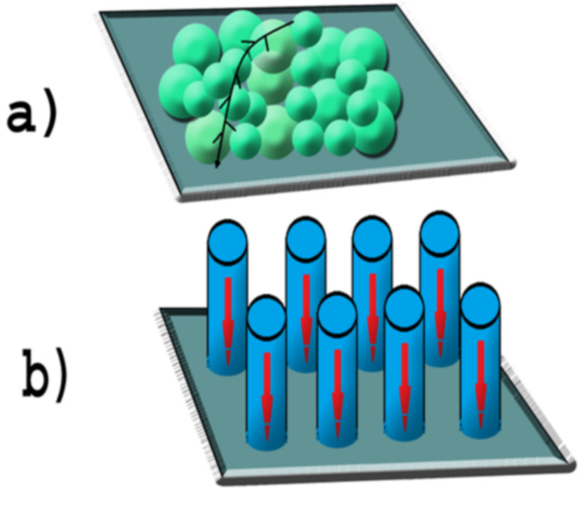
Perfectly ordered silicon nanowire array using self-assembly of silica beads show reduced transmittance of the incident light compared to the planar control sample, which indicates a strong light-trapping effect. Moreover, the apparent optical path thickness of the structure divided by its actual thickness, described as light-trapping path length enhancement factor is estimated to have increased by 73 times for the Si NW array in the air-mass-ratio (AM) of 1.5 G spectrum (Garnett, 2010).

In addition, 3-D nanostructures made of amorphous materials are also of great interest as an anti-reflecting layers for solar cells. Zhu et al fabricated a-Si:H nanocones using the wafer-scale Langmuir- Blodgett assembly and etching technique (Zhu, 2009). The length and the tip diameter of each nanocone is ~600 and ~20 nm respectively, while the base diameter is ~300 nm. These a-Si:H nanocone arrays have shown enhanced absorption of ~90% at angles of incidence up to 60°.It is further noted that by inserting a dielectric layer on the top of NW surface, the light absorbance of the nanowire device increased by about 102%(Liu, 2011). In fact, the 3-D arrays of the nanostructures resemble the botanical forests, which are the natural form of light harvesting structures (Rui, 2012).Separation of photo induced charge-carriers before recombination is important for generation of photo electricity. The carrier collection efficiency, which is determined by the relationship between the recombination time of photo-induced carriers and the collection time of photo-carriers from the material surface to the circuit (Ning, 2011) is an another factor determining the overall efficiency of the photon conversion devices. There are two ways to enhance the carrier-collection efficiency: (a) To extend the charge carrier recombination time or (b) to reduce the collection time of the photo-induced charge carriers.

Quasi-one dimensional (1-D) nanomaterials (nanowire, nanopillars, nanotubes, cones, etc) have been extensively investigated as nano-electronic and nano-opto-electronic materials because of their best, fast and controllable carrier transport along the long the axis (Rui, 2012), which favor the electron-collection than the nanoparticles because of the reduced collection time (Ning, 2011). These materials favor the photo-induced charge carriers to travel only across a reduced pathways and hence to reach the charge-separating junction before recombination. One dimensional (1-) single crystalline Zinc Oxide demonstrates that collection efficiency is enhanced due to the far shorter collection-time (Martesion, 2006). Single crystalline nanowires of TiO_2 have shown the electron mobility even higher in the case of single crystalline ZnO nanowires (Law, 2005). The radial electric field, which might be exhibited by one dimensional nanowires prevents the carrier recombination, especially in hetero-structures. This, larger recombination time might account for the one dimensional TiO_2 nanostructures for having enhanced electron collection efficiency (Ning, 2011). Vertically aligned arrays of radial p-n junction nanorod solar cells have been proposed, in which the arrays act as tiny solar cells (Spurgeon, 2008). Such a rod geometry allows high carrier collection efficiency as the photo-induced charge carriers have to travel shorter path ways to reach to the charge separating junction.

Silicon (Si), having high surface recombination velocity is preferable for Si nanowire fabrication with larger diameter to reduce the surface to volume ratio, with a passivation layer on the wire surface to reduce surface recombination (Rui, 2012). A device physics model, developed by Kayes et al for the radial p-n junction nanowire/nanorod solar cells provides the geometry to significantly improve the efficiencies of cells made from materials having low recombination in the depletion region and diffusion lengths lesser than their optical thickness (Barnham, 2006). The densely packed nanorods, each having a p-n junction in the radial direction are

Figure 4. Schematic electron transfer in (a) zero dimensional and (b) one dimensional nanostructures. Adapted from Ning et al. (2011).



oriented with the rod axis parallel to the incident light (Kehan, 2009). Gold catalyzed Si nanowire growth and single wire radial p-n junction solar cells have been fabricated with a-si and silicon nitride surface passivation coatings (Keizenberg, 2011). Such devices have been reported to have efficiencies of ~ 9%.

Several II-VI group compounds have smaller surface recombination velocities than silicon (Fan, 2009) and as such II-VI group compound semiconductor core-shell nanowire photovoltaic devices have been demonstrated. CdS/Cu_2S nanowire photovoltaic devices showed better performance than their thin film counterparts (Tang, 2011) because of better carrier collection efficiency (Bragnolo, 1980). Similarly, III-V compound semiconductor nanowire arrays were also demonstrated for PVs such as Magnesium doped gallium nitride nanowire array (Teng, 2008), indium phosphate core-shell nanowire array (Goto, 2009).

Three dimensional (3D) p-n junction formed by polycrystalline p-CdTe embedded n-CdS nanopillar array was demonstrated (Fan,2011). Due to the low surface recombination velocity and hence the better collection efficiency of the carriers in II-VI compound materials, these are promising for highly efficient future photovoltaics (Kapadia, 2010).Another major class of nanomaterials i.e nanoparticles have been extensively explored for PV application. These nanocrystal quantum dots (Ross, 1982) are usually made of direct band gap semiconductors, which have led to thin film solar cells based on silicon or conductive transparent oxide (CTO), like Indium Tin Oxide (ITO), substrate with a coating of nanocrystals (Elena, 2009). The motivation behind the related research rests in their size-dependent band-gap properties (Peng, 2001; Rogach, 2002), multiple-exciton generation (MEG) (Corwine, 2004) per photon and enable to breakdown the current thermodynamic limits; Also, many nanoparticles are compatible with solution based synthesis process and hence nanoparticle based PV fabrication can potentially utilize high throughput, low temperature and low cost processes, such as ink-jet printing (Hou, 2009). Since nanoparticles have different emission and absorption spectra, which depends on their particle size, these raise the theoretical limits by adapting to the incoming solar light spectrum (Elena, 2009).

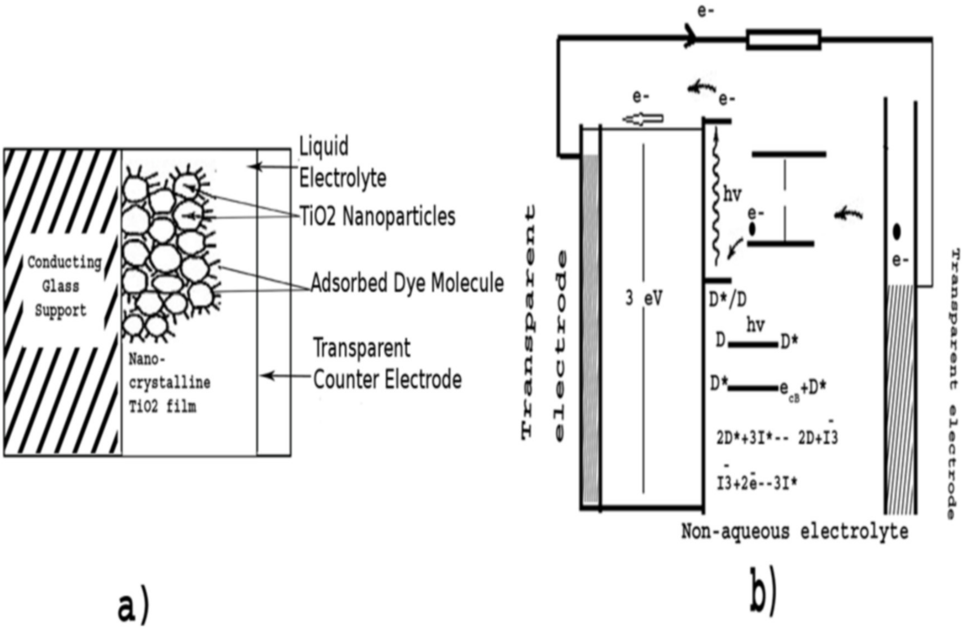
Conventionally, one photon with energy above band-gap energy generates only one electron-hole pair and rest of the extra energy is wasted as thermal energy due to energy conservation. Thus, the thermodynamic limit sets the highest possible efficiencies of 33% for a single junction solar cell (Schokely, 1961). In multiple-exciton generation (MEG) process, a single high energy photon excites two or more electron-hole pairs due to discrete energy levels in quantum-dots (Luther, 2008; Gur, 2005). These discrete energy levels in quantum dots slow down the dissipation of extra energy, which is possessed by created excitons. The slowing down of dissipation of energy leads to the creation of new excitons which is in contrast to conventional photovoltaic devices, where the extra energy is quickly dissipated as thermal energy because of the inelastic carrier-photon scattering (Mary D, 2008). The main focus in quantum-dot photovoltaic devices has been mainly on the relationship between the quantum confinement and the multiple-exciton generation process. Considering that the coulomb-coupling and density of energy states do not cancel each other, it has been found that as the quantum-dot volume decreases, the MEG rates increase. In an another argument by Lin et al, MEG efficiency is more appropriately described by the calculations using fixed relative photon energy, rather than single absolute photon energy for each quantum-dot, as both effective coulomb-coupling and density of energy states are energy dependent (Lin, 2010).

Excitation energy threshold for MEG process was first reported by Schaller and Khilmov for PbSe nanocrystals (Schaller, 2004). It was reported that the MEG process takes place when the incoming energies were more than three times than the band-gap energy of PbSe nanocrystals. At photon energies of four times the band-gap energy, with 3.9 nm diameter PbSe quantum-dot crystals, three excitons per photon were yielded for every photo-excited quantum-dot (Ellingson, 2005). Several other groups have also reported MEG process on CdSe quantum-dots (Schaller, 2005), InP quantum-dots (Stubbs, 2010), PbTe quantum-dots (Murphy, 2006), and Si quantum-dots (Beard, 2007).Based on the above briefly discussed nanostructures, a number of solar conversion devices have been fabricated using Si, TiO_2, InP, CdS, GaAs, ZnO, CdSe, CdTe etc (Garnett, 2010; Fan, 2009; Cho, 2011; Kelzenberg, 2010; Colombo, 2009; Gur, 2005; Luther, 2008). Among them, Si nanowire based PV devices exhibited an efficiency of ~17.4% (Kelzenberg, 2011), hybrid-Si multiwire (MW)-planar solar cells ~11% efficiency (Kim, 2011), InP NPL solar cell ~8.1% efficiency (Cho, 2011), CdS NPL solar cells ~6% efficiency (Fan, 2009), Nanodome solar cell ~ 5.9% (Zhu, 2010), CdSe/CdTe bilayer quantum-dot solar cell ~2.9% efficiency (Gur, 2005), PbSe nanocrystal/metal PV cell ~2.1% efficiency (Luther, 2008).

