

Pharmaceutical Applications of Polymers for Drug Delivery

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1 Physicochemical Properties of Pharmaceutical Polymers

1.1 Introduction

Polymers represent an important constituent of pharmaceutical dosage forms. Indeed it is accepted that the formulation and clinical performance of pharmaceutical dosage forms, e.g., solid dosage forms (tablets, capsules), disperse systems (suspensions, emulsions, creams, ointments), implants, particulate systems (microcapsules, microparticles, nanoparticles, nanocapsules) and transdermal patches, is dependent on the physicochemical properties of the polymers used in their formulation. Unlike those polymers that are exclusively used in non-medical applications, pharmaceutical polymers represent a relatively small percentage of the overall worldwide polymer sales. Furthermore the various worldwide regulatory bodies, e.g., the Food and Drugs Administration, rigorously control the standards of these polymers to ensure that no adverse effects result from their use. As a result of these considerations the cost of pharmaceutical polymers is frequently more expensive than nonmedical polymers. However, these restrictions are outweighed by the benefits and the wide array of advantages that pharmaceutical polymers have offered to the design of modern dosage forms. The main reason for these advantages is the ability of pharmaceutical polymers to provide the pharmaceutical scientist with a wide choice of physical and chemical characteristics. Accordingly the desired properties can be obtained by altering the physicochemical properties of the polymer, c.g., polymer type, polymer molecular weight, monomer structure and, copolymerisation or blending with other polymers. For example cellulose ethers are available in a range of molecular weights offering a range of viscosities when formulated as aqueous systems. Certain polymethacrylates are soluble in alkaline pH making them suitable for enteric coatings (coatings which do not dissolve in the stomach but dissolve in the more alkaline regions of the gastrointestinal tract); however by changing the copolymer composition the polymer may be rendered insoluble and therefore used as an insoluble film coating for sustained release dosage forms.

The pharmaceutical applications of polymers range from their uses as binders in tablet formulations to viscosity and flow controlling agents in pharmaceutical liquids, suspensions and emulsions. Polymers are extensively used in film coatings to mask the unpleasant taste of the drug, to improve the stability of hydrophilic drugs, to facilitate handling and to modify the drug

release characteristics. In particular the availability of polymers has allowed the pharmaceutical scientist to design and formulate controlled release dosage forms in which the release of drug from the dosage form is, in part, controlled by the unique physicochemical properties of the polymer. Although polymers are also extensively used in the pharmaceutical packaging industry this review is concerned with the use of polymers for the formulation of dosage forms. In particular the use of pharmaceutical polymers for controlled drug delivery applications forms the main focus of this review. As the reader will appreciate, the field of controlled drug delivery is vast and therefore it is hoped that this review will provide an overview of the applications of pharmaceutical polymers in this expanding field. Due to space limitations, and where necessary, the reader will be directed to appropriate textbooks and specialised review articles for further information/insight into the various technologies and applications described herein.

1.2 Examples of Pharmaceutical Polymers

As described previously there are a wide range of polymers that are used as components of pharmaceutical formulations. Classification of these materials may be performed according to chemical structure however other classifications based on the pharmaceutical applications of the polymers are frequently used. In light of the specialist nature of these materials, this section will provide a brief overview of the main properties of some of the most frequently used pharmaceutical polymers. It should be noted that the polymers described represent those that are most commonly used in pharmacy although it is recognised that there will be other polymers not included in this list that have pharmaceutical applications. The use of these polymers and those described in the next section will be highlighted in the latter sections of the review.

1.2.1 Vinyl Polymers

1.2.1.1 Polymethacrylates

These are synthetic anionic and cationic polymers of dimethylaminoethylmethacrylates, methacrylic acid and methacrylic acid esters in varying ratios (**Figure 1**). The polymers are regarded as non-toxic and non-irritant and are primarily used as film coatings for solid dosage forms although other uses include: as binders for both aqueous and organic wet granulation process and as viscosity modifiers in some topical formulations.



Figure 1

General chemical structure of polymethacrylates

They may also be used as the matrix layers in the formulation of transdermal delivery systems (a.1). The general chemical name and properties of some commercially available polymethacrylates are given in **Table 1**.

1.2.1.2 Polyvinyl Alcohol

Polyvinyl alcohol is a water soluble polymer that is prepared by the hydrolysis of polyvinyl acetate and is represented by the formula $(C_2H_4O)_n$, where *n* varies between 500-5000. The degree of hydrolysis and the degree of polymerisation determine the physical properties of the polymer. The molecular weight of commercially available grades ranges from 20,000-200,000 g mol⁻¹. Due to its non-toxic nature it is used in topical pharmaceutical and ophthalmic formulations as a lubricating and a viscosity-modifying agent. It has also been used in sustained release formulations (255).

1.2.1.3 Polyvinylpyrrolidone (Povidone)

Polyvinylpyrrolidone (PVP; **Figure 2**) is a hydrophilic (non-ionic) polymer that possesses excellent aqueous solubility but is also freely soluble in alcoholic solvents, (e.g., ethanol), and chlorinated solvents, (e.g., chloroform and dichloromethane). It is available in a wide range of molecular weights (2,500 to 3,000,000 g mol⁻¹) and has been used extensively in the formulation of pharmaceutical systems. The predominant use of PVP is as a binder in the production of granules and (subsequently, following compression) tablets (a.2), however, other applications include as a polymer coating for granules and tablets, as a solubiliser in oral and parenteral formulations (a.3) and as a viscosity-modifying agent in a variety of topical formulations.

Table 1 Chemical Structure and Properties of Commercial Polymethacrylates			
Chemical Name	Trade Name	Properties	Applications
Poly (butyl methacrylate, (2-dimethyl aminoethyl) methylacrylate) 1:2:1 R^1 , $R^3 = CH_3$ $R^2 = CH_2CH_2N(CH_3)_2$ $R^4 = CH_3 C_4H_9$	Eudragit E	Cationic polymer. Soluble in gastric juices and weakly acidic buffer solutions pH~5.	Film coatings.
Poly(methacrylic acid, methacrylate) 1:1 1:2 R^1 , $R^3 = CH_3$ $R^2 = H$ $R^4 = CH_3$	Eudragit L Eudragit S	Anionic copolymers. Soluble in neutral to weakly alkaline solutions (pH~6-7) and form salts with alkali. Soluble in intestinal pH.	Enteric coatings; resistant to gastric juices.
Poly(ethyl acrylate, methylmethacrylate, trimethylaminoethyl methacrylate chloride) 1:2:0.1 1:2:0.2 R^{1} = H, CH ₃ R^{2} = CH ₃ C ₂ H ₅ R^{3} = CH ₃ R^{4} = CH ₂ CH ₂ N(CH ₃) ₃ ⁺ Cl ⁻	Eudragit RS Eudragit RL	Water insoluble copolymer. Water permeable films. Water impermeable films.	Water insoluble, used as film coats for sustained release.



Figure 2 Chemical structure of polyvinylpyrrolidone

1.2.1.4 Poly(acrylic acid) (Carbomer)

Poly(acrylic acid) is a high molecular weight polymer (7 x $10^5 - 4 x 10^9$ g mol⁻¹) that is crosslinked with either allylsucrose or allyl ethers of pentacrythritol and which contains between 56 and 68% w/w carboxylic acid groups. The structure of the acrylic acid repeating unit in poly(acrylic acid) is shown in **Figure 3**.

inorganic or organic base, highly viscous gels are produced. This is due to repulsion of the ionised carboxylic acid groups (a.4).

This polymer also has a wide range of other uses, e.g., as a binder in the formulation of granules (and hence tablets) (a.5) and as a matrix for sustained drug release (a.6). Furthermore it has been shown that poly(acrylic acid) exhibits strongly bioadhesive properties and accordingly this polymer has been used as a platform for controlled drug delivery to/at the site of application (a.7).

1.2.2 Cellulose Ethers

Cellulose ethers are formed by the alkylation of cellulose and arguably form the most important class of ethers used in pharmaceutical formulations. These polymers may be used to modify the viscosity of topical formulations, (e.g., gels, liquid formulation), for the stabilisation of colloidal and suspension dosage forms, as a coating on solid dosage forms (tablets) and as a matrix for the controlled release of therapeutic agents (255, a.8). The general structure of cellulose derivatives is presented in **Figure 4**.



Figure 3

Chemical structure of the acrylic acid repeating unit in poly(acrylic acid)

The primarily application of poly(acrylic acid) is as a viscosity modifier in the formulation of topical pharmaceutical products, (e.g., creams, gels), that are designed for application to local sites, (e.g., skin, eye, rectum) (a.4). The viscosity of poly(acrylic acid) is dependent on pH. At low pH poly(acrylic acid) forms colloidal dispersions of low viscosity, however, following neutralisation with a suitable



Figure 4 General structure of cellulose derivatives

Cellulose cthers are prepared by the reaction of purified cellulose with an appropriate alkylating agent under heterogeneous conditions, usually in presence of a base. The properties of the ether are largely dependent on the nature and extent of substitution. **Table 2** shows the general structure and properties of various cellulose ethers used in the pharmaceutical industry. The parent polymer, cellulose is a linear unbranched polysaccharide composed of substituted glucopyranose monosaccharides linked together at the 1,4 position by a β -anomeric configuration. The degree of substituted per anhydroglucose unit. The maximum value for DS

Table 2 Chemical Structure, Properties and Some Pharmaceutical Uses of Cellulose Ethers			
Cellulose Ether	Properties	Uses	
Methylcellulose (MC) R = H, CH ₃ (Methocel A [®] , Dow Chemicals)	Water soluble (DS = 1.6-2.4) Gelation temperature = 48 °C, $T_g = 150{\text{-}}160 \text{ °C}$ Film melting point 290-305 °C Viscosity range 10-15,000 MPa for 2% aqueous solution	Tablet coating and granulation Controlled release Water soluble thermoplastics Thickeners	
Ethylcellulose (EC) $R = C_2H_5$ (Ethocel [®] , Dow Chemicals)	Insoluble in water Soluble in chloroform, THF $T_g = 129-133$ °C $T_{Softening} = 152-162$ °C	Microencapsulation Sustained release tablet coating Tablet coating Water insoluble films	
Hydroxypropylcellulose (HPC) R = H or [-CH ₂ CH(CH ₃)O-] _m H (Klucel [®] , Hercules)	Soluble in cold water and polar organic solvents, insoluble in hot water and hydrocarbons Softens at ~130 °C, Chars at >260 °C MW: 80,000-1,150,000	Controlled release matrix Film coating Tablet binder	
Hydroxyethylcellulose (HEC) (Natrosol, Hercules)	$T_{\text{Softening}} = 135-140 \text{ °C}$ $T_{\text{Decomposition}} = 205 \text{ °C}$ Soluble in hot or cold water Insoluble in organic solvents Viscosity = 2-20,000 MPa for 2% aqueous solution.	Ophthalmic formulations Topical formulations Thickener Stabiliser Water binder	
Hydroxypropylmethylcellulose (HPMC) R = H, CH ₃ , -CH ₂ CH(OH)CH ₃ (Methocel E,K [®] , Dow Chemicals)	Hygroscopic Soluble in cold water, mixture of water and alcohol, insoluble in ethanol, ether $T_g = 165-180$ °C Chars at 225-230 °C	Tablet binder Viscosity increasing agent Stabilising agent Film coatings Ophthalmic preparations	
Hydroxyethylmethyl cellulose $R = H, CH_3 \text{ or } [-CH_2CH_2O-]mH$ (Culminal [®] , Hercules)	Viscosity = 100-70,000 MPa for 2% aqueous solution	Suspending and a thickening agent	
T _g = glass transition temperature THF: Tetrahydrofuran MW: molecular weight			

cannot exceed three as each anhydroglucose unit only has three hydroxyl groups available for reaction. Most water-soluble derivatives have a DS value of 0.4-2.0, whereas ethylcellulose, a water insoluble cellulose ether, has a DS value between 2.3 and 2.8. Cellulose ethers may also be characterised by the molar substitution (MS), which represents the number of moles of attached reagent per mole of anhydroglucose unit. Typical MS values for hydroxyalkyl ethers are between 1.5 and 4.0. Specific examples of commonly used cellulose ethers are presented next.