DYE SENSITIZED SOLAR CELLS

Dye-sensitized solar cell is an alternative offered by nanotechnology to the conventional silicon based photovoltaic devices and hence to the solar energy harvesting devices. A dye-sensitized solar cell is basically a photo-electrochemical (PEC) solar cell, which works on the principle of wide band-gap semiconductor sensitization by photo-excited dye molecules (Nazeeruddin, 2001; Wang, 2003; Gregg, 2003). A major advantage of the dye is that it absorbs visible light, which is more intense than the UV light absorbed by wide band-gap semiconductors, even though the energy of visible light is lower than the UV light (Ning, 2011) with an advantage of low cost materials. Gerishcer and Memming reported the sensitization of wide band-gap semiconductors by adsorbed monolayers of dye molecules in the late 1960's (Gerischer, 1972). In 1988-1991, a conceptual and practical breakthrough occurred when Gratzel's group first reported the DSSCs based on the low cost nanoparticles of TiO_2 (Oregan and Gratzel 1991; Vlachopolous, 1988) as nanoparticles provided larger surface area for the absorption of light harvesting dye molecules. The working principle of DSSCs is different from that of photovoltaics. In PVs, the absorption and the collection of photo-excited electrons takes place in the same semiconductor material while as in case of DSSCs, the generation and collection of photo-excited electron takes place in two different materials. The dye molecule absorbs the incident photon and hence an electron is excited from its ground state. Since the dye molecules are adsorbed on the semiconductor surface, the excited electron is transferred into the conduction band of semi-conducting material, leaving the dye molecule in an oxidized state. The transparent conducting oxide (TCO) accepts the electron, which then travels through the external circuit to the cathode. At the cathode, the triiodide(I_3^-) in the electrolyte accepts the traveling electron to yield iodide (I^-), which reduces the oxidized dye molecule. During this whole process, there is no net chemistry in terms of the chemicals created or destroyed in the device and hence the cell is regenerative (Kehan, 2009). Hence, the role of semiconducting material

Figure 5. Dye-Sensitized nanocrystalline TiO_2 PEC solar cell device structure. (b): Dye-Sensitized nanocrystalline TiO_2 PEC solar cell operational principle. Adapted from Satyen (2005).



is to offer a pathway for the excited excitons so as to travel to the external circuit and hence their properties are of great importance to determine the efficiency of DSSC. DSSCs have good solar -to-electricity yield of ~8% (Gratzel, 2001), which has further increased to ~11% (Grartzel, 2005).

The incident photo-to-current conversion efficiency (IPCE) is defined as

$$\text{IPCE} = \text{LHE}.\ \Psi_{\text{injection}}\ .\eta_{\text{collection}}$$

where LHE is the light harvesting efficiency, which can be subsequently improved by the use of nanostructures which can scatter more light for further absorption by the dyes and the use of well chosen dye. $\Psi_{\text{injection}}$ is the electron injection efficiency from the dye molecules to the conduction band of semiconductor dye-absorbent layer, which depends on the surface area contact between semiconductor material and the dye. $\eta_{\text{collection}}$ is the electron collection efficiency, which can be increased by the suppression of photo-exciton recombination rates. Regarding the enhancement of the above three factors i.e LHE. $\Psi_{\text{injection}}$, $\eta_{\text{collection}}$ several types of nanostructures have been synthesized as discussed below:

The nanoparticle film (~10 μm thick) provides a larger surface area (~ 1000 times higher) than the geometrical electrode area for better absorption of light-harvesting molecules (usually ruthenium-based dyes) (Kehan, 2009). Thus, anodes of DSSCs are typically constructed with nanoparticles of wide band-gap semiconductors such as CdTe, CdS (Singh RS, 2004), SnO_2 (Bedja, 1994), ZnO (Bedja, 1997; Hamann, 2008) or TiO_2 (Fessenden, 1995; Burke, 2008). However, a major hindrance in the enhancement of efficiency by the use of nanoparticles is the electron-trapping effect, because of large diffusion lengths. The isolated nanoparticles, surface states or defect states usually trap electrons. The trapping of electrons slows down the electron transport through diffusion and hence the recombination of electrons and holes competes with the electron accumulation into the anode and thus decreases the $\eta_{\text{collection}}$ (Fisher, 2000; Oekermann, 2004; Nelson, 1999; Van De Lagemaat, 2001). The large injection velocity should be at least 100 times faster than the recombination velocity, so as to suppress the electron-hole recombination and hence enhance the charge-collection efficiency (Gratzel, 2005).

Electron-collection efficiency is further enhanced by replacing nanoparticle anode by nanowire arrays as the electron transport is expected to be faster by several orders of magnitude, due to reduced electron trapping in crystalline nanowires (Law, 2005; Lee, 2008). The electron diffusivity of Dn = 0.05-0.5 $cm^2\ s^{-1}$ is estimated for ZnO nanowire. Compared with ZnO nanoparticles of Dn = 10^{-4} $cm^2\ s^{-1}$, the nanowire array anode can collect charge-carriers much more effectively (Kehan, 2009).Electron-collection-time can further be reduced by introducing another semiconductor shell with well aligned band-gap (Gabbala, 2008; law, 2006). The difference in the conduction band potentials of the shell and the core wire sets up a potential gradient (shell conduction band potential < core wire), which enhances the injection of electrons in the core and reduces the recombination rate. High electron mobility has also been for several other semiconductor nanowire structures such as Stannic Oxide (Gabbala, 2008), Gallium Nitride (Chen, 2010) etc. Stannic oxide and Gallium nitride nanowires have also shown good stability in electrolyte solution. However, nanowire exhibit smaller surface area than nanoparticle and hence because of the low dye loading, the efficiency of the DSSC with nanowire photo-anode is not enhanced (Ning, 2011). Further, Chen et. al. also found that if Gallium Nitride nanowire surface is modified with TiO_2 shell, the loading of the dye molecules is enhanced. This modification resulted in the enhanced cell efficiency from 0.003% to 0.44% (Chen, 2010). Boettcher et. al. also demonstrated the use of Silicon nanowire arrays prepared by Vapor-liquid-solid growth with copper as catalyst, yielding an efficiency of ~3% (Boettcher, 2010).

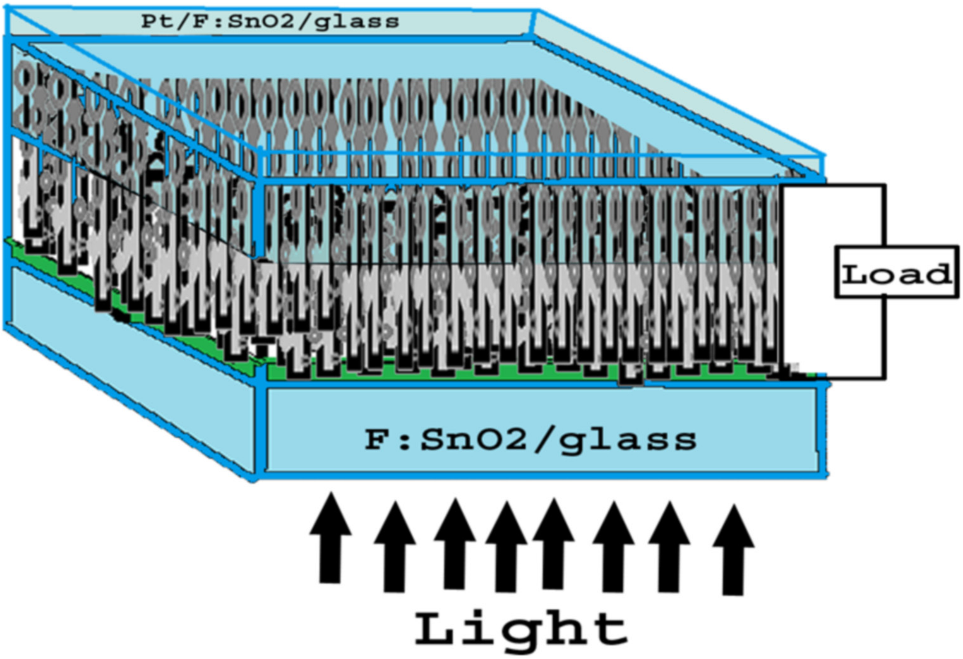
The double surfaced nanotubes (Hafez, 2010; Gabbal, 2008; Law, 2006; Zhu, 2007) have surface area comparable to the nanoparticles and thus show effective dye-loading and also display inhibited recombination characteristics (Zhu, 2007). In order to improve the electron transport path-ways, TiO_2 nanotubes have been fabricated (Paulose, 2006; Mor, 2006; Shankar, 2008) and a good efficiency has been obtained even though not better than the efficiencies obtained in nanoparticle anode DSSCs. Nanorod structures, which have lengths of 100-300 nm, diameter of 20-30 nm when employed as photo-anodes for DSSC yield an efficiency of 7.9% (Jiu, 2006) which is still lower than the best nanoparticle-based DSSC, because of the lower surface area of the nanowires. Consequently, hybrid anodes have been investigated to enhance the cell efficiency. Tan and Wu reported that 20 wt% (weight percent) TiO_2 nanotubes loaded on TiO_2 nanoparticles when employed as anodes, yield an enhanced efficiency of 8.6% (Tan, 2006). Also, TiO_2 nanowires, when loaded on TiO_2 nanoparticles with wt% of 5-10%, demonstrated an enhancement in the efficiency of the cell (Suzuki, 2006). Other way of increasing the efficiency of DSSC is by guiding light on to the nanostructures. In such a hybrid design, the ZnO nanowires were grown normally to the optical fiber. The incident light hence, falls normally to the fiber axis (NA) or parallel to the fiber axis (PA). Based on these two configurations, it was found that the fill factor, of PA case was three times as that of NA case, which suggested that the wave guiding property of optical fibers becomes excellent light trapping mechanism for the DSSCs (Weintraub, 2009).

The main advantage of the nanostructures for DSSCs is that these structures offer larger surface area for better dye loading. Hence, hierarchical nanostructures have been fabricated to explore the application of the these hierarchical nanostructures in DSSCs (Ko, 2011; Jiang, 2007). The ZnO-nanoforest provides extremely large surface area for dye absorption, high carrier extraction and increased light harvesting efficiency. Single Wall Carbon Nanotubes (SWCNTs) have extremely high electron mobilities and hence TiO_2 nanoparticles were deposited on single wall carbon nanotube arrays. Such a hybrid structure of SWCNT/TiO_2 film showed an improved charge-separation (Brown, 2008), when modified by a sensitizers. The incident photon to charge carrier efficiency was enhanced by a factor of 1.4 at all wavelengths, because of the the improved electron transport within the nanostructured TiO_2 film.

Quantum Dot Sensitized solar cells (QDSSCs), which are the combination of nanostructure architectures, provide another option to harvest solar energy. QDSSCs are analogous to the DSSCs, with the dye being replaced by quantum-dots (QD), which provide additional properties that are not available with the dye sensitized solar cells.The use of quantum dots in lieu of dye molecules have an advantage to tune the optical absorption through the selection of material as well as the particle size and better hetero-junction formation with the conductors of the quantum-dots. Also, QDSSCs have the unique potential capability to exploit the multiple electron-hole pair generation per photon (MEG) to achieve higher efficiency(Klimov, 2006; Hanna, 2006) and even greater than one by MEG (Nozik, 2002; Mary D, 2008). Due to high collection and transportation of charges, SWCNT have been explored; mainly focusing on the composite systems including carbon nanotubes with CdSe (Banerjee, 2004), CdS (Shi, 2004), TiO_2 (Banerjee, 2002) and SnO_2 (Han, 2003) nanocrystals. For example, CdS QDs can be deposited on SWCNTs with chemical methods. The CdS-SWCNT composite generates a photo-current from visible light with very high efficiencies (Sheeney-Haj-Ichia L, 2005).

The successful assembly of various nanocrystals, including single-component nanocrystals for-example, gold (Au), Silver (Ag) and Tin Oxide (SnO_2) and multi-component nanocrystals (SnO_2 and Ag) onto randomly dispersed multiwall carbon nanotubes (MWCNT), single wall carbon nanotubes (SWCNT) and vertically aligned MWCNTs has been demonstrated (Chen, 2006; Lu, 2007; Zhu, 2008). Other semiconductor materials like ZnO and TiO_2 have also demonstrated high charge transport and hence have been explored for QDSSCs. Quantum dot sensitized ZnO-nanowire solar cell, based on photo sensitization of ZnO nanowires with CdSe quantum dots has been demonstrated as shown in Figure 6. The ZnO nanowires were directly grown onto transparent and conducting FTO substrates (Law, 2005; Baxter, 2006; Greene, 2003), with CdSe quantum dots assembled onto ZnO nanowires. The excitation of electron-hole pairs in CdSe QDs takes place by the visible light photons, which generate photo-current. The injection of electrons into ZnO is facilitated by the QD and ZnO conduction band overlapping. The ZnO nanowire-based QDSSCs exhibit an efficiency of 0.4% while as TiO_2 nanotube based QDSSCs, with cadmium sulphide (CdS) quantum-dots exhibit an impressive efficiency of ~4.15% (Sun, 2008). These results clearly demonstrate that photo-electrochemical cell efficiency can be enhanced by depositing inorganic semiconductor QDs onto the TiO_2 nano-

Figure 6. Schematic of Quantum Dot Sensitized Solar Cells (QDSSCs). An array of vertically grown ZnO nanowires decorated with CdSe quantum dots, serves as photoanode. Adapted from Kehan et al. (2009).



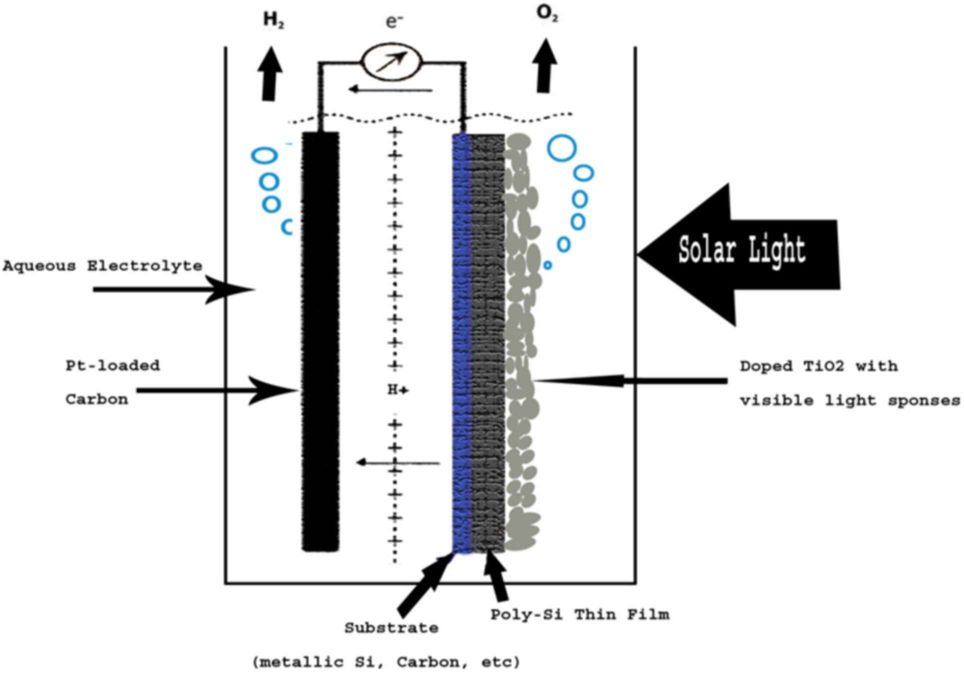
tube arrays. Further-more, maximum overlap of solar spectrum and the solar cell absorption spectrum by selecting tunable band-gap QDs can significantly improve the conversion efficiency of QDSSCs.

Hydrogen Production

Photo-voltaic devices and photo-electrochemical cells depend on the geographical location and operational time span to generate electrical energy from solar radiations. Since solar radiations vary in accordance with the geographical location and time hence, storage of this energy from PV's and PEC's becomes necessary for continuous and higher demand -times usage. Typically, such energy generated from PV's and PEC's is stored in the form of electricity in the batteries but this storage does not persist for long durations (Ning, 2011) and is subjected to losses. On the other-hand, if electrical energy produced from solar radiations were to be stored in the form of chemical bonds, it would result in higher efficiency and longer storage-times with negligible losses. One such alternative of storing solar energy is in the form of hydrogen; fulfilling the above mentioned properties and also being a clean source of energy, rather vector: it is as clean as the way used to produce it. One of the most attractive features of hydrogen, besides its clean production is the end product of its combustion, which is only water. So, by combining its clean production with its clean combustion, a fully environment friendly energy system is set up, with reduction in carbon emissions and dependency on fossil fuels (Elena, 2009).

At present, most of the global hydrogen production is done by steam reforming of the natural gas, which has 70-80% efficiency, with drawbacks of carbon dioxide emissions. However, clean hydrogen, which is produced from renewable sources of energy mainly through water electrolysis (Leung, 2007) constitutes only about 5% of the commercial hydrogen production. This hydrogen production and its usage in fuels is a clean alternative source with 70% of efficiency, but it consumes significant amount of electricity, which increases its cost of production considerably-in this two step process. Consequently, the direct production of hydrogen from renewables, avoiding all electrical and mechanical losses is the thrust area in this research for commercial hydrogen production.Artificial photosynthesis or water splitting by photocatalysis, is being actively researched for cheap hydrogen production and is one of the most promising and attractive methods for direct hydrogen generation

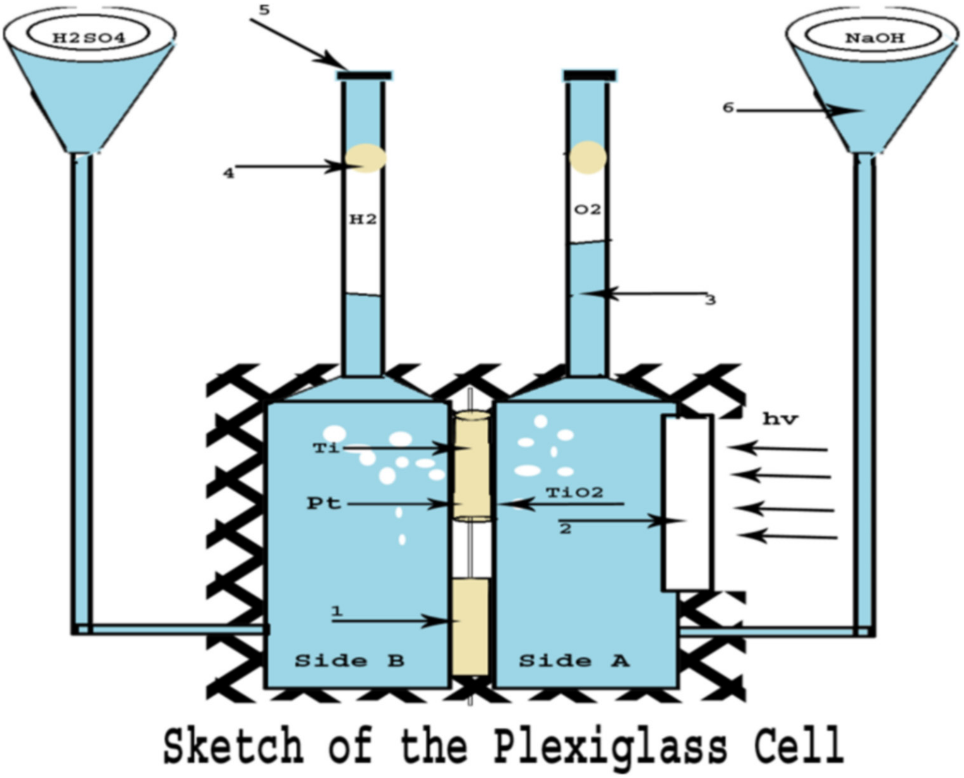
Figure 7. Schematic diagram of hydrogen production cell. Adapted from Ellena S et al. (2009).