1.2.2.1 Methylcellulose

Methylcellulose is a methyl ether of cellulose with approximately 27-32% of the hydroxyl groups substituted by methoxy groups. Commercially methylcellulose is available in a range of viscosity grades. It is used widely in the pharmaceutical industry as a granulation agent, as a coating for tablets, as an emulsifying agent, in controlled release pharmaceuticals and as a viscosity modifier in oral and topical preparations (a.9).

1.2.2.2 Ethylcellulose

Ethylcellulose is an ethyl ether of cellulose composed of β -anhydroglucose units joined together via the acetal linkage. It is a non-toxic, non-allergenic, non-irritant water insoluble material, which is primarily used as a hydrophobic coating or matrix to modify drug release but it may also be used to improve taste and to increase the stability of formulations (a.10). With regard to tablet coating applications, the availability of aqueous dispersions of ethylcellulose, (e.g., Aquacoat ECD, Surelease) has reduced the use of organic coating solutions thereby reducing the problems associated with organic solvent emissions.

1.2.2.3 Hydroxypropylcellulose

Hydroxypropylcellulose is a non-ionic, water-soluble, polyhydroxypropyl cellulose ether that is commercially available in a wide range of molecular weights (50000-1,250,000 g mol⁻¹). It is widely used in the pharmaceutical industry as a binder for tablets, in film coatings and as a controlled release matrix (255).

1.2.2.4 Hydroxyethylcellulose

Hydroxyethylcellulose is a non-ionic, water-soluble, hygroscopic polyhydroxyethyl ether of cellulose that is used in a range of pharmaceutical applications, such as a viscosity modifying agent in ophthalmic and topical formulations, in solid dosage forms as a matrix for controlled release, as a binder and as a film coating agent in solid dosage forms (255, a.11).

1.2.2.5 Hydroxypropylmethylcellulose

Hydroxypropylmethylcellulose (HPMC) is a partially O-methylated and partly O-2-hydroxypropylated cellulose ether, which is available in several grades with different DS and MS. It is widely used in the pharmaceutical industry as a binder for the production of tablets, as a viscosity-modifying agent and as a component of film coatings on tablets. In particular the use of HPMC as a directly compressible polymer for the production of controlled release tablets has been widely reported (a.11, a.12).

1.2.2.6 Hydroxyethylmethylcellulose

This is a partially O-methylated and partly O-(hydroxyethylated) cellulose. It is insoluble in hot water and organic solvents but dissolves in cold water. It is used as an excipient in a wide range of pharmaceutical formulations mainly as a coating for solid dosage forms and granules and as a suspending agent for disperse systems (a.13).

1.2.2.7 Sodium Carboxymethylcellulose

Carboxymethylcellulose (CMC) is an anionic polyelectrolyte that is available as the free acid or, more commonly, as the sodium salt (NaCMC) (**Figure 5**). The most commonly used CMC products possess DS values within the range 0.65 to 1.0 (a.14). Due to the polar nature of the carboxyl groups, NaCMC is soluble in both hot and cold water, forming clear mucilages (a.15). CMC is used in a wide range of pharmaceutical



Figure 5

Chemical structure of sodium carboxymethylcellulose

and related applications where thickening, suspending, stabilising, binding, and film forming properties are important, e.g., in the formulation of gels, suspensions and wound dressings.

1.2.3 Polyesters

Homopolymers and copolymers of lactic acid, glycolic acid and *\varepsilon*-hydroxycaproic acid jointly constitute the aliphatic polyesters. These polymers are non-toxic and in an aqueous environment undergo hydrolytic degradation through the cleavage of the ester linkage into the constituent carboxylic acids, which are then further metabolised. Different degradation rates may be obtained by altering the copolymer composition, molecular weight, crystallinity and stereochemistry of the monomers (a.16). Pharmaceutical polyesters are widely used in the formulation of various implantable and injectable drug delivery systems for the controlled release of therapeutic agents and vaccines. The following section provides a general overview of the physical properties of examples of this category of polymer however, specific examples of their pharmaceutical applications are presented in subsequent sections of the review.

1.2.3.1 Poly(lactide) and Related Copolymers

Lactic acid (2-hydroxypropanoic acid) is an organic acid that may be found as either the L(+) or D(-) stereoisomer. The lactic acid polymers can be synthesised by either polycondensation or by ring opening polymerisation, the choice of which is dependent on the required molecular weight of polymer. Typically polycondensation produces polyesters of low molecular weight. Frequently polyester copolymers are used in the pharmaceutical sciences, the properties of which are governed by the ratio of the two stereoisomers present along the chain. One example is the copolymer between polylactic acid and polyglycolic acid in which ratios of lactic to glycolic acid can vary from 85:15 to 50:50. Various other cyclic co-monomers such as ε caprolactone, δ -valerolactone can be incorporated into the lactide-based polymer (see Figure 6). The chemical structures of some pharmaceutically significant polyesters are presented in Figure 6 whereas the monomer composition and properties of some polylactides are described in Table 3. The structure of the copolymer is highly dependent on the difference in the reactivity of the two monomers; a higher difference in the reactivity can lead to the formation of a block copolymer and similar reactivity will lead to a more random copolymer (a.16, a.17).



Poly(lactide)



Poly(lactide-co-glycolide)



Poly(lactide-co-caprolactone)



Poly(*\varepsilon*-caprolactone)

Figure 6

Chemical structure of some pharmaceutically relevant polyesters

Pure poly lactic acid (PLA) is a semi crystalline polymer whereas polymers prepared from meso and racemic lactides are amorphous. The melting temperature (T_m) , degree of crystallinity and solubility are dependent on the MW, thermal history, optical purity and the copolymer ratio.

1.2.3.2 Poly(*\varepsilon*-caprolactone)

Poly(ε -caprolactone) is prepared by the ring opening polymerisation of ε -caprolactone. It has been widely studied as a matrix for controlled-release systems in a range of geometries. Poly(ε -caprolactone) degrades slower than polyhydroxy acids and is therefore preferred for controlled release devices with a longer life-time (a.18). More recently an interest has been shown in poly(ε -caprolactone) as a medical device biomaterial (107, a.19).

Table 3 Physicochemical Properties and Suppliers of Some Pharmaceutically Relevant Aliphatic Polyesters			
Generic Name	Trade Name	Manufacturer	Properties
Poly(D-Lactide) (D-PLA)	Purasorb PD	PURAC	Semi-crystalline
Poly(L-Lactide) (L-PLA)	Purasorb PL Lactel L-PLA Medisorb 100L	PURAC Birmingham Polymers Inc. (BPI) Alkermes Inc	Semi-crystalline T_{nf} 173-178 °C $T_{g'}$ 60-65 °C Soluble in MeCl ₂ , CHCl ₃ MW: >100,000 Tensile strength: 55-82 MPa % Elongation: 5-10 Modulus: 2.8-4.1 GPa
Poly(DL-Lactide) (DL-PLA)	Purasorb PDL Lactel DL-PLA Medisorb 100DL	PURAC BPI Alkermes Inc	Amorphous $T_{g'}$ 55-60 °C Soluble in MeCl ₂ , THF, EtOAc, CHCl ₃ MW: 4000-6000 Tensile strength: 27-41 MPa % Elongation: 3-10 Modulus: 1.4-2.8 GPa
Poly(E-caprolactone) (PCL)	Lactel DL-PLA	BPI	Semi-crystalline T_{nf} 58-63 °C $T_{g'}$ -65 to -60 °C Soluble in MeCl ₂ , C_3H_6O , CHCl ₃ MW: 80-150,000 Tensile strength: 21-34 MPa % Elongation: 300-500 Modulus: 206-344 MPa
Polyglycolide (PGA)	Purasorb PG Lactel PGA Medisorb 100PGA	PURAC BPI Alkermes Inc	Semi-crystalline T_{nf} 225-230 °C $T_{g'}$ 35-40 °C Soluble in hexafluoro-isopropanol MW: >100,000 Tensile strength: >68 MPa % Elongation: 15-20 Modulus: 6.9 GPa
Poly(DL-Lactide-co- glycolide) (DL-PLGA) (75:25) DL-PLGA (85:15) DL-PLGA (50:50) DL-PLGA (65:35)	Purasorb PDLG Lactel DL-PLGA Medisorb DL	PURAC BPI Alkermes Inc	Amorphous $T_{g'}$: 45-55 °C Soluble in MeCl ₂ , THF, EtOAc, $C_{3}H_{6}O$, CHCl ₃ MW: 40,000-100,000 Tensile strength: 41-55 MPa % Elongation: 3-10 Modulus: 1.4-2.8 GPa

1.2.4 Silicones

Polysiloxanes or silicones describe a family of organosilicon compounds and represent the most commercially important inorganic polymer. The polymer backbone is composed of alternating silicon and oxygen atoms (**Figure 7**). The properties of these polymers are highly dependent on the organic group attached to the silicon atom and can exist in the form of low viscosity oil to gels, rubbers and solid resins (a.20).



Silicone $R = CH_3$

Figure 7 Chemical structure of silicone

The unusual rotation around the Si-O bond allows the polymer chain to be highly flexible while maintaining the structural integrity. The ease by which different organic groups can be substituted along the polymer chain extends the properties of these polymers (a.20). Silicones are inert and compatible with the body tissues and hence have found applications in the pharmaceutical industry, mainly in the production of a variety of medical devices such as cardiac valves, hydrocephalus shunts, intravaginal controlled drug delivery implants and intraocular lenses. Silicones are also used in a variety of aesthetic and reconstructive prostheses such as breast, ear and joint prostheses.

1.2.5 Polysaccharides and Related Polymers

Polymers within this category are found abundantly in nature and are highly stable, non-toxic and biodegradable. Chemical modification may be readily performed to produce semi-synthetic polymer derivatives. Traditionally polysaccharides have been used as viscosity modifying agents for the stabilisation of disperse systems, (e.g., suspensions and emulsions), and for the formulation of gels. However, as the number of available polymers in this category has increased, so has the range of applications of these polymers. Examples of polymers within this category are presented next.

1.2.5.1 Chitosan

Chitin is a white, hard, inelastic mucopolysaccharide that is the supporting material of crustaceans and insects. It is a homopolymer consisting of N-acetyl glucosamine units linked through a β (1-4) linkage and has a 3D α -helical configuration, which is stabilised by hydrogen bonding. Chitin is insoluble in water and most organic solvents and accordingly the pharmaceutical uses of this polymer are limited. Chitosan, a copolymer comprising of glucosamine and N-acetyl glucosamine, is produced by the partial deacetylation of chitin and comprises a series of polymers with different molecular weights (50 kDa to 2000 kDa), viscosities and degrees of deacetylation (40-98%). The nitrogen atom of chitosan is a primary aliphatic amine and is therefore soluble in organic acids such as acetic and formic acids (Figure 8). Chitosan has been primarily formulated as microparticles for injectable and topical applications (a.21, a.22).



Chemical structure of Chitosan

The chemical properties and pharmaceutical applications of chitosan are summarised in **Table 4**.

Table 4 Chemical Properties and Pharmaceutical Applications of Chitosan			
Chemical properties	Pharmaceutical uses		
Cationic polyamine	Drug delivery (cationic nature allows the formation of		
High charge density at pH<6.5	complexes with the drug/excipient molecules)		
Adheres to negatively charged surfaces	Controlled drug release (gel forming ability in low pH media, has a high charge density at pH<6.5)		
Forms gels and polyanions	Fast release dosage forms		
Chelates to various transition metals	Peptide delivery		
Reactive hydroxyl and amino group	Adsorption enhancer for hydrophilic drugs		

1.2.5.2 Carrageenan

Carrageenan is a linear polysaccharide based on galactan containing glucose residues that is commercially extracted from red seaweed. It is a large molecule, composed of up to 1000 residues and accordingly structural variation is frequently observed. Three main types of carragcenan, defined by structural differences, are used in the formulation of pharmaceutical dosage forms and are termed kappa (κ), iota (ι) and lambda (λ) carrageenan. Carrageenan forms thermoreversible gels in aqueous solutions and also in the presence of cations and can therefore be used to modify the rheological properties of solutions. This polymer is used in the pharmaceutical formulations for stabilisation of disperse systems, viscosity modification and for the formation of gels (a.23).