from primary renewable energy source, both economically and technically (RSC, 2008; Zuttel, 2002). Nanotechnology is envisioned to provide tools that can make hydrogen production possible from solar energy, in a clean, environmental friendly and low cost way. Such a system consists of a photosensitive nano-semiconductor electrode, an electrolyte which may be an acid or alkaline and a counter electrode as shown in Figure 7. A photosensitive catalyst is exposed to sunlight, which produces electron hole pairs. Holes, so produced diffuse into the interface with water and hence water would be oxidized to produce oxygen. At the counter electrode,the electrons, which are transported through the back contact reduce water to hydrogen (Ning, 2011). For this purpose, a variety of nanostructured systems based on ZnO, TiO_2, CdS, $CuInSe_2$, SiC etc have been explored (Li, 2010; Shankar, 2009; Jang, 2008; Sebastian, 2008; Silva, 2008; Ni, 2007). Among these materials, TiO_2 is the most promising candidate as it fulfills all the above mentioned requirements (Elena, 2009). However, in this process, there are several drawbacks, which reduce the practical solar-to-hydrogen conversion efficiency of such devices. For-example, in case of TiO_2, the band gap is around 3.2 eV and hence only UV light of the solar spectrum would be workable. Also, oxygen and hydrogen recombination takes place to produce water back and the recombination of electron-hole pairs at the site of production decrease the available electron-hole pairs for water splitting (Ni, 2007). In order to surmount these barriers, a number of approaches have been proposed, which have been classified into two main categories (a) addition of chemical additives and (b) the modification of photo-catalyst. The addition of chemical additives, which are sacrificial reagents or hole scavengers, react with the valence band holes irreversibly avoiding charge recombination. These include inorganic ions such as S^{2-},$/SO_3^{2-}$, Ce^{4+}/Ce^{3+}, IO^{3-}/I^- and hydrocarbons such as ETDA, Ethanol, Methanol, Lactic acid etc (Abe, 2001; Sayama, 2002; Lee, 2004; Nada, 2005). The photocatalytic modification includes (a) noble metal loading, such as Ni, Cu, Ag, Rh, Au, Pd, Pt inhibit charge recombination (b) ion doping, including transition metal and rare earth metal ions as well as anions like nitrogen and sulphur expand the photoresponse to visible region (c) dye sensitization, as in DSSC's (d) coupling of semiconductors and (e) metal ion implantation (Elena, 2009). In one way or the other, many of these modifications, which have been mentioned above have been discussed in earlier sections, discussing different properties of nanomaterials/structures with the aim to enhance the photon absorption and suppress the charge recombination.

Different nanostructured anode materials have thus been synthesized to enhance the hydrogen production. An increased IPCE has been found with 3.7% nitrogen doped ZnO nanorods as compared to pure ZnO nanorods (Yang, 2009) with the efficiency of ~0.15% due to low IPCE in greater than 400 nm wavelength. Double side ZnO nanorod arrays on Indium Tin Oxide glass, decorated with cadmium selenide on the other side yielded an high IPCE of 45% in the wavelength range of

Figure 8. Sketch of the Plexiglas cell for photo catalytic water splitting, with separate H_2 *and* O_2 *production 1: Cation exchange membrane 2: Glass filter window 3: Burette 4: stopcock 5: Rubber septum 6: Reservoir. Adapted from Elena Selli et al. (2007).*



300-600 nm. Due to the stability and suitable band positions, Titanium dioxide, Zinc oxide and strontium titanate have been widely used as anode for water photo-splitting (Ning, 2011). Smaller band gap materials such as Fe_2O, CuO/Cu_2O, Tungsten Nitride and other III-V and II-VI compound semiconductors have also been proposed for the anode materials. Branched copper oxide nanowire arrays showed a solar-to-hydrogen conversion efficiency of 0.6%. Core-shell nanorod arrays of CuO/ZnO, due to its antireflection property of nanorod array, wider absorbance spectra, better carrier collection and charge separation showed increased IPCE of 0.71% (Berrreca, 2009; Zhao, 2010; chakrapani, 2009; Araya, 2010; Hensel, 2010; Ye, 2005).

CONCLUSION

Solar-Energy and nanotechnology together have the potential to resolve the problems of present and future generations. By incorporating nanotechnology, the cost of solar-energy utilization systems, which is directly related to the low conversion-efficiency, diluted energy-density of solar energy, costly materials and fabrication processes, new ways have been explored to reduce it and thus, nanostructures have made it possible to realize the goal of cost-effective and cost-efficient economies based energy industry. The goal is to notably increase the efficiency and hence reduce the cost of production. Side-by-side, it has also made it logical to realize the goal of clean energy and thus helping to survive better.

This review summarizes how nanoparticles, nanotubes, nanocones, nanodomes, nanowires, nanopillars, nanoforests, quantum dots and nanocomposites etc contribute to the realization of the efficient photovoltaics, DSSCs, QDSSCs and solar hydrogen production. The different factors related to solar conversion-efficiency have been modified at individual levels and to some extent, a couple of these together. For-example in case of nanodome structure, both the factors of antireflection and light trapping effects are achieved. Similarly, all the major efficiency related factors need to be modified on the same table. Over the last decade, the development of nanoscience and nanotechnology has provided new designs and strategies to develop nanostructured architectures for efficient solar energy conversion systems. Further-more, one does not require to focus only on the production of the sustainable energy but also on better storage of this energy. By achieving little in both these goals together, it would mean a higher achievement at individual levels. Even though at present we are far away from a truly sustainable energy system, the scientific community has found a way, through nanotechnology and hence acceleration in the development of cost-effective technologies is to be focused. The significantly improved photon management is likely to deliver a new generation of cost-effective and cost-efficient photovoltaic, photo-electrochemical and hydrogen production systems.

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KEY TERMS AND DEFINITIONS

Artificial Photosynthesis: Separation of hydrogen and oxygen molecules from water using solar light.

Cost-Effective and Cost-Efficient: Energy harvesting technology should not be too expensive to commercialize and even, if it is not, it should be highly effective enough to full the energy demands.

Dye-Loading: The adsorption of dye molecules onto the surface area of nanoparticles.

Energy-Harvesting Technologies: In most cases, energy cannot be directly used as received but it needs to be harvested in other forms.. For-example, solar light cannot be directly used to light bulbs. It, first, needs to be converted into electricity by using photovoltaic technology.

Ink-Jet Printing: A type of computer printing that creates a digital image by droplets of nanomaterial-ink onto desired substrates.

Nanotechnology: In simple sense, it is the tunning or manipulating the shape and size of materials at nanoscale (10^{-9}m).

Chapter 11

Convergence of Nanotechnology and Microbiology

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ABSTRACT

The convergence of nanotechnology with microbiology is a nifty interdisciplinary research area that could amplify the limits of technology, enhance global health through formation of different drugs that can be effective against different infectious diseases, and for treatment of drinking water to kill the pathogens and make it safe for public use. Bacteria, fungi, actinomycetes, and plants have been successfully used for the formation of nanoparticles of silver, gold, zinc, etc. As the microorganisms, especially bacteria, are becoming resistant to the commonly used antibiotics, an alternative antimicrobial agent that can be effective against the antibiotic-resistant bacteria is needed. In the present chapter, the author highlights the relationship between these two mighty disciplines. The chapter deals with many aspects like antimicrobial activity of nanoparticles, formation of nanoparticles using micro-organisms, etc. The green synthesis of nanoparticles is emerging as a new field of science; hence, it is discussed in detail.

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INTRODUCTION

Nanotechnology is emerging as one of the leading subject of interest for researchers. Nanoparticles preparation and application in various fields like catalysis, electronics, environmental, pharmaceutical and biotechnology has been expanded significantly. Microbiology relates to nanotechnology at number of levels. It is well known that many organisms can produce inorganic materials either intra or extracellularly. For example, unicellular organisms such as magnetotectic bacteria produce magnetic nanoparticles and diatoms synthesize siliceous materials. Many bacterial entities are nano-machines in nature, including molecular motors like flagella &pilli. Bacteria also form biofilms by the process of self-assembly (e.g the formation of curti film by E.coli). Nanotechnology can be used to study the process of biofilm formation, a key medical problem. It can also be used to study the self-assembly of viral capsids as we desperately need anti-viral drugs.

World is facing a new problem of water scarcity. The availability of drinking water is decreasing rapidly due to water pollution and climatic change. Microorganisms like bacteria viruses and protozoa are a great threat to the available fresh water resources. These organisms can contaminate the water bodies resulting in different kind of water born diseases like cholera hepatitis etc. overcoming this challenge is becoming increasingly difficult as the demand of safer water grows with the increasing in world population and climate change threatens to take away a large fraction of already scarce fresh water. Nanotechnology can enable both safer and sustainable solutions to these problems. By the help of nanotechnology we can develop new processes and enhance the performance of existing treatment process. Nanotechnology can address emerging disinfection challenges to make water safe for consumption (e.g., photocatalytically enhanced disinfection, biofouling-resistant membranes, biofilm and corrosion-resistant surfaces, and sensors for pathogen detection)

Bacteria which are not exposed to large concentrations of metal ions may also be used to synthesize nanoparticles. It has long been reported that among the eukaryotes yeasts are explored mostly in the biosynthesis of semiconductor nanoparticles. Fungi have also been used for the synthesis of nanoparticles. The use of fungi is potentially excited since they secret large amounts of enzymes and simpler to deal with in the laboratory.

Biosynethesis of nanoparticles from plants, bacteria, fungi is gaining interest as the process is less time consuming and economical compared to chemical synthesis. Many bacteria have been successfully used for the preparation of gold, silver, zinc and other nanoparticles. Biologically synthesized nanoparticles are being widely used in the field of medicine. For the last two years extensive work has been done to develop new drugs from natural products because of the resistance of microorganisms to the existing drugs.

Liposomes discovered in mid 1960s were the original models of nanoscaled drug delivery devices. They are spherical nanoparticles made of lipid bilayer membranes with an aqueous interior but can be unilamellar with a single lamella of membrane or multilamellar with multiple membranes. They can be used as effective drug delivery systems. Cancer chemotherapeutic drugs and other toxic drugs like amphotericin and hamycin, when used as liposomal drugs produce much better efficacy and safety as compared to conventional preparation.

Viral vectors used for gene transfer have the limitations of safety concerns and stimulation of immune system with production of antibodies against the viral vectors. Further, naked DNA cannot cross the negatively charged cell membrane as these are also negatively charged (Peters A et al 2000). Hence,there is a need for other modes of transfer of genetic material such as nanoparticles based gene therapy. Liposomes measuring less than 100 nm can be used for the delivery of genetic material into cells. Liposomes incorporated with polyethylene glycol and galactose target liver-cells effective due to their rapid uptake by liver Kupffer cells. Thus gene therapy may be tried with such liposomal nanoparticles for various liver disorders such as Wilson's disease and hereditary hemochromatosis.