1.2.5.3 Tragacanth

Tragacanth is a naturally occurring dried gum with a molecular weight of 840,000 g mol⁻¹ that is used as an emulsifying and suspending agent in a range of pharmaceutical formulations. It is extracted from *Astragalus gummifer Labillardière* and other species of *Astragalus*. The main constituent (60-70%) of the gum is bassorin, a water insoluble polysaccharide. The rest of the gum contains mainly tragacanthin, the water soluble component, whereas traces of cellulose, starch, protein and ash are also present. The hydrolysis of tragacanth produces L-arabinose, D-xylose, D-galactose and D-galacturonic acid. It is stable in both flaked and powdered form, however in an aqueous environment it is prone to microbial attack (a.24).

1.2.5.4 Acacia

Acacia is an odourless and colourless dried gum obtained from the stems and branches of species of *Acacia* and is composed of loose aggregates of sugars and hemicelluloses. The main constituent of the gum is arabic acid that is chemically associated with arabinose, galactose and rhamnose, as well as metals such as calcium and magnesium (a.25). It is used in the pharmaceutical industry as an emulsifying and a stabilising agent mainly for oral and topical formulations. Other uses include tablet binders, suspending and viscosity increasing agent, and in the formulation of lozenges.

1.2.5.5 Poly(alginic acid)

Poly(alginic acid), commonly termed alginate, is a natural polysaccharide which is a block copolymer of β -D-mannuronic acid (M) and α -L-guluronic acid (G). The homopolymer regions of mannuronic acid and guluronic acid are interspersed with regions of alternating (MG) copolymer structure. It is used as a thickening and suspending agent in creams, pastes and gels. Furthermore, it has been formulated as microparticles for drug delivery applications and, in addition, is extensively used as a wound dressing due to the excellent swelling properties and biocompatibility (a.26).

1.2.5.6 Xanthan Gum

Xanthan gum is a polysaccharide that is widely used in both oral and topical formulations due to its compatibility with most pharmaceutical ingredients and its stability over a wide range of both pH (3-12) and temperature (10-60 °C). The polymer backbone is composed of four β -D-glucose units covalently attached via a 1-4 linkage. The repeat unit is composed of five sugar residues with one glucuronic acid, two glucose and two mannose units. On alternating anhydroglucose units the polymer has a trisaccharide side chain composed of a glucuronic acid and two mannose units. The polymer chains in solution exist as single, double or triple helical structure. Xanthan gum is used as a suspending, stabilising, thickening and emulsifying agent. It has also been used in the preparation of sustained release matrix tablets (a.27). A synergistic rheological effect is observed when xanthan gum is mixed with inorganic suspending agents such as magnesium aluminium silicate with ratios between 1:2 and 1:9 giving optimum properties.

1.2.6 Miscellaneous Polymers

In this section the properties of other polymers that may not be classified into the previous categories and which are used in pharmaceutical dosage forms are described.

1.2.6.1 Gelatin

Gelatin is an amphoteric animal protein composed of 19 amino acids possessing a molecular weight of 15,000-25,000 gmol⁻¹. There are two types of gelatin that are produced by partial acid (type A) or partial alkaline (type B) hydrolysis of collagen and which possess different isoelectric points. It is a water-soluble polymer and, due to its biodegradable and non-toxic nature, is widely used in the pharmaceutical industry as a coating agent on solid dosage forms, to produce pharmaceutical films, as a gelling agent, as a tablet binder and to increase the viscosity of topical formulations. It has also been used for the microencapsulation of drugs and as a biodegradable matrix in implantable drug delivery systems (a.28, a.29).

1.2.6.2 Polyanhydrides

Polyanhydrides are composed of a hydrophobic polymer backbone containing hydrolytically labile

anhydride linkages. As a result, both their physicochemical properties and degradation are dependent upon the chemical structure, molecular weight, crystallinity and copolymer composition, if applicable. The degradation rate may be controlled by adjusting the hydrophobic and hydrophilic substituents of the polymer; increasing hydrophobic properties decreasing the rate of degradation. **Tables 5 and 6** provide an overview of the advantages, disadvantages, properties and uses of various polyanhydrides (a.30).

One anhydride copolymer that has received considerable attention is poly(vinylmethylether-*co*-maleic anhydride) (Gantrez[®]; ISP). This copolymer

Table 5 Advantages and Disadvantages of Polyanhydrides		
Advantages	Disadvantages	
Easily prepared from low cost resources, in a one step synthesis requiring no purification steps.	Hydrolytic instability.	
Their molecular structure is well defined and properties can be varied by monomer selection.	be enhanced by the introduction of an imide group into the	
Degrade at a predictable rate into carboxylic acids, which are non-toxic and many are naturally occurring constituents of the body. These are completely eliminated from the body in weeks to months.	polyanhydride. Low film and fibre forming properties.	
Processable by low temperature injection moulding and extrusion. Sterilisation using gamma radiation causes a minimal effect to the polymer properties.	Depolymerise into low molecular weight polymers in organic solution and if stored at room temperature.	

Table 6 Physicochemical Properties of Selected Polyanhydrides				
Polyanhydride	Specific examples	Properties		
Aliphatic	Poly(sebacic acid) Poly(adipic acid)	Brittle, crystalline, fast degradation melt below 50-90 °C. Soluble in chlorinated hydrocarbons.		
Unsaturated	Poly (fumaric anhydride) Poly (4,4'-stilbene dicarboxylic acid anhydride)	Homopolymers are crystalline and insoluble in organic solvents, copolymers with aliphatic acids renders it less crystalline and soluble in chlorinated hydrocarbons.		
Aliphatic/aromatic	Poly-[(<i>p</i> -carboxyphenoxy) alkanoicanhydride]	Display a zero-order hydrolytic profile for 2-10 weeks, the length of the alkanoic chain determines the degradation time. mp <100 °C, soluble in chlorinated hydrocarbons.		
Poly(ester-anhydrides) and poly(ether anhydride)	Di-, tri- block polymers of poly(caprolactone), poly(lactic acid) poly(hydroxybutyrate)	mp = 97-176 °C MW: 13,000 Stimulate new bone formation.		
Fatty acid anhydrides	Polymers of dimmers of oleic acid and erucic acid with sebacic acid.	Low melting polymers which are soluble in organic solvents and degrade into naturally occurring amino acids. MW: 8000-48,000.		
Branched anhydrides	Poly (sebacic acid) branched with poly(acrylic acid)	Less crystalline, low melting temperature and low viscosity, faster degradation, useful for manipulating the structure		
mp = melting point				

has been reported to possess strongly bioadhesive properties, particularly following complexation with PVP, and, as a result, this copolymer has been used as a major component of topical formulations (a.19, a.31) to aid retention of the dosage form at the site of application.

1.2.6.3 Polyethylene Glycols

Polyethylene glycol (PEG), which has a general formula $(HO-(CH_2CH_2O)_n-CC_2CH_2OH)$, is a polyether diol usually manufactured by the aqueous anionic polymerisation of ethylene oxide. It is non-immunogenic and non-toxic and is eliminated by a combination of renal and hepatic pathways, making this polymer ideal for parenteral and solid dosage form preparations. The available molecular weights range from 500-20,000 g mol⁻¹ and can be obtained with low polydispersities:

$$\left(\frac{M_n}{M_w} < 1.05\right)$$

PEG is an amphiphilic polymer that is soluble in both aqueous and organic solvents. In addition it has a low level of cellular and protein absorption and is therefore grafted to surfaces of medical devices to prevent deposition of proteinaceous material or bacterial surface growth. It is also conjugated to proteins and to colloidal dosage forms, e.g., liposomes, to minimise their recognition by the immune system. Furthermore, PEG have been widely reported to increase the solubility of poorly soluble therapeutic agents when formulated as liquid formulations, e.g., oral solutions, injections, and as solid dispersions (a.32).

1.2.6.4 Polyethylene Oxide

Polyethylene oxide (PEO) is a non-ionic homopolymer of ethylene oxide with the chemical formula $(CH_2CH_2O)_n$ where *n* represents the average number of oxyethylene groups. It is prepared from polymerisation of ethylene oxide using a catalyst. PEO is a water-soluble polymer that is also soluble in organic solvents such as acetonitrile, chloroform and methylene chloride. This polymer has been shown to have low levels of toxicity and is completely and rapidly eliminated from the body. It is primarily used as a tablet binder and a thickening agent. Depending upon the molecular weight, which controls the swelling characteristics, it can be used to formulate immediate or sustained release formulations (a.33).

2 Applications of Polymers for the Formulation of Conventional Dosage Forms

As described in the introduction to this review, the delivery of therapeutic agents is facilitated by the use of pharmaceutical polymers. The wide range of physicochemical properties offered by these materials may be utilised to improve both the clinical and nonclinical, (e.g., manufacturing, stability), properties of dosage forms. In this section a concise overview of the role of pharmaceutical polymers in the formulation and manufacture of conventional dosage forms is provided. For the purpose of this review conventional dosage forms may be defined as those in which there is limited control of drug release into the surrounding biological fluid by the dosage form.

2.1 Solid Dosage Forms

Solid dosage forms such as capsules and tablets are the most frequently used dosage forms due to their relative ease of administration, production and identification, the latter being facilitated by their characteristic shapes and colour and, in some cases, the embossed presence of the manufacturer's name. Solid dosage forms are generally more stable than their liquid counterparts and are therefore preferred for poorly stable drugs. These dosage forms are manufactured efficiently and packaged and shipped at a lower cost than their liquid counterparts.

2.1.1 Tablets

Tablets are solid dosage forms prepared by compressing a therapeutic agent that has previously been mixed/ granulated with pharmaceutical excipients (primarily polymers). These constitute the most popular dosage form, accounting for about 70% of all pharmaceuticals produced. Tablets allow the accurate administration of drug and can be mass produced, simply and quickly, thereby keeping the manufacturing costs to a minimum. Drug release from tablets may be tailored to meet the pharmacological requirements. The subject of tablets has been extensively reviewed within textbooks and only the role of polymer excipients in the manufacture of tablets will be briefly discussed in this section.

In tablet manufacture polymers are frequently used as binders and disintegrants. Binders are materials that act as adhesives to bind the powders together during wet granulation. This process facilitates reproducible compression of the granulated powders into tablets. Common binding agents include starch, gelatin, PVP, EC and HPMC. Disintegrants are included in many tablet formulations to initiate the disintegration of the tablet so that the surface area of the tablet fragments is increased and the drug is released rapidly. This process of disintegration occurs due to extensive polymer swelling following contact with biological fluids. Examples of polymeric disintegrants include starch, PVP and sodium CMC. In addition to these polymers, microcrystalline cellulose may be used as compression aids to facilitate compression of powders and granules whereas polymers may be used as diluents to ensure that the size of the tablet is sufficient to aid manufacture.

2.1.2 Capsules

Capsules are solid dosage forms that are generally composed of gelatin and which, dependent on the composition, may be categorised as either hard capsules or soft capsules. In the former category the capsule shell is composed of gelatin, sugar, water and colorant (if required). The gelatin capsule is filled with the active ingredients and additionally, diluents or fillers. Fillers such as starch and microcrystalline cellulose are used to obtain the proper fill volume in the capsule and may also provide cohesiveness to the powder to aid capsule filling. To assist with the de-aggregation of the capsule contents in the gastrointestinal (stomach) fluids, various starch derivatives such as pre-gelatinised starch and sodium starch glycolate are added to the capsule contents.

Conversely, soft gelatin capsules are made of gelatin that has been plasticised by the addition of glycerin or sorbitol. This capsule type is used to hermetically seal and encapsulate liquids, suspensions or dry powders. The manufacturing methods for the production of hard and soft gelatin capsules are different and require separate specialist equipment.

2.1.3 Film Coatings of Solid Dosage Forms

Coating tablets with a thin polymeric film is commonly performed to modify drug release, mask the taste of therapeutic agents, to enhance the stability of the drug within gastrointestinal fluids or may be used for purely aesthetic reasons. The film is usually 10-100 μ m thick and is composed of at least one polymer, a plasticiser and, when required, other minor additives such as colorants and opacifiers. In situations where the tablets may be brittle and/or exhibit poor handling characteristics, polymeric film coatings possessing a high modulus of elasticity and high tensile strength may be used to improve tablet strength. Many drugs are sensitive to moisture and various polymers with low water permeability are used as film coatings to prevent the ingress of moisture (a.34). Three classes of polymers are used as coatings for solid dosage forms, namely:

- 1. Water soluble polymers, (e.g., MC, HEC and HPMC)
- 2. Water insoluble polymers such as EC, which are used mainly for controlled drug delivery
- 3. Polymers used as enteric coating materials that are soluble above a certain pH, such as HPMC phthalate, cellulose acetate phthalate, or those that dissolve following enzymic degradation.

Generally a mixture of water soluble and insoluble polymers is used to increase or decrease the resulting release rate of the drug in controlled drug delivery systems. For example, coatings composed of EC and HPMC blends are often used for this purpose. HPMC in contrast to EC is soluble in water and leaches out of the film coating creating pores through which the drug can diffuse. Film coatings composed of mixed polymers such as pectin, chitosan and HPMC degrade in presence of bacterial enzymes and have been shown to be capable of retarding the release of tablet core material until they reach the colon an environment rich in such enzymes (a.35, a.36).

Methacrylic acid copolymers are used as enteric coatings as these contain carboxylic groups that are ionised whenever the pH of the environment exceeds 5. Enteric coating dosage forms remain intact in the stomach and then release the drug in the upper intestine. In pure water or dilute acids the coating is insoluble. The pH at which these polymers dissolve is dependent on the content of the carboxylic acid in the copolymer. The polymers commonly used for enteric coatings are anionic polymethacrylates such as copolymers of methacrylate and ethylacrylate (Eudragit®; Degussa), cellulose-based polymers such as cellulose acetate phthalate (Aquateric[®]; FMC Corporation) and polyvinyl acetate (PVA) derivatives such as polyvinyl acetate phthalate (Coateric[®]; Colourcan Ltd). Until relatively recently, film coating of solid dosage forms was performed using solventbased acrylic polymer coatings however, due to the toxicity and environmental implications, these have been replaced by water-based coatings. For example,

emulsion-based systems containing acrylate copolymers as the internal phase were some of the first aqueous polymer dispersions (a.37).

The use of polymer coatings for the controlled release of drugs is described in more detail in a later section of the review.

2.2 Disperse Systems

A disperse system can be defined as a heterogeneous system in which one substance is dispersed as solid or liquid particles in the dispersion medium. Pharmaceutical examples of these include suspensions, emulsions, creams, ointments and aerosols. The particle size of the dispersed phase is dependent on the route of administration and may vary from about 1 µm for inhalation to 10-100 µm for ophthalmic application and 200 µm for oral use. Disperse systems are prone to various forms of instability such as segregation, coalescence and caking, which can lead to inaccurate dosing and consequently the formulation of disperse systems is often challenging to the pharmaceutical scientist. To enhance the physical stability and clinical performance of these systems it is necessary to include a range of pharmaceutical excipients, including surfactants, electrolytes and polymers, the latter being used control the rheological characteristics and hence the rate of coalescence/sedimentation (a.38).

Various synthetic and natural hydrophilic polymers are extensively used to enhance the physical stability of pharmaceutical disperse systems. Examples of these include alginates, carrageenan and xanthan gum, whereas a wide range of synthetic polymers has also been used for this purpose, e.g., cellulose ethers, poly(acrylic acid), PVP and PVA.

2.3 Gels

Gels are polymeric systems in which the presence of physical or chemical crosslinks between the adjacent polymer chains restricts chain mobility, thereby enhancing the rheological structure. Chemically crosslinked gels are commonly referred to as hydrogels and have been used extensively within the medical device industry as hydrophilic, biocompatible coatings and, additionally, due to their ability to absorb large quantities of aqueous fluid, as wound dressings. Examples of hydrogels that are used for this purpose include poly(hydroxyethylmethaerylate), poly(methacrylic acid) and poly(acrylamide) that have been crosslinked with the appropriate agent (a.39). Within the pharmaceutical industry physically crosslinked gels are primarily used as drug delivery platforms, e.g., for the local delivery of drugs to the skin, oral cavity, vagina, rectum. In these systems, polymer mobility is restricted but not to the same extent as their chemically crosslinked counterparts. In physically crosslinked gels, gelation is dependent on several physicochemical factors including chemical structure of the polymers, polymer molecular weight, composition of the solvent, pH and temperature (a.40, a.41).

Whilst all polymers have a specific concentration at which gelation occurs, certain polymers additionally form gels under specific conditions. For example sodium alginate is widely used to form gels by either reducing the pH or by an electrostatic interaction with divalent cations such as calcium. Poly(acrylic acid) only undergoes gelation at pH 7 following neutralisation of the pendant carboxylic acid groups. Xanthan gum forms thermoreversible gels at concentrations above 0.5% whereas HPMC and MC undergo reversible thermogelation at > 50 °C, due to hydrophobic interactions between molecules caused by the presence of the methoxyl substituents (113, 237).

2.4 Transdermal Drug Delivery Systems (Patches)

Transdermal drug delivery systems are used for the controlled delivery of therapeutic agents across the skin to the systemic circulation. Such systems have been used for several clinical applications including pain management, cessation of smoking, treatment of heart disease and hormone replacement, where the convenience of use and controlled and prolonged drug delivery has ensured their role in disease management. Pharmaceutical polymers form an integral part of the design of transdermal drug delivery systems. Typically polymeric layers may be used as the protective outer covering to protect the dosage form from external damage. There may be a layer in which the drug is dispersed/dissolved within a polymeric matrix, which acts to control drug release to the skin. In addition, there is an adhesive layer, which is used to locate and maintain the dosage form at the site of application. Alternatively, in certain designs, the adhesive layer may additionally operate as the drug reservoir. Typical adhesives used in transdermal patches include acrylates, polyisobutylenes and silicones. More specific details of the design and operation of transdermal drug delivery systems are described in Section 3.

3 Applications of Polymers for Controlled Drug Delivery

Over the past four decades an interest has developed in the design and formulation of dosage forms that control the subsequent release of drug from the dosage form into the surrounding biological fluids. Consequently, this rate process effectively controls the pharmacological properties of the therapeutic agent. Central to the development of such systems is role of pharmaceutical polymers. In light of the current and continuing importance of this category of drug delivery system the following section provides a concise overview of the range of designs of controlled release drug delivery systems and the contribution/significance of polymers to their function. The reader should be reminded that the following sections are designed to provide an overview of controlled release drug delivery systems and where necessary references to more specialist literature are included.

3.1 Introduction: Principles of Controlled Drug Delivery

The treatment of disease states has traditionally involved the use of multiple daily dosing of a therapeutic agent using a conventional dosage form, e.g., tablets or capsules. Following administration, the drug is absorbed into the systemic circulation in a stepwise fashion involving:

• Drug diffusion through the matrix of the dosage form.

- Drug dissolution within the aqueous fluid of the gastrointestinal tract.
- Drug diffusion through the aqueous fluid of the gastrointestinal tract to the surrounding tissue, e.g., the villi of the small intestine.
- Absorption of the drug across the wall of the gastrointestinal tract.
- Entry into the systemic circulation and deposition at the required site of action.

In conventional oral drug delivery systems, drug is released from the dosage form within a short (defined) period allowing subsequent absorption into the systemic circulation. Under these circumstances, the onset and duration of effect of a therapeutic agent is controlled by the absorption step. It is assumed that by ensuring greater concentrations of the drug at the site of action or absorption, the mass and rate of drug absorption will increase and this will in turn result in greater concentrations of drug in the systemic circulation (a.42, a.43). Following administration, drug absorption from conventional oral dosage forms may be rapid. A typical profile of the concentration of drug in the plasma as a function of time following administration of two doses of a conventional oral dosage form is shown in Figure 9. In this figure three regions may be observed, namely the sub-therapeutic range, in which the concentration of drug in the systemic circulation is insufficient to render a therapeutic response, the therapeutic window, the region where the control of





Typical profile of the drug plasma concentration as a function of time following oral administration of two doses of a conventional oral dosage form, (e.g., tablet, capsule).

the disease state is optimal (depicted as a shaded region) and lastly, the region in which the concentration of the drug exceeds the maximum safe plasma concentration.

Whilst conventional oral dosage forms may be used to treat acute and chronic disorders, there are several associated problems, including the requirement for multiple dosing (a factor that may lead to poor patient compliance) and the possible development of side effects due to the drug plasma concentration exceeding the maximum safe concentration. These two problems may be effectively resolved by the use of controlled release systems, i.e., formulations in which the release of drug and hence the absorption into the systemic circulation is controlled by the dosage form itself. The use of such systems enhances the predictability and reproducibility of drug release and, due to the greater control of plasma drug levels; controlled release systems generally require an overall reduced dose of drug.

Through appropriate knowledge of the physicochemical properties of both the therapeutic agent and the polymeric constituents of the formulation, controlled release systems may be formulated to ensure that the frequency of dosing is dramatically reduced and furthermore, as depicted by the broken line in **Figure 10**, the concentration of therapeutic agent is maintained within the therapeutic window for a prolonged period, thereby reducing the incidence of side-effects.

There are several strategies by which controlled release dosage forms may be formulated, all of which

involve the use of polymers and a range of geometries to control the rate at which the drug diffuses from the dosage form and hence dissolves in the biological fluids. Whilst there are systems that involve the modification of the solubility of the therapeutic agent (by chemical modification or insoluble salt formation) or involve the use of slowly dissolving polymers, due to the restricted scope of this technical report only the design and use of diffusion controlled release systems will be considered. For the purpose of this report diffusion controlled release systems will be discussed in three categories, namely reservoir systems, matrix systems and miscellaneous diffusion controlled drug release systems. Furthermore, an introduction to the use of stimuli responsive diffusion controlled release systems will be provided. Before describing the design and function of these various systems and, in light of its importance to drug delivery, it may be appropriate to clarify what is meant by drug diffusion. Drug diffusion is a process in which there is random movement of drug molecules from a region of high concentration (the dosage form) to a region of low concentration, i.e., the surrounding biological fluids. Even from this limited description the reader will have been alerted to the significance of drug diffusion. This process is critical for drug movement both from the dosage form and within the aqueous biological environment and, in addition, it is involved in the movement of drug molecules across biological membranes. For further information on the principles of diffusion and the importance to the performance of pharmaceutical systems a range of references is provided (a.44-a.48).





Figure 10

Typical profiles of drug plasma concentration as a function of time following the oral administration of two modified/controlled release dosage forms. The solid line represents a repeat action (pulsatile) dosage form whereas the solid line represents a controlled release dosage form

3.2 Reservoir Systems

In these systems the drug-containing core is separated from the biological fluids by a water insoluble polymeric coat or layer, depending on the geometry of the drug delivery system. Examples of polymers that are commonly used as the polymeric coats/layers include, ethylcellulose, poly(ethylenevinylacetate), silicone and various acrylate copolymers. A diagrammatic representation of the design and operation of a reservoir system is presented in **Figure 11**.



Figure 11

Diagrammatic representation of the design and operation of a reservoir controlled release system

Drug release from these systems occurs by a number of steps, initially involving the partitioning of the drug into the polymeric coat/layer. The drug then diffuses from the inner to the outer side of the coat/layer due to the difference in concentration gradient and at this stage partitions into the surrounding biological media. Mathematically, the rate of drug diffusion (termed the flux, J) across the polymeric coat/layer may be defined as the product of the diffusion coefficient (D)

and the concentration gradient $\left(\frac{dC}{dx}\right)$ as follows:

$$J = -D\frac{dC}{dx} \tag{1}$$

Assuming steady state conditions the above equation may be integrated to produce Equation 2:

$$J = -D\frac{\Delta C}{h} \tag{2}$$

Where h refers to the polymer coating/layer thickness.