The rapid and sensitive detection of pathogenic bacteria at the point of care is extremely important. Limitations of most of the conventional diagnostic methods are the lack of ultrasensitivity and delay in getting results. A bioconjugated nanoparticle-based bioassay for *in situ* pathogen quantification can detect a single bacterium within 20 minutes. Detection of single-molecule hybridization has been achieved by a hybridization-detection method using multicolor oligonucleotide-functionalized QDs as nanoprobes. In the presence of various target sequences, combinatorial self-assembly of the nanoprobes via independent hybridization reactions leads to the generation of discernible sequence specific detection of multiple relevant sequences

A spectroscopic assay based on SERS using silver nanorods, which significantly amplify the signal, has been developed for rapid detection of trace levels of viruses with a high degree of sensitivity and specificity. The technique measures the change in frequency of a near- infrared laser as it scatters viral DNA or RNA. That change in frequency is as distinct as a fingerprint. This novel SERS assay can detect spectral differences between viruses, viral strains, and viruses with gene deletions in biological media. The method provides rapid diagnostics (60s) for detection and characterization of viruses generating reproducible spectra without viral manipulation. This method is also inexpensive and easily reproducible. The use of nanoparticles as tags or labels allows for the detection of infectious agents in small sample volumes directly in a very sensitive, specific and rapid format at lower costs than current in-use technologies. This advance in early detection enables accurate and prompt treatment.

Quantum dot technology is currently the most widely employed nanotechnology in this area. The recently emerging cantilever technology is the most promising. The technology strengthens and expands the DNA and protein microarray methods and has applications in genomic analysis, proteomics, and molecular diagnostics. Waveguide technology is an emergent area with many diagnostic applications. Nanosensors are the new contrivance for detection of bioterrorism agents. All these new technologies would have to be evaluated in clinical settings before their full import is appreciated and accepted.

In this chapter we will discuss about the importance of microbiology in nanotechnology and vice versa. Microbiology and nanotechnology convergence can do wonders in medical science and other applied fields.

BACKGROUND

Nanoparticles and Their Antimicrobial Activity

Antibacterial activity is related to compounds that locally kill bacteria or slow down their growthwithout being in general toxic to surrounding tissue. Most current antibacterial agents are chemically modified natural compounds (Von, 2006), for instance, b-lactams (like penicillins), cephalosporins or carbapenems. Also, pure natural products, such as aminoglycosides, as well as purely synthetic antibiotics, for example, sulfonamides, are often used. In general, the agents can be classified as either bactericidal, which kill bacteria, or bacteriostatic, slowing down bacterial growth. Antibacterial agents are paramount to fight infectious diseases. However, with their broad use and abuse, the emergence of bacterial resistance to antibacterial drugs has become a common phenomenon, which is a major problem. Resistance is most often based on evolutionary processes taking place during, for example, antibiotic therapy, and leads to inheritable resistance. In addition, horizontal gene transfer by conjugation, transduction or transformation can be a possible way for resistance to build up (Witte, 2004). Such antibacterial-resistant strains and species are informally referred to as superbugs and contribute to the emergence of diseases that were under good control for many years. One prominent example is bacterial strains causing tuberculosis (TB) that are resistant to previously effective antibacterial treatment. Indeed, it is estimated that nearly half a million new cases of multidrug-resistant tuberculosis (MDR-TB) occur worldwide every year (Oldenburg, 2004); Thus, due to the fact that bacteria developed resistance against many common antibacterial agents, infectious diseases continue to be one of the greatest health challenges worldwide. In addition, drawbacks for conventional antimicrobial agents are not only the development of multiple drug resistance, but also adverse side effects. Drug resistance enforces high-dose administration of antibiotics, often generating intolerable toxicity. This has prompted the development of alternative strategies to treat bacterial diseases (Rakow, 2000). Among them, nanoscale materials have emerged as novel antimicrobial agents. Especially, several classes of antimicrobial NPs and nanosized carriers for antibiotics delivery have proven their effectiveness for treating infectious diseases, including antibiotic-resistant ones, in vitro as well as in animal models (Baker, 2006). The bacterial cell wall is designed to provide strength, rigidity, and shape, and to protect the cell from osmotic rupture and mechanical damage [Huh, 2011). According to their structure, components, and functions, the bacteria cell wall can be divided into the two main categories: Gram positive (+) and Gram negative (–). The wall of Gram-positive cells contains a thick layer (i.e., 20–50 nm) of peptidoglycan (PG), which is attached to teichoic acids that are unique to the Gram-positive cell wall(singleton, 2004).

The structure of the cell wall plays an important role in tolerance or susceptibility of bacteria in the presence of NPs. For instance, vancomycin (van)-functionalized Ag and TiO2 NPs have the capacity to target van-sensitive bacteria (Scott, 2006). In the van-sensitive bacterium, Desulfotomaculum, the D-Ala-D-Ala structure on the surface of the cell wall can be recognized by vancomycin. By contrast, it is impossible for vancomycin to penetrate into van-resistant bacteria and access the D-Ala-D-Ala structure moiety. This is due to the fact that van-resistant bacteria have an additional outer membrane, which covers the cell surface. Bacterial cell wall properties can play a crucial role in diffusion of NPs inside biofilm matrixes (Ashkarran, 2012). The expression of the major cell-wall anchored proteinase PrtP is responsible for altering the surface of *Lactococcus lactis* from a hydrophilic to an extremely hydrophobic one. In fact, the expression of PrtP in L. lactis 2 changes the physicochemical properties without architectural modifications during biofilm formation. Sensitivity is not only related to the structure of the cell wall in Gram-positive and Gram-negative bacteria Role of growth rate. Another factor that can influence the tolerance of bacteria against NPs is the rate of bacterial growth. Fast-growing bacteria are more susceptible than slow-growing bacteria to antibiotics and NPs. It is possible that the tolerance property of slow-growing bacteria is related to the expression of stress-response genes. One of the major shortcomings of anti-bacterial drugs and NPs, is their failure to fight with bacteria [e.g., *S. aureus* (+)] that have the capability to produce biofilms. The exact mechanisms of NP toxicity against various bacteria are not understood completely. NPs are able to attach to the membrane of bacteria by electrostatic interaction and disrupt the integrity of the bacterial membrane (Baek,2011). Nanotoxicity is generally triggered by the induction of oxidative stress by free radical formation, that is, the ROS, following the administration of NPs. TiO2 NPs photocatalysis can increase peroxidation of the polyunsaturated phospholipid component of the lipid membrane and promote the disruption of cell respiration (Thill, 2006). The mechanisms of NP toxicity depend on composition, surface modification, intrinsic properties, and the bacterial species. The toxicity of copper NPs depends on the combination of several factors such as temperature, aeration, pH, concentration of NPs, and concentration of bacteria (*E. coli*). The high temperature, high aeration, and low pH decrease the agglomeration and increase the toxicity. In fact, the lower agglomeration provides more available surface area for interaction with bacterial membranes and for solubilization of copper ions, which leads to more toxicity (Wan, 2011). Metallic and ionic forms of copper produce hydroxyl radicals that damage essential proteins and DNA. The combination of biogenic Ag NPs with antibiotics has efficient antibacterial activity. In fact, the ampicillin damages the cell wall and mediates the internalization of Ag NPs into the bacteria. These NPs bind to DNA and inhibit DNA unwinding, which leads to cell death. Moreover, Ag NPs modified with titanium are toxic to *E. coli* and *S. aureus*. Ag NPs naturally interact with the membrane of bacteria and disrupt the membrane integrity, and silver ions bind to sulfur, oxygen, and nitrogen of essential biological molecules and inhibit bacterial growth. The aforementioned studies show that suitable NPs can be selected to fight against specific bacteria.

The emergence of antibiotic- and/or multidrug-resistant bacteria is recognized as a crucial challenge for public health. Killing of antibiotic-resistant bacteria requires multiple expensive drugs that may have side effects. As a result, treatments are costly and require more time. NPs can offer a new strategy to tackle multidrug-resistant bacteria (Wang, 2011). Four types of silver carbon complexes (SCCs) with different formulations including micelles and NPs have efficient toxicity against medically important pathogens such as *P. aeruginosa* (–), *Burkholderia cepacia* (–), methicillin-resistant *S. aureus*, multidrug-resistant *Acinetobacter baumannii* (–), and *Klebsiella pneumoniae* (–) in the range of 0.5–90 mg/l (Wang, 2011). The SCCs are able to inhibit the growth of bio-defense bacteria such *B. subtilis* and *Yersinia pestis* (–) (Wang, 2011). Targeting bactericidal NPs to specific bacteria or specific infected tissue is an efficient prospect in treating infection because this phenomenon minimizes side effects and enhances antibacterial activity.Nitric-oxide releasing NPs (NO NPs) are broad spectrum antibacterial agents that are able to inhibit the growth of many antibiotic-resistant and sensitive clinically isolated bacteria such as *K. pneumoniae, Enterococcus faecalis* (+), *Str. pyogenes, E. coli, and P. aeruginosa* (–). The toxicity of these NPs depends on the delivery of NO to the target. These NPs are able to change the structure of the bacterial membrane and produce reactive nitrogen species (RNS), which lead to modification of essential proteins of bacteria (Leid, 2012). Beside NO NPs, ZnO NPs are toxic to antibiotic (methicillin)-resistant bacteria such as *Streptococcus agalactiae* (+) and *S. aureus*. These NPs are able to disorganize and damage the cell membrane and increase the permeability, which leads to cell death. The polyvinyl alcohol (PVA)-coated ZnO NPs are able to internalize the bacteria and induce oxidative stress. The toxicity of ZnO NPs is concentration-dependent and these NPs are mildly toxic at low concentration.