Based on the previous equations the rate of drug release

$$\left(\frac{dM}{dt}\right)$$
 may be expressed by:

$$\frac{dM}{dt} = \frac{D_m AK}{h} \tag{3}$$

Where:

- D_m refers to the diffusion coefficient of the drug within the polymer membrane,
- A is the surface area of the dosage form, and
- K is the partition coefficient of the drug (between the polymeric coat/layer and the biological solution). The partition coefficient is frequently expressed as the ratio of the solubility of the drug in the polymeric phase to that in aqueous solution.

Equation 3 specifically relates to the diffusion of the therapeutic agent through the polymeric matrix however in the biological environment one other factor must be considered, namely the diffusion of the drug through the hydrodynamic (unstirred) diffusion layer. This is a stagnant layer of fluid that is present on the surface of the drug delivery system through which the drug must diffuse prior to entry into the main bulk of the biological fluids. To facilitate these considerations Equation 3 must be expanded.

The rate of drug release per unit area of dosage form

$$\left(\frac{M}{t}\right)$$
 may then be described as follows:

$$\frac{M}{t} = \frac{C_p K D_d D_m}{K D_d h_m + D_m h_d} \tag{4}$$

Where:

- C_p refers to the saturation solubility of the drug in the polymeric coat/layer,
- K is the partition coefficient,
- D_d is the diffusion coefficient of the drug in the hydrodynamic layer,
- D_m is the diffusion coefficient of the drug in the polymer coat/layer,
- h_m is the thickness of the polymer coat/layer, and
- h_d is the thickness of the hydrodynamic layer.

Interestingly, this equation defines the parameters that will influence the subsequent delivery of therapeutic agents and is consequently used to engineer drug release. For a more comprehensive mathematical description of drug release from reservoir systems the reader is invited to consult the excellent text by Chien (a.47).

There are several drug delivery systems that are designed to provide reservoir controlled drug release and, rather than laboriously describe each of these, the design and operation of selected examples of these, namely the Ocusert, Progestasert and Transderm-Nitro systems, will be presented. Reservoir controlled release systems may be manufactured in a wide range of geometries including conventional tablets/pellets, laminated films and other defined shapes, (e.g., hemispheres, cylinders, rods). Similarly there are a number of methods by which these systems may be produced. For example pellets, spheres and tablets may be coated with an insoluble polymeric coating using conventional spray/film coating techniques, e.g., pan coating, air suspension coating (a.49, a.50). Alternatively, planar (laminated) drug delivery systems, e.g., transdermal patches, are manufactured using extrusion or film casting techniques. All reservoir systems share a common design, namely the drug core is housed within a polymeric barrier. The choice of the composition of the polymeric membrane is performed according to the physicochemical properties of the drug, particularly the ability of the therapeutic agent to diffuse through the polymer coating at the appropriate rate, the chosen manufacture method and the proposed route of administration to the patient.

3.2.1 The Ocusert System

The delivery of therapeutic agents to the eye for the treatment of disorders of the eye, (e.g., glaucoma),

using conventional drug delivery systems, e.g., drops, ointments, is an inefficient process. This is primarily due to the rapid clearance of drugs from the surface of the eye due to blinking and tear flow. One method by which the efficiency of ocular drug delivery may be improved is through the use of polymeric implants that are implanted under the lower cul-de-sac of the eye (a.47). The Ocusert represents one such example that has been designed to release either $20 \,\mu g \, h^{-1}$ or $40 \,\mu g \, h^{-1}$ of a therapeutic agent (pilocarpine) for a seven day period following implantation. In design terms the Ocusert is an ellipsoidal shaped implant that is composed of several layers, diagrammatic representations of which are shown in **Figures 12 and 13**.

In this system pilocarpine is dispersed within an alginic acid matrix which is sandwiched between two layers each composed of poly(ethylene-co-vinyl acetate). These layers act as the rate controlling membranes. The fourth layer is composed of an opaque, annular ring that is housed beneath the ratecontrolling layer and, as both the rate controlling membranes and the drug-containing matrix are transparent, the function of this ring is to offer visibility of the device following instillation. Drug release from this delivery system occurs by diffusion. Initially lachrymal (tear) fluid diffuses through the rate controlling membranes and enters into the inner (alginate) matrix at which stage dissolution of pilocarpine occurs. Now in the molecular state, pilocarpine diffuses from the region of high concentration (the drug-containing matrix) to the lachrymal fluid through the rate controlling membrane. The release of pilocarpine from this system is zero order and may be mathematically described using a modification of Equation 4 (see Equation 5).





Diagrammatic representation of the Ocusert ocular drug delivery system (Diagram adapted from Chien (1992) [a.47])



Figure 13

Cross-sectional view of the Ocusert ocular drug delivery system. Pilo 20 and 40 refer to systems that release pilocarpine at 20 or 40 µg h⁻¹, respectively, (adapted from Chien (1992) [a.48])

$$\frac{dM}{dt} = \frac{DKC_s}{h} \tag{5}$$

Where:

dM/dt is the rate of pilocarpine release,

- *D* is the diffusion coefficient of pilocarpine through the polymeric rate controlling membrane,
- K is the membrane:solution partition coefficient,
- C_s is the saturated pilocarpine concentration in the lachrymal fluid within the alginic acid matrix, and
- h is the thickness of the rate controlling layers.

There are two design features of the Ocusert system that are important determinants of the subsequent performance, namely the thickness/composition of the rate controlling membrane and the selection of the salt form of the therapeutic agent. Unlike some reservoir controlled drug delivery systems (which are water impermeable), the rate controlling membrane is designed to facilitate and control the rate of diffusion of lachrymal fluid into the inner drug-containing layer of the device. This is a key design component for a number of reasons. Firstly, drug release may only occur whenever a saturated solution of pilocarpine is present within the alginic acid layer and therefore the rate of ingress of fluid will influence the subsequent rate of dissolution of pilocarpine. Secondly, the choice of the drug salt will directly affect the saturated drug solubility (C_s) . It is worth noting that zero-order release of pilocarpine only occurs whenever a saturated solution of drug is maintained within the inner polymer matrix

and therefore, the use of soluble salts of pilocarpine, whilst increasing the rate of release of drug, will ensure that the period over which zero-order release occur is reduced. Whenever insufficient drug remains within the alginic acid layer to maintain a saturated drug solution, drug is released according to first order kinetics (a.47, a.48). According to Equation 5 the rate of release of pilocarpine may be altered by modification of the thickness of the rate controlling membranes. However, to facilitate higher rates of release of pilocarpine, e.g., 40 µg h⁻¹, the diffusion coefficient of the drug is increased by the inclusion of a plasticiser in the poly(ethylenevinylacetate) membranes. For this purpose di(2-ethyl-hexyl)phthalate has been used. A typical release profile of pilocarpine from the Pilo-20 system is shown in Figure 14.

In clinical studies the Ocusert system has been shown to lower intra-ocular pressure, the main (and sight threatening) symptom of glaucoma, for periods up to one week (a.47). Furthermore, there were fewer side effects associated with this system and patient compliance was improved in comparison with the conventional pilocarpine eye drop formulation. One disadvantage of the Ocusert system was the discomfort to some patients and potential retention problems within the eye (a.43).

3.2.2 The Progestasert System

A second example of a reservoir controlled drug delivery system is the Progestasert intra-uterine device (IUD), a medicated implant that is used for contraceptive purposes. In the 1960s IUDs emerged



Figure 14

Typical release profile of pilocarpine from the Pilo-20 Ocusert ocular controlled release system (adapted from Chien 1992 [a.47])

as an available method of contraception that prevented implantation of the ovum due to the mechanical effects of the device on the uterine endometrium. It is accepted that to achieve greater contraceptive efficiency larger IUDs should be used, as these offer greater coverage of the endometrium. However, patients using these larger IUDs will be more prone to side-effects including bleeding, cramps and possibly expulsion (a.47). One method by which the contraceptive efficacy of these devices may be improved whilst lowering the incidence of side effects is to use the IUD to locally deliver contraceptive agents to the endometrium at a defined rate for a prolonged period. Local delivery of progesterone is advantageous for a number of reasons. Most noticably, the drug is rapidly metabolised following oral administration and therefore requires frequent oral administration of high doses of this drug.

Progestasert is an example of a reservoir controlled drug delivery device that is implanted in the uterus and releases 65 µg day⁻¹ of progesterone for one year (a.47, a.51). A diagram of the Progestasert drug delivery system is presented in Figure 15. In this a defined mass (38 mg) of microcrystals of the therapeutic agent (and barium sulfate) is suspended in silicone oil, the latter designed to offer opacity to the system for visualisation of the device in vivo by X-rays. This disperse liquid phase is housed with the IUD which is composed of ethylene vinyl acetate. The horizontal section of the IUD is manufactured from polyethylene, however this is solely involved with the mechanical interaction with the endometrium and is not involved in drug release. Drug release from this system occurs by the initial



Diagrammatic representation of the Progestasert system (adapted from Chien 1992) [a.47]

dissolution of the drug suspension within the silicone oil. Following this drug diffusion through silicone oil to the inner surface of the polymeric structure and partitioning of the drug molecules into ethylene vinyl acetate occur. In a similar fashion progesterone diffuses through this polymer (rate controlling) membrane to the interface of the device and biological fluid, at which stage partitioning of the drug into the biological fluids follows. The success of the Progestasert device is considerable. The pregnancy rate in women who use the T-shaped drug free device is between 18 and 22%, however, the use of the Progestasert system that was designed to deliver 65 µg day⁻¹ of progesterone to the endometrium has been reported to be 1.1% (a.52).

3.2.3 Reservoir Designed Transdermal Patches

A third example of the use of reservoir systems for controlled drug delivery may be observed in the transdermal delivery of therapeutic agents. Transdermal drug delivery involves the diffusion of the drug through the skin and ultimately absorption into the systemic circulation. One of the anatomical purposes of the skin is to protect the body from the ingress of possibly dangerous chemicals and therefore it is little surprise that only a limited number of therapeutic agents possess the appropriate physicochemical properties to traverse this anatomical barrier. There are three main anatomical barriers that therapeutic agents must partition into and diffuse through prior to possible absorption into the systemic circulation, namely the stratum corneum (a keratinised layer at the outermost region of the skin), the viable epidermis and the dermis, into which the microcirculation may be found (a.42, a.53). Traditionally, topical formulations have been used for the treatment of localised disorders, e.g., infection, itch, inflammation, however opportunities exist for the use of the skin as a portal for the controlled delivery of drugs into the systemic circulation. Skin penetration occurs in a series of stages involving drug penetration from the dosage form into and diffusion through the stratum corneum, partitioning into and diffusion through the lower layers of the epidermis, partitioning into the dermis and diffusion to the walls of the microcirculation. Further partitioning into the microcirculation allows the distribution of the drug through the systemic circulation to the target organ. Whilst all three layers offer resistance to drug diffusion, the major barrier to drug absorption is the stratum corneum. The authors accept that this description of the physicochemical and biological aspects of transdermal drug delivery is abridged and therefore it is advised that any reader who wishes to gain more information on this aspect of drug delivery should consult the excellent texts by Barry (a.54), Osborne and Amann (a.55) and Walters (a.56). However, the details provided previously should be sufficient to enable the reader to appreciate the following sections.

There are several available transdermal therapeutic systems including reservoir membrane designs and, as will be discussed in subsequent sections, matrix designs. A typical reservoir transdermal therapeutic system is shown in **Figure 16**.

As may be observed the drug delivery system is composed of several layers, namely a metallic backing layer, which is impermeable to drug diffusion thereby preventing drug loss, the drug containing reservoir, a rate controlling membrane and an adhesive layer, which facilitates the location and retention of the drug on the skin. The system also contains a release liner, which is present on the surface of the adhesive layer and is removed prior to use. The mechanism of drug release is similar to other reservoir controlled drug delivery systems and involves the following steps:

- (a) Drug dissolution within the reservoir matrix.
- (b) Drug diffusion to and partitioning into the membrane.
- (c) Drug diffusion within the membrane and partitioning into the adhesive layer.
- (d) Drug diffusion within the adhesive and partitioning into the *stratum corneum*.

With the exception of the metallic backing layer, manipulation of the physicochemical properties of the other layers represents opportunities for the engineered control of drug release from these systems. For





Cross-sectional diagram of the design of a reservoir transdermal therapeutic (patch) system (adapted from Chien 1992) [a.47]

example, the matrix into which the drug is dissolved or dispersed may be a solid polymer or a viscous paste in which the drug is dispersed within silicone oil or other compatible liquids. However, of fundamental importance to the design of these systems is the composition of the rate controlling membrane as this, in accordance with other reservoir type systems, controls drug diffusion into the adjacent adhesive layer and in so doing represents the rate-limiting step in the diffusion process. In addition the choice of adhesive is important, as is the performance of these systems and must facilitate drug diffusion, be hypoallergenic and offer appropriate adhesion (and removal) properties. As mentioned previously, examples of commonly used adhesives include silicones and acrylate co-polymers.

The rate of release of therapeutic agents from reservoir transdermal systems may be conveniently described by the following equation:

$$\frac{dM}{dt} = \frac{K_{m/r}K_{a/m}D_aD_m}{K_{m/r}D_mh_a + K_{a/m}D_ah_m}C_R$$
(6)

Where:

- C_R is the drug concentration present in the matrix,
- $K_{m/r}$ and $K_{a/m}$ are the reservoir/membrane and membrane/adhesive partition coefficients,
- D_m and D_a are the diffusion coefficients of the drug in the rate controlling membrane and the adhesive layer, and
- h_m and h_a are the thicknesses of the rate controlling membrane and the adhesive layer.

Several commercial products have been formulated with this type of design, such as the Transiderm-Nitro[®] (Novartis Pharma BV) system, delivering glyceryl trinitrate in a once daily system (a.57), the Durogesic[®] (Janssen-Cilag) patch system that delivers the opiate analgesic, fentanyl over a period of 72 hours (a.58) and the Catapres-TTS system (Boehringer Ingelheim), a once weekly treatment for hypertension. Examples of other related transdermal systems have been described by Hadgraft and Guy (a.59).

3.3 Matrix Systems

In matrix designed drug delivery systems, the drug is homogeneously dispersed, either at the molecular scale or as solid particles, within a polymeric medium. In comparison to reservoir systems, the manufacture of matrix designed drug delivery systems is more straightforward and may be performed using a number of different approaches. Examples of these include:

(a) Mixing of a polymer with the drug particles followed by direct compression into tablets.

This is termed a direct compression method and has been used in several studies for the production of matrix controlled release systems. For example Choi and co-workers (a.60) described the production of tablets containing dihydrocodeine bitartrate by direct compression of the drug with poly(ethylene oxide). Cellulose derivatives, e.g., HPMC or sodium carboxycellulose have received considerable attention for this application and examples of the application of these systems for the production of controlled release dosage forms have been reported (a.61-a.64). In these studies the use of two polymers offers opportunities to engineer the required drug release rate. Other approaches that have been examined include the compression of cellulose derivatives with acrylate derivatives (Eudragit E100) (a.65) and the combination of poly(ethylene oxide) with HPMC in a multilayered tablet design (a.66). As the reader will appreciate these are exemplars of the technology and there are numerous examples of these systems within the pharmaceutical literature.

(b) Dissolving the drug and polymer in an appropriate solvent followed by solvent removal.

This method has been examined by several authors for the production of matrix drug delivery systems. In some cases the drug is dissolved/dispersed within a polymer solution, followed by easting into an appropriate mould prior to solvent removal (a.67-a.70). In addition to the physicochemical parameters that are outlined in the equations (described next), the choice of solvent for the solubilisation of the polymer and the rate of solvent removal have been reported to affect drug release (a.71). Matrix drug-containing systems have also been used as drug release coatings for medical devices. Schierholz and co-workers (252) described the release of ciprofloxacin, fosfomycin, gentamicin and flucloxacillin from polyurethane that had been prepared by solvent evaporation. Similarly the physicochemical and antimicrobial properties of PVP-I containing poly(Ecaprolactone) films, prepared by solvent evaporation and designed for use as coatings for medical devices, were described by Jones and coworkers (107, a.72).

Whilst the previous examples have described the preparation of films/coatings, other manufacturing methods may be used to produce matrix systems. Two methods that have received considerable attention for the production of microparticles are spray drying and the (emulsion) solvent evaporation methods. A detailed description of these methods is beyond the scope of this review, however, the interested reader is directed to excellent reviews on these topics (a.73-a.75).

(c) Incorporation of a drug into a polymer by polymerisation of a drug-monomer mixture or by hydrogel swelling within a drug solution.

The use of chemically crosslinked hydrogels as a matrix for controlled drug delivery has received considerable attention within the pharmaceutical and related sciences. The incorporation of drugs into these systems is performed by either polymerisation and crosslinking of the monomer in the presence of dissolved or dispersed drug or, alternatively, by immersion of the crosslinked hydrogel in a drug solution to allow drug absorption into the polymer matrix. The majority of studies within the pharmaceutical literature have favoured the use of the latter method as this ensures that residual monomer may be removed from the sample prior to drug inclusion. However there are cases in which the former method is required, for example in the preparation and use of antibiotic-containing bone cements (99, a.76, a.77). There are several examples in the scientific literature of the production of drug-loaded hydrogels by immersion swelling in a drug solution. Examples of these include the incorporation of model drugs within crosslinked poly(vinyl alcohol) (117), the incorporation of gentamicin within radiation crosslinked poly(2methoxyethylacrylate-co-dimethyl acrylamide) and poly(2-methoxyethylacrylate-co-acrylamide) hydrogels (a.78), the formulation of insulinloaded poly(acryloyl-hydroxyethyl starch)-PLGA microspheres (a.79), the incorporation of gentamicin sulfate within interpenetrating polymer networks composed of poly(acrylic acid) and gclatin (32) and the loading of hydrogel contact lenses with a range of therapeutic agents commonly administered to the eye (a.80). It has been reported in these and related studies that the uptake of the drug is dependent on the chemical properties and the degree of crosslinking of the hydrogel (which directly influence the polymer swelling properties) and the choice of solvent in which the hydrogel is immersed (a.81). In addition to the physicochemical properties of the drug, the subsequent release of drug is dependent on the mass of incorporated drug and the type of and degree of crosslinking within the hydrogel. Further mathematical considerations of the factors influencing drug release from these systems are described in subsequent sections.

(d) Curing a polymer in the presence of dissolved/ dispersed drug.

Certain polymers, e.g., silicone may be formulated into implantable dosage forms, e.g., intravaginal rings or as medicated medical devices. Processing of these systems involves crosslinking of polydimethylsiloxane at an elevated temperature in the presence of a catalyst. Medicated intravaginal silicone drug delivery systems has been used clinically for several decades for contraceptive purposes and for the synchronisation of oestrus in farm animals (a.47, a.82). However more recently these systems have been reformulated for the treatment of symptoms of the menopause (a.82), for the controlled delivery of oxybutinin (for the treatment of urinary incontinence) (a.83) and for the delivery of nonoxynol-9 to prevent transmission of sexually transmitted diseases (a.84).

As may be discerned from the previous description, matrix drug delivery devices are composed of drug that is either dissolved or dispersed within a polymeric matrix. Diffusion of the drug through the polymeric matrix is the rate-controlling step and is therefore responsible for the resultant pharmacological properties. To understand the mathematical aspects of drug release from matrix systems it is important to consider the nature of drug release. As is shown in Figure 17, the drug is initially dispersed throughout the dosage form. Following ingestion/insertion the drug that is present at the surface of the drug delivery system will diffuse from the matrix into the adjacent biological fluids. This initial release is poorly controlled and is referred to as the burst effect. Drug release then occurs by diffusion of the drug through the matrix and dissolution in the surrounding fluids. As a result of this two major consequences are observed. Firstly, it may be assumed that the drug delivery system is composed of an infinite number of drug-containing layers. Therefore, as drug diffusion proceeds from the outside of the device, each sequential release of drug results in the production of a drug free zone, often termed the zone of depletion, as depicted in Figure 17.



Figure 17

Representation of drug release from an insoluble polymer matrix

This phenomenon was illustrated by Roseman and Higuchi (a.85) who examined the release of a steroid, medroxyprogesterone acetate, from silicone cylinders. Secondly, unlike reservoir type systems in which zeroorder release of drug occurs, the mass of drug released from matrix systems decreases as a function of time (due to the increasing diffusional path length). Higuchi (a.86-a.88) derived an expression to model drug release from these systems based on the following assumptions:

- (i) Sink conditions are operative and therefore drug release is controlled by the delivery system.
- (ii) A pseudo-steady state is maintained during drug release.
- (iii) The diffusion coefficient of the drug through the delivery system remains constant.
- (iv) The diameter of drug particles (if present) is less than the average distance of drug diffusion through the matrix.
- (v) There is no interaction between the drug and the matrix.

Full derivations of the mathematical models that are used to describe drug release from matrix systems are not included in this text due to space limitations, however, the interested reader who wishes to gain further understanding of this aspect should consult the original papers by Higuchi (a.86-a.88) and the excellent texts by Baker (a.89) and Chien (a.47).

In the modelling of drug release from matrix systems, several important factors must be considered, namely the shape of the device, the state of the drug (dissolved/ dispersed) within the polymeric matrix and the loading of drug. Accordingly, the effect of these factors on drug release will be briefly considered.

(i) Drug dissolved within the polymer matrix

In situations where the drug is dissolved in the polymer matrix (termed monolithic systems), e.g., hexetidine dissolved in polyvinyl chloride (PVC) (a.90), the

release rate of drug $\left(\frac{dM}{dt}\right)$ from a slab geometry may be described using the following equations:

(a) Over the first 60% of the release rate (a.89, a.91):

$$\frac{dM}{dt} = 2M_o \left(\frac{D}{\pi L^2 t}\right)^{0.5}$$
(7)

Where:

- M_o is the total amount of drug dissolved in the polymer matrix,
- M is the mass of drug release at time t,
- L is the thickness of the slab, and
- D is the diffusion coefficient.

As may be observed a plot of the rate of drug release

against
$$\left(\frac{1}{\sqrt{t}}\right)$$
 is linear.

Alternatively, the fractional mass of drug release may be mathematically related to time as follows:

$$\frac{M_t}{M_o} = 4 \left(\frac{Dt}{\pi L^2}\right)^{0.5} \tag{8}$$

Therefore, as may be observed, a linear relationship exists between the fractional mass of drug released and the square root of time.

(b) In the final portion of the release rate:

$$\frac{dM}{dt} = \frac{8DM_o}{L^2} e^{\frac{\pi^2 Dt}{L^2}}$$
(9)

As may be observed the rate of drug release is no longer directly proportional to $t^{-0.5}$.

The mathematical description of drug release from monolithic systems of other geometries has been similarly reported (for example Ritger and Peppas, a.91).

(ii) Drug dispersed within the polymer matrix (<5% w/w loading)

Whenever the drug is dispersed in the polymer at low concentrations, drug release from a slab geometry may be described using the Higuchi model (a.85-a.87). Thus:

$$\frac{dM}{dt} = \frac{A}{2} \left(\frac{DC_s [2C - C_s]}{t} \right)^{0.5}$$
(10)

or in terms of the mass of drug released (M):

$$M = A \Big[DC_s \Big(2C - C_s \Big) t \Big]^{0.5}$$
(11)

Where:

- M is the mass of drug released at time t,
- A is the surface area of the device,
- *D* is the diffusion coefficient of the drug in the polymer,
- C_s is the saturation solubility of the drug in the polymer matrix, and
- *C* is the drug loading in the polymer matrix.

As the drug loading (C) is in excess of the solubility of the drug in the polymeric matrix (C_s) , these equations may be simplified as follows:

$$\frac{dM}{dt} = \frac{A}{2} \left(\frac{2DC_s C}{t}\right)^{0.5}$$
(12)

and

$$M = A \left[2DC_s Ct \right]^{0.5} \tag{13}$$

The directly proportional relationships between the rate of drug release and $t^{-1/2}$ and between the fractional mass of drug released and \sqrt{t} are valid over the vast majority of the release curve. These relationships are however invalid whenever the concentration of drug within the dosage form falls below the saturation solubility of the drug in the polymer matrix (a.89, a.92).