NPs in water can significantly promote the horizontal conjugative transfer of multidrug-resistance genes mediated by the RP4, RK2, and pCF10 plasmids (Friedman, 2011). Here, nanoalumina can promote the conjugative transfer of the RP4 plasmid from *E. coli* to *Salmonella sp.* by up to 200-fold compared with untreated cells. The nanoalumina is able to induce oxidative stress, damage bacterial cell membranes, enhance the expression of mating pair formation genes and DNA transfer and replication genes, and depress the expression of global regulatory genes that regulate the conjugative transfer of RP4 (Friedman, 2011). Defense mechanisms of tolerant bacteria against NPs Several naturally adapted bacteria are tolerant to specific toxins or NPs that are present in the environment. Cu-doped TiO2 NPs are able to inhibit the growth of *Mycobacterium smegmatis*, but have no effect against *Shewanella oneidensis* (Wu,2010). These NPs release Cu2+ ions, which might be the main cause of toxicity, because the antibacterial activity of Cu-doped TiO2 NPs was decreased in the presence of chelating agents such as EDTA. Sh. oneidensis MR-1 has excellent resistant against several concentrations of Cu2+ and Cu-doped TiO2 NPs because of the production of extracellular polymeric substances (EPSs) under NP stress. This bacterium is able to absorb NPs on the cell surface and to decrease the amount of ionic Cu in the culture medium. Therefore this bacterium can be regarded as a promising candidate for cleaning of metal oxide NPs from the environment. *B. subtilis* and *Pseudomonas putida* (–) can physically adapt to nC60 [buckminsterfullerene (C60) introduced as colloidal aggregates in water] (Fang, 2007). *P. putida* increases cyclopropan fatty acids and decreases unsaturated fatty acid levels, but *B. subtilis* increases the transition temperature and membrane fluidity in the presence of nC60. These physiological adaptation responses of bacteria help to protect the bacterial membrane against oxidative stress. TiO2 and Al2O3 NPs are able to be internalized by *E. coli* and *Cupriavidus metallidurans* CH34, but these NPs are toxic only against *E. coli* (Simon, 2009). The resistance mechanism of *C. metallidurans* CH34 is not yet understood completely. The tolerance mechanism of this bacterium may be related to physical properties of their PG layer and/or products of genes that are located in the plasmids and are able to stabilize the plasma membrane or efflux of NPs. Many bacteria are able to tolerate NO NPs using various mechanisms. For example *P. aeruginosa, E. coli*, and *Sal.typhimurium* induce the expression of genes that are responsible for repairing of DNA and altering the metal homeostasis in the presence of NO NPs . In this condition, *K. pneumoniae* produces the enzyme flavohemoglobin, which neutralizes nitrosative stress (Frey, 2002).

Formation of Nanoparticles Using Microorganisms

Traditionally nanoparticles were produced only by physical and chemical methods. But these methods employ undesirable chemicals in the synthesis process, creating environmental concerns which include contamination from precursor chemicals, use of toxic solvents and generation of hazardous by-products (Xu, 2006). Some of these methods also have problems with the stability, controlled crystal growth and aggregation of the nanosize particles. Consequently, use of biological system like microbes for the synthesis of various nanoparticles has emerged as a novel research area. Various studies on the microbial synthesis of nanoparticles demonstrated the use of certain fungi and bacteria (Mukherjee, 2001), in the successful synthesis of nanoparticles of varied shapes and sizes with potential antibacterial activity. One such clique of microbes are the endophytes whose potential in the biogenic synthesis of nanoparticles has not yet been studied completely. Bacon et al. defined endophytes as "microbes that colonize living internal tissues of plants without causing any immediate, overt negative effects" (Bacon, 2004), whereas Strobel and colleagues suggested that the relationship can range from mutualistic to bordering on pathogenic (Strobel, 1996). The most frequently encountered endophytes are fungi and bacteria that co- exist with each other (Sunkar, 2012). Very few reports are available where in endophytic fungi were used for the synthesis of nanoparticles. One such study employed an endophytic fungus (*Colletotrichum* sp.) isolated from geranium leaves (*Pelargonium graveolens*) for the extra-cellular synthesis of gold nanoparticles (Shankar et al, 2003). Another study revealed the use of *Aspergillus clavatus* (AzS-275), an endophytic fungus isolated from sterilized stem tissues of *Azadirachta indica* and reported about the antibacterial effect of silver nanoparticles synthesized by it (Verma et al,2010).

The synthesis of inorganic materials may occur either intracellularly or extracellularly. Numerous recent publications have highlighted the potential of microorganisms, particularly bacteria (including thermophiles) and fungi, to synthesize or sequester metallic and/or oxide nanoparticles. The native metabolic process of the microorganisms can lead to the precipitation of nanoparticles in the external environment of a cell or inside the cell. Fungi are considered as extremely good candidates for such processes. The extracellular synthesis of silver and gold nanoparticles by the fungus *Colletotrichum* sp. or *Aspergillus fumigatus* have been reported. Similarly, extracellular synthesis of silver nanoparticles in the fungus *Fusarium semitectum* was also reported while possible medicinal applications of these silver nanoparticles have also been envisaged. In the case of *Verticillium* species reduction of the metal ions occurred intracellularly leading to the formation of gold and silver nanoparticles in the size range 2–20 nm.

Nanotechnology involves the tailoring of materials at the atomic level to attain unique properties, which can be suitably manipulated for the desired applications. Currently, there is a growing need to develop environmentally benevolent nanoparticles synthesis processes that do not use toxic chemicals in the synthesis protocol. Microorganisms, such as bacteria and fungi, now play an important role in the remediation of toxic metals through the reduction of the metal ions. The ability of some microorganisms such as bacteria and fungi to control the synthesis of metallic nanoparticles should be employed in the search for new materials (Mandal et al, 2006). Biosynthetic methods have been investigated as an alternative to chemical and physical ones. Biologically synthesized silver nanoparticles could have many applications, as in spectrally selected coatings for solar energy absorption, as intercalation material for electrical batteries, as optical receptors, as catalysts in chemical reactions, as antimicrobials, and in bio-labeling (Duran et al, 2005)and other applications, such as spectrally selective coatings for solar energy absorption and intercalation material for electrical batteries (Klaus et al,2001), as optical receptors (Schultz et al, 2000), catalysts in chemical reactions, bio labeling(Hayat, 1989), etc. However, it is only recently that microorganisms have been explored as potential bio factory for synthesis of metallic nanoparticles such as cadmium sulphide, gold and silver (Sastry, 2003). To achieve the objective of developing simple and eco-friendly technology researchers in this field have turned to biological systems. Holmes et al. have shown that the bacteria, when exposed to cadmium ions resulted in intracellular formation of CdS particles in the range of20–200nm (Holmes, 1995).Sastryetal (Sastry, 2003)have reported that fungus sp. and, when exposed to gold and silver ions, reduced the metal ion fairly rapidly and formed respective metallic nanoparticles. Klaus et al. have observed that the AG259, isolated from a silver mine, when placed in a concentrated solution of silver nitrate produced silver nanoparticles of well-defined size and distinct morphology within the periplasmic space of the bacteria (Klaus, 2001). A novel biological method for synthesis of silver nanoparticles using *Vericillum* was proposed by Mukherjee and coworkers (Mukherjee, 2001); the two-step mechanism was suggested. The first step involves trapping of the Ag+ ions at the surface of the fungal cells. In the second step, the enzymes present in the cell, reduce silver ions. So, our aim is to biologically synthesize silver nanoparticles using fungus and characterized by means of UV-Vis spectroscopy and Transmission electron microscopy (TEM).

Nanotechnology is an emerging field in the area of interdisciplinary research, especially in biotechnology. The synthesis of silver nanomaterials/nanoparticles extensively studied by using chemical and physical methods, but the development of reliable technology to produce nanoparticles is an important aspect of nanotechnology. Biological synthesis process provides a wide range of environmentally acceptable methodology, low cost production and minimum time required. At the same time the biologically synthesized silver nanoparticles has many applications includes catalysts in chemical reactions (Kumar, 2003), biolabelling, antimicrobial agent, electrical batteries (Peto, 2002)and optical receptors (Krolikowska,2003, Klaus, 2001).Microbial source to produce the silver nanoparticles shows the great interest towards the precipitation of nanoparticles due to its metabolic activity. Of course the precipitation of nanoparticles in external environment of a cell, it shows the extracellular activity of organism. Extracellular synthesis of nanoparticles using cell filtrate could be beneficial over intracellular synthesis, the fungi being extremely good candidates for extracellular process and also environmental friendly. There are few reports published in literature on the biosynthesis of silver nanoparticles using fungal as source (Husseiny et al, 2007).

Green Synthesis of Nanoparticles and its Advantage over Metallic Nanoparticles

In recent past, nanoparticles preparation and its applications in various fields like catalysis, electronics, environmental, pharmaceutical and biotechnology, has been expanded significantly. Metal nanoparticles are usually in sizes ranging from 1-100nm and possess unique physical and chemical properties. Especially, silver nanoparticles have been attributed to their small size, more surface bulk atoms and high surface area permits them to highly interact with microbial membranes. Besides, silver is used in the medical field as best topical bactericides from the ancient time. Many physical or chemical methods that are currently available for silver nanoparticle production include chemical reduction, mechanical smashing, a solid-phase reaction, freeze-drying, spread drying and precipitation. Unfortunately, many of these methods have several disadvantages such as high cost, consumption of high energy; need to maintain high pressure and also high temperatures.

Chemical synthesis methods lead to the presence of numerous toxic chemical species adsorbed on the surface of nanoparticles that may have adverse effects in medical applications. Synthesis of nanoparticles using microorganisms or plant parts can potentially eliminate this problem by making the nanoparticles more biocompatible. Biological synthesis of nanoparticles provides advancement over chemical and physical methods as it is a cost effective and environment friendly and in this method there is no need to use high pressure, energy, temperature and toxic chemicals. Using plant parts for nanoparticles synthesis can be advantageous over other biological processes by eliminating the elaborate process of maintaining cell cultures (Roe 2008, Salton, 1996). It can also be suitably scaled up for large-scale synthesis of metal nanoparticles.

The growing need of environmental friendly nanoparticles, researchers are using green methods for the synthesis of various metal nanoparticles. But nowadays, plant extract has been used as reducing and capping agent for the synthesis of nanoparticles which could be advantageous over photochemical reduction, heat evaporation, electrochemical reduction, and chemical reduction methods. Several bio- logical systems including bacteria, fungi, and yeast have been used in synthesis of nanoparticles. Silver nanoparticles have attracted intensive research interest because of their important applications as antimicrobial, catalytic, textile fabrics and plastics to eliminate microorganisms. Because of such a wide range of applications, numerous methods concerning the fabrication of silver nanoparticles, as well as various silver-based compounds containing ionic silver (Ag+) or metallic silver (Ag0) have been developed. The synthetic methods used for the preparation of silver nanoparticles, some toxic chemical used as a reducing agent such as NaBH4, citrate, or ascorbate is most commonly used. In recent years, plant-leaf extracts synthesis of nanoparticles is gaining importance due to its simplicity and eco-friendliness. Biosynthesis of nanoparticles using plant extracts is the favorite method of green, eco-friendly production of nanoparticles and exploited to a vast extent because the plants are widely distributed, easily available, safe to handle and with a range of metabolites. The plant material used for biosynthesis of nanoparticles includes Angiospermic plants such as *Helianthus annus, Oryza sativa, Zea mays, Sorghum bicolor, Eucalyptus hybrida, Artocarpus heterophyllus* and Gymnospermic plants such as *Cycas* and *Rosa rugosa, Stevia rebaudiana, Chenopodium album, Macrotyloma uniforum, Acalypha indica, Cycas, Piper longum, Nicotiana tobaccum* and many more.