Several authors have modelled the release rates of therapeutic agents from monolithic dispersions of cylindrical and spherical geometries. These approaches have been summarised by Baker (a.89).

(iii) Drug dispersed within the polymer matrix (5-15% w/w loading)

Whenever the loading of drug is further increased within the polymer matrix, deviations in the relationships between both the rate of drug released and the mass of drug released and time, as described by Higuchi (a.86, a.87) and shown in Equations 12 and 13 have been reported (a.89, a.93). According to Equation 13, the effect of drug loading on the mass of drug released may be normalised by plotting M/ \sqrt{C} against \sqrt{t} (the slope being 2ADC.). Therefore, using this approach the slopes from dosage forms of identical geometry but differing in drug loading should be identical. However, as portrayed by Baker and co-workers (a.93) this is not the case whenever the drug loading exceeds 5% w/w. The explanation for this discrepancy involves the dissolution of drug particles at the surface of the dosage form that, in turn, results in the formation of pores, which fill with the dissolution medium. The presence of pores at the surface of the delivery system enhances the permeability. This effect is therefore augmented as the drug loading is increased, a phenomenon that is not accounted for in the Higuchi model. Therefore, to account for this discrepancy, modification of the Higuchi model is required to account for the effect of drug loading on permeability. Accordingly the relationships between the mass of drug released and the rate of drug release and time may be defined (Equations 14 and 15, respectively).

$$M = A \left(2DC_s Ct \frac{1+2\frac{C}{\rho}}{1-\frac{C}{\rho}} \right)^{0.5}$$
(14)

and

$$\frac{dM}{dt} = \frac{A}{2} \left(\frac{2DC_sC}{t} \bullet \frac{1+2\frac{C}{\rho}}{1-\frac{C}{\rho}} \right)^{0.5}$$
(15)

Where, in addition to the notation described previously, ρ is the density of the permeant, i.e., the dissolution or biological fluid.

(iv) Drug dispersed within the polymer matrix (>15-20% w/w loading)

As the loading of drug increases particle-particle contact occurs and, as a result, the mechanism of drug release from these systems, whilst diffusion controlled, differs from the previous examples. Following contact with the dissolution medium/biological fluids, drug particles dissolve and pores that subsequently fill with fluid are formed. Due to the contact between particles, solid particles that are in contact with the fluid filled pores will dissolve thereby extending both the pore volume and length. This process continues and in so doing a series of fluid filled channels is formed (**Figure 18**).

Drug release does not occur by diffusion through the polymer matrix but by diffusion through the fluid filled pores. To accommodate these considerations, Higuchi (a.88) modified the original equations for a slab geometry and as a result the relationships between the mass of drug released and the rate of drug release and time were reported (Equations 16 and 17, respectively).

$$M = A \left[2 \left(\frac{\varepsilon}{\tau}\right) D C_s C t \right]^{0.5}$$
(16)

and

$$\frac{dM}{dt} = \frac{A}{2} \left(\frac{2D\varepsilon C_s C}{\pi} \right)^{0.5}$$
(17)

Where:

- M is the mass of drug release at time t,
- A is the surface area of the slab,
- *D* is the diffusion coefficient of the drug through the fluid filled pores,
- C_s is the saturation drug solubility in the dissolution/ biological fluid,
- C is the drug loading,
- *e* is the porosity of the matrix, i.e., the volume fraction of the pores that are filled with fluid, and
- t is the tortuosity of the matrix.

Two further points require clarification concerning Equations 16 and 17. Firstly porosity reflects the volume occupied by the particles that will eventually form pores due to particle dissolution and drug diffusion. Increasing the mass of solid drug particles within the matrix will automatically increase the frequency of particle-particle contact and will therefore increase the volume occupied by the pores. The porosity of the matrix may be enhanced by the inclusion of soluble salts, (e.g., sodium chloride, potassium chloride), non-ionic agents, (e.g., mannitol), and hydrophilic polymers, (e.g., PVP, PEG, HEC) within the polymer matrix that dissolve upon contact with aqueous fluids. In so doing the



Figure 18

Diagrammatic representation of drug release from heterogeneous matrix systems

porosity and hence the rate of drug release may be engineered to meet the particular requirements of the dosage form. In addition the term tortuosity features in the modified form of the Higuchi equation. This parameter reflects the effective diffusional path length of a drug molecule through the fluid filled pores. This parameter cannot be easily controlled nor directly quantified.

One application of matrix controlled drug release that will be known to many readers is in the area of transdermal patches. One example of the design of these systems has been described in the previous section concerning reservoir controlled drug release in which drug release is controlled by a specific layer within the dosage form. It has been shown that the stratum corneum effectively acts to control the diffusion of the drug across the skin thereby obviating the need for the inclusion of a rate controlling membrane (a.47, a.59). As a result commercially available transdermal systems are available in which the therapeutic agent is dissolved/ dispersed within the transdermal adhesive, which, following removal of the release liner, is located on the surface of the skin. This design is depicted in Figure 19.

Alternatively the drug may be dispersed/dissolved in a polymeric layer in an island dressing design (**Figure 20**). As the adhesive surrounds the drug containing matrix, this design may be advantageous for systems in which the incorporation of the drug directly within the adhesive may compromise the performance of this layer (a.94).

The rate of drug release $\left(\frac{dM}{dt}\right)$ from matrix transdermal systems may be mathematically described as:

$$\frac{dM}{dt} = \sqrt{\left(\frac{C_s CD}{2t}\right)}$$
(18)

Where:

- *C* refers to the initial mass of drug dispersed/dissolved in the matrix,
- C_s refers to the saturation solubility of the drug in the polymer matrix, and
- *D* is the diffusion coefficient of the drug in the polymer matrix.





Matrix transdermal drug delivery system in which a therapeutic agent is dispersed/dissolved in the adhesive layer (adapted from Chien 1992) [a.47]





Matrix transdermal drug delivery system based on an island dressing design [adapted from Chien 1992 (a.47)]

At steady state the mass of drug released (M) as a function of time is described by Higuchi's diffusion model:

$$M = \sqrt{\left(2C - C_s\right)C_s Dt} \tag{19}$$

3.4 Swelling Controlled Release Systems

In the previous sections the release of therapeutic agents from reservoir and matrix designs were described. Whilst the designs of these systems differ, it is assumed that the shape and dimensions of the devices do not change during the course of drug release. This is due to the hydrophobic nature of the polymers used in the formulation of these systems. Hence in the reservoir systems the thickness of the coating remains constant whereas in matrix systems there is a defined thickness of the device, (e.g., slab, cylinder, sphere), over which diffusion occurs. As a result, in the equations that describe drug release the thickness of the system/ membrane is defined. However, in many drug delivery systems, the dimensions of the dosage form will change during the course of drug release due to swelling of the polymer matrix. Although the mechanism for drug release is diffusion, the equations defined by Higuchi are not valid and therefore other mathematical expressions are required to define the relationship between drug release and time. Examples of systems that exhibit swelling controlled release are physically crosslinked and chemically crosslinked gels. In terms of controlled drug release, chemically crosslinked hydrogels, e.g., poly(hydroxyethylmethacrylate), have been used to provide controlled drug release from medical devices (a.95), whereas swelling controlled physical hydrogels may be easily manufactured by directly compression of drug with a hydrophilic polymer, e.g., HPMC.

To fully understand the effect of swelling on drug swelling, it is necessary to initially examine the effect of aqueous fluids on the physical state of the hydrophilic polymers in swelling controlled release systems. According to Alfrey and co-workers (a.96), the diffusion of aqueous fluid into such systems may be three different regions, namely:

- (i) A region at the interface between the device and polymer in which the polymer is completely swollen due to maximal extension of the polymer chains.
- (ii) A relatively thin layer in which the polymer chains are undergoing both hydration and relaxation from the glassy state.

(iii) An inner zone composed of the glassy (unhydrated) polymer.

Classification of the behaviour of swelling systems is performed according to the relative rates of water ingress, (i.e., polymer hydration), and polymer relaxation and therefore, three scenarios may be defined:

- (a) The rate of diffusion of the aqueous phase is less than the rate of polymer relaxation, termed Case 1 (Fickian) diffusion.
- (b) The rate of diffusion of the aqueous phase is greater than the rate of polymer relaxation, termed Case 2 diffusion. Therefore polymer relaxation represents the rate-determining step.
- (c) Whenever the rate of solvent diffusion is similar to the rate of polymer relaxation, this is referred to as non-Fickian (anomalous) diffusion.

The classification of the various drug delivery systems as described previously will affect drug release, as discussed next:

(i) Case 1 diffusion

In case 1 diffusion the rate limiting step is the diffusion of aqueous fluid into the delivery system. Accordingly, the relationship between the mass of fluid absorbed by the drug delivery system and time may be defined using Fick's law (Equation 18).

$$\frac{M_t}{M_o} = 4 \left(\frac{Dt}{\pi L^2}\right)^{0.5} \tag{20}$$

Where:

- M_t is the mass of fluid absorbed at time t,
- M_o is the mass of fluid absorbed at equilibrium,
- L is the thickness of the slab, and
- *D* is the diffusion coefficient of aqueous fluid in the polymer matrix.

Equation 20 is relevant for systems in which an equilibrium fluid uptake is observed. In physically crosslinked hydrogels an equilibrium uptake is not observed due to the dissolution of the polymer in the region adjacent to the bathing solution.

Case 1 diffusion is observed in chemically crosslinked hydrogels in which drug loading has been performed by immersion of the polymer in a solution of drug. Drug uptake into the polymer will occur until equilibrium swelling has occurred. Subsequent immersion of this equilibrium-swollen system in an aqueous/biological fluid will result in conventional drug release according to Equation 8.

i.e.,
$$\frac{M}{M_o} \alpha \sqrt{t}$$
 (a.89, a.91)

Examples of swollen polymers that exhibit the above release properties include, poly(hydroxyethyl-methacrylate) and co-polymers with other acrylates, (e.g., methacrylic acid), poly(vinyl alcohol) and crosslinked PVP.

(ii) Case 2 diffusion

In case 2 diffusion the rate limiting step is the relaxation of polymer chains, i.e., the transition from the glassy to rubbery state. Therefore the rate of penetration of aqueous fluid into the dosage form is controlled by polymer relaxation. Concurrent with this ingress of fluid is the dissolution of the dispersed drug within the swollen gel region of the delivery system and subsequent diffusion of drug from the dosage form to the adjacent biological fluid (a.89, a.97). In the light of the two contrasting diffusion processes, mathematical modelling of drug release from these systems is difficult. Therefore, generic power law models are frequently used to describe the uptake of water into and the release of drug from the delivery system (Equations 21 and 22, respectively).

$$M_{\rm w} = kt^n \tag{21}$$

Where:

- M_w is the mass of water absorbed by the dosage form (generally quantified by measuring the change in mass or by thermogravimetric analysis),
- *k* and *n* arc constants associated with each formulation and method of manufacture of the dosage form.

Similarly drug release may be modelled as follows:

$$\frac{M}{M_{\infty}} = kt^n \tag{22}$$

Where:

M is the mass of drug release at time t,

- M_{∞} is the drug loading,
- k is a constant, and
- *n* is the release exponent.

Characterisation of the mechanism of drug release from these systems may be performed by consideration of the magnitude of the release exponent (a.98). When n = 0.5 drug release has occurred by Fickian (Higuchi) diffusion. A release exponent value of 1.0 is indicative of Case 2 (zero-order) drug release whereas whenever 0.5 < n < 1.0, the mechanism of drug release is anomalous.

Case 2 drug delivery systems have been widely reported for both chemically and physically crosslinked hydrogels. Recently Jones and co-workers (a.99-a.102) have reported the formulation of physical gels that exhibit case 2 release and anomalous release of therapeutic agents that were designed for application to the oral cavity for the treatment of infection and inflammation. In these both the therapeutic agent and selected polymeric components are dispersed within a polymer gel matrix in which the available water was physically bound within the gel structure. Following implantation of these systems into the oral cavity, biological fluids were imbibed into the formulation, thereby facilitating swelling of the suspended polymer. This swelling therefore impeded drug diffusion and accordingly a non-linear relationship between the mass of drug released and \sqrt{t} was observed.