Phytomining is the use of hyper accumulating plants to extract a metal from soil with recovery of the metal from the biomass to return an economic profit (Lamb, 2001). Hyper accumulator species have a physiological mechanism that regulates the soil solution concentration of metals. Exudates of metal chelates from root system, for example, will allow increased flux of soluble metal complexes through the root membranes(Vedpriya, 2010). It has been observed that stress tolerant plants have more capacity to reduce metal ions to the metal nanoparticles (Ankamwar, 2005).

Temperature plays an important role to control the aspect ratio and relative amounts of gold nanotriangles and spherical nanoparticles. Temperature variations in reaction conditions results in fine tuning of the shape, size and optical properties of the anisotropic nanoparticles (Armendariz et al, 2004). More than 90% of leaf extracts of two plants- *Magnolia Kobus* and *Diopyros kaki* was converted to gold nanoparticles at a reaction temperature of 95 °C in few minutes, suggesting reaction rates higher or comparable to those of nanoparticle synthesis by chemical methods (Song et al, 2009). The size of gold nanoparticles was shown to increase at higher reaction temperatures as explained by an increase in fusion efficiency of micelles which dissipates supersaturation (Muralidharan, 2011).The reaction mechanism for the formation of magnetite nano particles have been found to be influenced by pH

(Faiyaz et al, 2010) .Other than pH and temperature other factors also play role in nanoparticle synthesis. The size and crystallinity of magnetite nanoparticles was found to increase with increasing molar ratios of ferric/ferrous ions during synthesis by hydrothermal synthesis method according to the Schikorr reaction (Mizutani, 2008).

Nanotechnology in Drug Delivery System

Nanomedicine involves utilization of nanotechnology for the benefit of human health and wellbeing. The use of nanotechnology in various sectors of therapeutics has revolutionized the field of medicine where nanoparticles of dimensions ranging between 1-100 nm are designed and used for diagnostics, therapeutics and as biomedical tools for research. It is now possible to provide therapy at a molecular level with the help of these tools, thus treating the disease and assisting in study of the pathogenesis of disease. Conventional drugs suffer from major limitations of adverse effects occurring as a result of non-specificity of drug action

Current modalities of diagnosis and treatment of various diseases, especially cancer have major limitations such as poor sensitivity or specificity and drug toxicities respectively. Newer and improved methods of cancer detection based on nanoparticles are being developed. They are used as contrast agents, fluorescent materials, molecular research tools and drugs with targeting antibodies. Paramagnetic nanoparticles, quantum dots, nanoshells and nanosomes are few of the nanoparticles used for diagnostic purposes. Drugs with high toxic potential like cancer chemotherapeutic drugs can be given with a better safety profile with the utility of nanotechnology. These can be made to act specifically at the target tissue by active as well as passive means. Other modalities of therapy such as heat induced ablation of cancer cells by nanoshells and gene therapy are also being developed. This review discusses the various platforms of nanotechnology being used in different aspects of medicine like diagnostics and therapeutics. The potential toxicities of the nanoparticles are also described in addition to hypothetical designs such as respirocytes and microbivores. The safety of nanomedicine is not yet fully defined. However, it is possible that nanomedicine in future would play a crucial role in the treatment of human diseases and also in enhancement of normal human physiology. Designing of drugs with greater degree of cell specificity improves efficacy and minimizes adverse effects. Diagnostic methods with greater degree of sensitivity aid in early detection of the disease and provide better prognosis., Nanotechnology is being applied extensively to provide targeted drug therapy, diagnostics, tissue regeneration, cell culture, biosensors and other tools in the field of molecular biology. Various nanotechnology platforms like fullerenes, nanotubes, quantum dots, nanopores, dendrimers, liposomes, magnetic nanoprobes and radio controlled nanoparticles are being developed. Development of newer drug delivery systems based on nanotechnology methods is being tried for conditions like cancer, diabetes, fungal infections, viral infections and in gene therapy. The main advantages of this modality of treatment are targeting of the drug and enhanced safety profile. Nanotechnology has also found its use in diagnostic medicine as contrast agents, fluorescent dyes and magnetic nanoparticles

Liposomes discovered in mid 1960s were the original models of nanoscaled drug delivery devices. They are spherical nanoparticles made of lipid bilayer membranes with an aqueous interior but can be unilamellar with a single lamella of membrane or multilamellar with multiple membranes. They can be used as effective drug delivery systems. Cancer chemotherapeutic drugs and other toxic drugs like Amphotericin and Hamycin, when used as liposomal drugs produce much better efficacy and safety as compared to conventional preparations. These liposomes can be loaded with drugs either in the aqueous compartment or in the lipid membrane. Usually water soluble drugs are loaded in aqueous compartment and lipid soluble drugs are incorporated in the liposomal membrane (Gregoriadis, 1972). The major limitation of liposome is its rapid degradation and clearance by the liver macrophages (McCormack), thus reducing the duration of action of the drug it carries. This can be reduced to a certain extent with the advent of stealth liposomes here the liposomes are coated with materials like poly oxyethylene(Illum, 1984) which prevents opsonisation of the liposome and their uptake by macrophages (Senior et al, 1991). Other ways of prolonging the circulation time of liposomes are incorporation of substances like cholesterol (Kirby, 1983), polyvinylpyrollidone polyacrylamide lipids (Torchilin, 1994) and hightransition temperature phospholipids distearoylphosphatidylcholine (Forssen, 1992). The term Nanomedicine refers to the application of nanotechnology to diagnosis and treatment of disease. It deals with the interactions of nanomaterials (surfaces, particles, etc.) or analytical nanodevices with “living” human material (cells, tissue, bodyfluids). It is an extremely large field ranging from in vivo and in vitro diagnostics to therapy including targeted delivery and regenerative medicine. The concept of “Clever”drug targeting system includes the coordinating behavior of three components: the targeting moiety, the carrier and the therapeutic drug. The first one recognizes and binds the target. The second one carries the drug. The third one provides a therapeutic action to the specific site.

Nanotechnology in Water Treatment

Water is the most important natural resource for the substance of life. The challenge for the world is to keep the water resources safe for consumption. Many microorganisms like bacteria, viruses and protozoa can cause waterborne diseases. Climate change is another threat to take away a large fraction of the freshwater. The purification of drinking water can be done by removing the contaminants like microbes and chemicals. Nearly a billion people worldwide do not have access to clean drinking water, and millions die each year from waterborne diseases contracted from unsafe water. The contaminants in the water are too small that it is not possible to tell whether the water is safe for drinking just by visual examination. We need to remove or reduce the concentration of particulate matter, parasites, algae, viruses, fungi and a range of dissolved chemicals.

Nanotechnology provides many promising solutions for improving "decentralized" or "point-of-use water treatment basically, becoming more efficient and effective about removing all the contaminants in water to make it safe to drink. The technologies discussed in this particular presentation deal with membranes or nano-filters–that either have nano-sized pores, or that utilize nanomaterials (carbon nanotubes) to filter out contaminants. There are other nanotechnologies related to water purification – everything from nanosensors to detect contaminants in the water, nanomaterials to help with water pollution remediation, to new desalination technologies and everything in between. The nanofilters for water purification are the most developed technologies.

The market for nanotechnology used in water and wastewater worldwide reached USD 1.6 billion in 2007 and is expected to reach USD 6.6 billion in 2015. Filtration was the dominant application in 2007 at about 43%, but desalination and irrigation are expected to deliver the most revolutionary results by 2015 and there- after. Nanotechnologies help to reduce desalination process costs and reduce water use in irrigation. In 2015, filtration is expected to account for 30%, desalination for 23% and irrigation for 6% of the USD 6.6 billion total. One of the fastest growing of the smaller market segments is disinfection with broad applications and benefits. Nanotechnology is generally used in areas where there is a need to address contaminants at the molecular level. In several cases (e.g. membrane technology), nanotechnology has been in use as a conventional water treatment technique for many years although the term "nanotechnology" was not in common use when the products and systems were introduced. Many nanotechnology developments for water purification are enhancements of conventional technologies, while others under development offer novel approaches (e.g. the adaptation of sensors, developed for healthcare (AZ Nanotechnology, 2009), to water treatment and monitoring systems (Altair Nano, 2009).

Nanotechnology can enable both safer and sustainable solutions for clean water by both enhancing the performance of existing treatment processes and developing new (modular) processes. For microbial control, the overarching goal is to develop antimicrobial systems that sense and selectively target waterborne pathogens for safer water disinfection, diagnosis of pathogenic disease, and mitigation of biofouling and biocorrosion in a manner that is eco-responsible, broadly accessible, and practical. Previous research suggests a great potential for nanotechnology-enabled microbial control (Li et al, 2008). Nanotechnology can address emerging disinfection challenges, help restore and improve aging water infrastructure, mitigate the large water footprint of O&G extraction (e.g., by reducing the abandonment of biofouled production wells and the overdosing of biocides), and provide opportunities to develop leading-edge technologies that enhance industrial competitiveness in the global market of water management. This prospect is timely because current technologies are reaching their limits in meeting increasingly stringent water quality standards and dealing with emerging contaminants, such as pharmaceuticals, personal care products, and viruses.

Nanotechnology can also contribute to integrated urban water and wastewater management by enabling a distributed and differential water treatment and reuse paradigm where water and wastewater are treated locally to the level required by the intended use. This would minimize water quality degradation within aging distribution networks, alleviate dependence on large and centralized system infrastructure (e.g., use only basic treatment near the source water to enhance distribution, and complement it by tailored POU treatment), exploit alternative water sources (e.g., recycled waste-water or storm water) for potable, agricultural, or industrial use, and decrease energy requirements for treating and moving water (Qu et al, 2012). Many manufactured nanoparticles can inactivate microbial cells using a wide variety of antimicrobial mechanisms. Some nanoparticles interact directly with microbial cells to disrupt the integrity of the cell membrane (e.g., carbon nanotubes) and interrupt respiration and energy transduction (e.g., fullerenes and Ceric oxide [CeO2]). Other nanoparticles act indirectly by producing secondary products that serve as disinfection agents (e.g., reactive oxygen species [ROS] generated by titanium dioxide [TiO2] or dissolved metal ions released by silver nanoparticles [AgNPs]). The most widely used antimicrobial nanoparticles are AgNPs, which are used in a wide variety of microbial control applications, from disinfecting medical devices and home appliances to water treatment. Silver was a prevalent antibiotic before the advent of penicillin. The silver ions (Ag+) that are released from AgNPs interact with thiol groups in proteins, which can inactivate respiratory enzymes or create oxidative stress associated with intracellular ROS generation. One elusive question has been whether the AgNPs exert "particle-specific" antimicrobial activity upon contacting cells, beyond the known antimicrobial activity of released Ag+. Recently, we found that Ag+ is the determinant molecular toxicant. Direct particle-specific biological effects were ruled out by observing a lack of toxicity of AgNPs when synthesized and tested under strictly anaerobic conditions that preclude silver (Ag[0]) oxidation and Ag+ release. Furthermore, the toxicity of various AgNPs (of different coatings and sizes) accurately followed the dose-response pattern of bacteria exposed to Ag+ (added as silver nitrate [AgNO3]) (Xiu et al,2012). Therefore, AgNP morphological properties known to affect antimicrobial activity are indirect effectors that mainly influence Ag+ release. This suggests that antibacterial activity could be controlled by modulating Ag+ release, possibly through the manipulation of oxygen availability, particle size, shape, and/or type of coating. Furthermore,Ag+ is more susceptible than AgNPs to binding by common natural ligands, such as chloride, phosphate, sulfide, and natural organic matter, which decreases its bioavailability. AgNPs may serve as a more bioavailable vehicle for effective delivery of Ag+ to the bacteria. Another well studied and widely available inorganic nanomaterial is TiO2, which has great potential to enhance the photo disinfection of both water and air. The antibacterial effect of TiO2 involves ROS production (e.g., hydroxyl radicals) when the nanoparticles are illuminated by ultraviolet (UV-A) light (320 to 400 nanometers [nm]). UV-A is a minor component of visible light, and sunlight is generally not very effective in activating TiO2 for photocatalytic disinfection.

Nevertheless, the doping of TiO2 with common elements (e.g., nitrogen [N], sulfur [S], and boron [B]) can enable activation by sunlight, thereby enabling its use in remote locations without electricity. Nobel metals can also improve the photosensitivity of sunlight-irradiated TiO2 and increase its photo catalytic activity under UV irradiation. The enhancement is related to improved electron-hole separation and/or an increase in surface area for light adsorption. Zinc oxide [ZnO] nanoparticles also exhibit antimicrobial properties, although they are more commonly used to absorb UV light in sunscreens, coatings, and paints. Several mechanisms have been postulated to explain the antibacterial activity of ZnO. Similar to AgNPs, the dissolution and release of metal ions (i.e., zinc cation [Zn2+]) is an important mechanism. Apparently, Zn2+ binds to bacterial cell membranes, promotes disorganization of the phospholipids, and retards microbial growth. ZnO is also photosensitive and generates hydrogen peroxide, which has antimicrobial properties.

Adverse Effect of Nanoparticles on Human Health: Concerns and Precautions

Scientists world-wide are continuing to discover unique properties of everyday materials at the sub micrometer scale (Feynmam, 1991). This size domain is better known as nano- (a billionth) meter domain. These novel properties of common materials observable only at the nano-scale dimensions have already found their first commercial applications (Salata, 2004). For example, nanomaterials are present in some sunscreens, toothpastes, sanitary ware coatings and even food products. Manmade nanoparticles ranges from the well-established multi-ton production of carbon black and fumed silica for applications in plastic fillers and car tyres to microgram quantities of fluorescent quantum dots used as markers in biological imaging. As nanosciences are experiencing massive investment worldwide there will be a further rise in consumer products relying on nanotechnology (NanoBussiness Alliance, 2003). While benefits of nanotechnology are widely publicised, the discussion of the potential effects of their widespread use in the consumer and industrial products are just beginning to emerge. Both pioneers of nanotechnology Anon, 2003)and its opponents (UK Report, 2004)are finding it extremely hard to argue their case as there is limited information available to support one side or the other. It has been shown that nanomaterials can enter the human body through several ports. Accidental or involuntary contact during production or use is most likely to happen via the lungs from where a rapid translocation through the blood stream is possible to other vital organs (Nemmar 2001)[69]. On the cellular level an ability to act as a gene vector has been demonstrated for nanoparticles (Xiang et al, 2003). Carbon black nanoparticles have been implicated in interfering with cell signaling (Brown et al, 2004). There is work that demonstrates uses of DNA for the size separation of carbon nanotubes (Zheng et al, 2003). The DNA strand just wraps around it if the tube diameter is right. While excellent for the separation purposes it raises some concerns over the consequences of carbon nanotubes entering the human body. The pathogenic effects of inhaled solid material depend primarily on achieving a sufficient lung burden (Moolgavkar, 2001). The lung burden is determined by the rates of deposition and clearance. Logically, for any dust or fibre, a steady-state dose level will be achieved when the rates come into balance. This is only true when the solid material does not interfere with the clearance mechanisms. In respect to the burden the chemical and physical properties of the material itself are important insofar as they influence deposition and clearance rates. Spherical solid material can be inhaled when its aerodynamic diameter is less than 10 micron. The smaller the particulates the deeper they can travel into the lung, particles smaller than 2.5 micron will even reach the alveoli. Ultrafine particles (nanoparticles with an aerodynamic diameter of less than 100 nm) are deposited mainly in the alveolar region. Fibres are defined as solid materials with a length to diameter ratio of at least 3:1. Their penetration into the lung depends on the aerodynamic properties. Fibres with a small diameter will penetrate deeper into the lungs, while very long fibres (>>20 micron) are predominantly stuck in the higher airways (Lippmann, 1990). The mucociliary escalator dominates the clearance from the upper airways; clearance from the deep lung (alveoli) is predominantly by macrophage phagocytosis. The mucociliary escalator is an efficient transport system pushing the mucus, which covers the airways, together with the trapped solid materials towards the mouth. The phagocytosis of particles and fibres results in activation of macrophages and induces the release of chemokines, cytokines, reactive oxygen species, and other mediators; this can result in sustained inflammation and eventually fibrotic changes. The phagocytosis efficiency can be affected by the (physical-chemical) characteristics of the solid material (see below); moreover, fibres too long to be phagocytized (fibres longer than the diameter of the alveolar macrophage) will only be cleared very slowly.

Epidemiological studies have reported a close association between particulate air pollution and cardiovascular adverse effects such as myocardial infarction (Peters et al, 2001). The latter results from rupture of an atherosclerotic plaque in the coronary artery, followed by rapid thrombus growth caused by exposure of highly reactive subendothelial structures to circulating blood, thus leading to additional or complete obstruction of the blood vessel. Nemmar*et al*(2002) studied the possible effects of particles on haemostasis, focusing on thrombus formation as a relevant endpoint. Polystyrene particles of 60 nm diameter (surface modifications: neutral, negative or positive charged) have a direct effect on haemostasis by the intravenous injection. Positively charged amine-particles led to a marked increase in prothrombotic tendency, resulting from platelet activation. A similar effect could be obtained after the intratracheal administration of these positively charged polystyrene particles, which also caused lung inflammation (Nemmar et al, 2003). It is important to indicate that the pulmonary instillation of larger (400 nm) positive particles caused a definite pulmonary inflammation (of similar intensity to 60 nm particles), but they did not lead to a peripheral thrombosis within the first hour of exposure. This lack of effect of the larger particles on thrombosis, despite their marked effect on pulmonary inflammation, suggests that pulmonary inflammation by itself was insufficient to influence peripheral thrombosis. Consequently, the effect found with the smaller, ultrafine particles is most probably due, at least in part, to their systemic translocation from the lung into the blood.

Epidemiologic studies have provided valuable information on the adverse health effects of particulate air pollution in the community, indicating that nanoparticles act as an important environmental risk factor for cardiopulmonary mortality. Particle-induced pulmonary and systemic inflammation, accelerated atherosclerosis, and altered cardiac autonomic function may be part of the patho-physiological pathways, linking particulate air pollution with cardiovascular mortality. Also, it has been shown that particles deposited in the alveoli lead to activation of cytokine production by alveolar macrophages and epithelial cells and to recruitment of inflammatory cells. An increase in plasma viscosity, fibrinogen and Creative protein has been observed in samples of randomly selected healthy adults in association with particulate air pollution (Peters 1997, Peters, 2000).

Some administrative controls that should be considered for safety include:

- Providing known information to workers and students on the hazardous properties of the nanomaterial precursors or products;
- Educating the workers and students on the safe handling of nanomaterials;
- Restricting access to areas by using signs or placards to identify areas of nanoparticle research;

- Transport dry nanomaterials in closed containers;
- Handle nanoparticles in suspension on disposable bench covers;
- Always perform nanoparticle aerosol generating activities in a fume hood, externally ducted biological safety cabinet, or glove box;
- Clean the nanomaterial work area daily at a minimum with a HEPA-vacuum or wet wiping method;
- Wear latex or nitrile gloves when handling nanoparticle powders and nanoparticles in suspension (glove changes should be performed frequently);
- Wear chemical splash goggles when working with nanomaterials in suspension or dry powdered form;
- Wear lab coats. Lab coats should be laundered on a periodic basis. Do not take lab coats home for laundering;
- Wear commercially available arm sleeves in situations where dermal contact with nanoparticles in powder or in suspension are expected;
- Wear closed-toe shoes (if necessary cover shoes with commercially available booties).

CONCLUSION

Nanotechnology is emerging as one of the great area of research. Microbiology and nanotechnology together can do wonders and solve many problems. Different microorganisms can be used for formation of nanoparticles of silver, gold, titanium, etc .The biosynthesis of nanoparticles is of great interest as the method is safe, eco-friendly and cost effective. Nanoparticles have been used against different bacteria as antimicrobial agents. The problem with the antibiotic is their ineffectiveness against the drug resistant bacteria and biofilms. This problem can be solved by using nanoparticles. The use of nanotechnology in water purification can solve one of the great problem that world is facing. Another important application of nanotechnology is in drug delivery system .The use of nanoparticles as tags or labels allows for the detection of infectious agents in small sample volumes directly in a very sensitive, specific and rapid format at lower costs than current in-use technologies. This advance in early detection enables accurate and prompt treatment. Despite of so many advantages of nanotechnology it is important to take up the precautionary measures when working with nanomaterials. Many researchers have suggested that there may be some adverse effects associated with the use of nanoparticles hence further research is needed to find out the risk associated with the use of nanoparticles.

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KEY TERMS AND DEFINITIONS

Antimicrobial: A substance which inhibits or suppresses the growth of microorganisms.

Drug Delivery: Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect.

Green Synthesis: The Use of living organisms for the production of desirable product e.g. nanoparticles.

Liposome: A liposome is an artificially-prepared vesicle composed of a lipid bilayer.

Nano Toxicity: Nano toxicity is the study of the toxicity of nanomaterials.

Nanoparticle: A microscopic particle smaller than 100nm.

Pathogen: Any microorganism which has the ability to cause disease.

Related References

To continue our tradition of advancing information science and technology research, we have compiled a list of recommended IGI Global readings. These references will provide additional information and guidance to further enrich your knowledge and assist you with your own research and future publications.

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