Readers who are interested in the formulation and physicochemical/biological properties of hydrogels may be interested in the following reviews (a.39, a.103, a.104).

3.5 Biodegradable Systems

Biodegradable systems are those in which a therapeutic agent has been incorporated into a matrix that is composed of a biodegradable polymer, i.e., a polymer that will undergo controlled degradation within a biological environment. As a result, following implantation, the molecular weight of the polymer matrix will be reduced due to, for example, hydrolysis of crosslinks or hydrolysis of the main polymer chain, and in so doing the previously insoluble polymer matrix will be rendered soluble in the biological fluids thereby facilitating elimination. There are several examples of biodegradable polymers that have been examined for controlled release applications. These include poly(lactic acid), poly(glycolic acid) and their copolymers (70, 253, a.105-a.111), $poly(\varepsilon$ - caprolactone) (107, 258, 259, 260, a.18, a.69, a.70, a.112), poly(*ortho* esters) (a.113-a.117) and polyanhydrides (a.29, a.118-a.123). Other examples of the formulation and clinical applications of biodegradable drug delivery systems may be found in the text by Park and co-workers (a.97).

Mathematical modelling of drug release from biodegradable systems requires consideration of the relative rates of polymer degradation and drug diffusion. Two defined scenarios may be established, as described next.

Scenario 1: The rate of drug diffusion is less than the rate of polymer degradation.

Under these conditions drug release from devices of defined geometries may be described as follows (a.89, a.97):

(i) For spherical geometry:

$$\frac{M_t}{M_{\infty}} = 1 - \left(1 - \frac{(k_o t)}{(Ca)}\right)^3 \tag{23}$$

(ii) For cylindrical geometry:

$$\frac{M_t}{M_{\infty}} = 1 - \left(1 - \frac{(k_o t)}{(Ca)}\right)^2 \tag{24}$$

Where:

- k_o is the drug release rate,
- C is the initial loading of drug, and
- a is the initial radius of the drug delivery system
- (iii)For a slab of thickness 2*a* (twice that of the radius in the previous equation)

$$\frac{M_t}{M_{\infty}} = 1 - \left(1 - \frac{(k_o t)}{(Ca)}\right)^1 = \frac{(k_o t)}{(Ca)}$$
(25)

From the previous equations it may be seen that zeroorder release is only observed from slab geometry.

Scenario Two: The rate of drug diffusion through the polymer matrix is greater than the rate of polymer degradation.

If the rate of drug diffusion within the matrix is significantly greater than the rate of polymer degradation, the rate of release of the drug may be described using Higuchi's equations and accordingly the mass of drug released is proportional to \sqrt{time} . However, if degradation of the polymer matrix is occurring simultaneously with drug release, the polymer matrix may not be considered to be inert, thereby invalidating the assumptions proposed by Higuchi. As the polymer matrix degrades, the rheological properties and hence the resistance to drug diffusion are reduced. Higuchi's equation must therefore be modified to include a description of the rate of bond cleavage (assumed to follow first order kinetics), as shown next (a.89):

$$M_t = A \left(2DC_s e^{kt} Ct \right)^{0.5} \tag{26}$$

Where:

- M_t is the mass of drug released at time t
- A is the surface area of the device
- C_s is the saturation solubility of the drug in the polymer matrix
- *D* is the diffusion coefficient of the drug through the polymer matrix
- e^{kt} is the expression describing the rate of polymer degradation
- C is the initial loading of drug in the polymer.

Due to the ability of biodegradable polymers to undergo dcgradation within biological fluids, these systems have been used exclusively as pharmaceutical implants; polymer degradation obviating the need for implant removal. In addition to their use as injectable microspheres (253, a.105, a.124), biodegradable polymers have found a variety of uses including:

- implants for the treatment of brain tumours (a.109).
- implantable intravitreal drug delivery systems (a.111).
- as delivery systems for bone tissue engineering/ repair (70, a.110, a.125, a.126).
- as delivery systems for implantation into the oral cavity (111, a.69, a.70, a.127-a.129).
- as novel vaccine delivery systems (a.129-a.140).

- as delivery systems for antisense nucleotides (a.108, a.141-a.147).
- as coatings for medical devices for the prevention of infection and/or encrustation (107, a. 148-a. 150).
- as platforms for tissue engineering (15, 16, 18, 33, a.151-a.158).

This list serves to highlight the potential uses of biodegradable polymers.

3.6 Osmotically Controlled Drug Delivery Systems

In these systems the difference between the osmotic pressure within a formulation and the surrounding biological fluids is used as the driving force for drug release. The first osmotic systems were developed by the Alza Corporation in the 1970s and since this time both the number and types of designs of these systems have increased. The basic design of the OROS system, one of the original elementary osmotic pumps, is presented in Figure 21. For the purpose of this review the design and function of this system will be described as an exemplar of osmotic drug delivery systems. The factors influencing drug release from the OROS system will be described. Unfortunately an in depth consideration of the wide range of designs is impractical in light of the space limitations imposed by this text. The reader who is interested in this topic is directed to an excellent review by Verma and co-workers (a.159).

As may be observed, the first (elementary) osmotically controlled drug delivery systems were composed of two primary regions, namely a tablet core (containing the drug and when required an osmotic pressure modifier) and a semi-permeable membrane. The general mechanism of drug release from these systems involves the diffusion of gastrointestinal fluid across the semipermeable membrane at a controlled rate and dissolution of the drug and, if present, the osmotic pressure modifier to produce a saturated drug solution within the tablet core. As the number of molecules in solution increases, the osmotic pressure within the tablet core increases. The outer coating (semi-permeable membrane) is rigid, and therefore to reduce the osmotic pressure within the tablet, the saturated drug solution is emitted from the tablet core through a laser-drilled orifice.

The rate of entry of biological fluid across the semipermeable membrane into the tablet core will directly affect the rate of drug dissolution and may be defined using the following equation:

$$\frac{dv}{dt} = \frac{A}{h} L_p (\sigma \Delta \pi - \Delta p)$$
(27)

Where:

 $\frac{dv}{dt}$ is the rate of water influx into the tablet core,

- A is the surface area of the semi-permeable membrane,
- h is thickness of the semi-permeable membrane,
- L_p is the diameter of the orifice,
- σ is a reflection coefficient,
- $\Delta \pi$ is the osmotic pressure difference between the interior of the tablet and the surrounding biological fluids, and
- Δp is the hydrodynamic pressure difference between the interior of the tablet and the surrounding biological fluids.



Figure 21



The reflection coefficient refers to the propensity of the semi-permeable membrane for the diffusion of drug. Ideally the semi-permeable membrane should only allow the diffusion of aqueous fluid into the tablet core and not the subsequent diffusion of the dissolved drug in the reverse direction. Under these circumstances, the reflection coefficient should be 1 and can therefore be eliminated from Equation 27.

Similarly as the diameter of the laser-drilled orifice is increased, the hydrostatic pressure within the tablet is decreased and therefore $\Delta \pi >> \Delta p$. Furthermore, the osmotic pressure within the tablet vastly exceeds that of the surrounding biological fluids and thus $\Delta \pi$ may be reduced to π . Under these conditions, equation 27 becomes:

$$\frac{dv}{dt} = \frac{A}{h} L_p \sigma \pi C \tag{28}$$

The rate at which the saturated drug solution is pumped

from the dosage form $\left(\frac{dM}{dt}\right)$ is defined by:

$$\frac{dM}{dt} = \frac{dv}{dt} \times C \tag{29}$$

Where:

C is the (saturated) concentration of drug in the expelled fluid.

From Equations 28 and 29 it may be concluded that zero-order release may be obtained if the permeability characteristics of the semi-permeable membrane are controlled, namely the area, thickness, the diffusion coefficient of water across the membrane, and a saturated concentration of drug is maintained within the tablet core (by the correct choice of drug salt and inclusion of excipients). In the original OROS system the semi-permeable membrane was composed of cellulose acetate and the osmotic pressure of the core was controlled by the inclusion of salts. If a nonsaturated drug solution is present in the tablet core non zero-order release occurs (a.47, a.159).

As may be apparent, there are several formulation factors that influence drug release from osmotically controlled systems, including drug solubility, osmotic pressure, the number and size of the delivery orifice and the physicochemical properties of the semipermeable membrane. These will be discussed individually next:

(i) Drug solubility

As outlined previously, zero-order drug release may only occur if a saturated drug solution is maintained within the tablet core. Furthermore, drug release rate is directly proportional to the drug solubility. Therefore, the control of release rate is more difficult if the drug has either high or low drug solubility. If the solubility is too high, then the duration of the maintenance of a saturated drug solution is low, whereas, if the drug solubility is too low then the rate of drug release is low (a.43, a.159-a.161). The solubility of drugs within the tablet core may be reduced by the inclusion of excipients. For example McClelland and co-workers (a.162) and Zentner and co-workers (a.163) described the effects of inclusion of sodium chloride on the solubility and release of diltiazem hydrochloride from an osmotically controlled system. The inclusion of sodium chloride reduced the solubility from 590 µg mL⁻¹ to 155 µg mL⁻¹ and in so doing the delivery system released approximately 75% of the drug in a zero-order fashion for a 14-16 h period.

For drugs that possess low water solubility a number of formulation strategies have been examined to enhance their solubility and hence the rate of release from osmotically controlled drug delivery systems. Examples of these approaches include:

- The use of swellable polymers in the tablet core: in one patent (a.164) the tablet core was formulated to contain the drug, an osmotic pressure enhancing agent and swelling agents, whereas the tablet was coated with a semi-permeable membrane composed of PVP-co-vinyl acetate) and PEO. The controlled rate of swelling ensured constant drug release.
- The use of effervescent combinations: in this approach the tablet is manufactured and an effervescent mixture (citric acid and sodium bicarbonate) is introduced into the tablet core via the delivery orifice. Following permeation of water into the tablet core, effervescence occurs that causes a suspension of drug to be dispensed from the delivery orifice (a.165).
- The use of soluble complexes of the drug with cyclodextrins (a.166).
- The use of soluble salt forms of poorly soluble drugs.

Other strategies to enhance the solubility of poorly soluble drugs for use in osmotically controlled release systems have been described by Chien (a.47) and Verma and co-workers (a.159).

(ii) Modification of the osmotic pressure within the dosage form

From Equation 28 it may be observed that the rate of drug release from an osmotically controlled system is directly proportional to the osmotic pressure within the tablet. As a result the osmotic pressure is an important design consideration for these systems. Osmotic pressure is a colligative property and is therefore dependent on the number of ions and molecules in solution. If the solubility of the drug is low, the inherent osmotic pressure within the tablet will be low and therefore the rate of drug release will be low. Under these conditions the inclusion of excipients, e.g., mannitol, sodium chloride, potassium chloride or hydrophilic polymers, is required within the tablet core. Upon dissolution within the tablet the osmotic pressure will increase thereby enhancing the rate of release of the therapeutic agent (a.47, a.167).

(iii) The delivery orifice

As previously described the delivery orifice is the exit portal of the device for the drug solution. The dimensions of the orifice are important for two reasons. Firstly, if the diameter is too small the contribution of hydrodynamic pressure will be significant and, as a result, zero-order release may not be observed. If the orifice is too large, solute diffusion from the orifice may be affected. The optimum size of the orifice may be calculated using the following equation (a.160, a.168):

$$A = \left(\frac{LV}{t}\right)(8\pi)\sqrt{\frac{\eta}{\Delta P}}$$

Where:

- A is the cross-sectional area of the orifice,
- L is diameter of the orifice,
- V is the volume of solution released per unit time,
- η is the viscosity of the solution released from the tablet core, and

 ΔP is the hydrodynamic pressure difference.

The effect of the diameter of the orifice on drug release has been reported to be dependent on the size range of the orifice. For example, increasing the diameter of the orifice within the range of 0.25-1.41 mm did not significantly increase drug release however drug release was rapid whenever the diameter was increased to 2.0 mm (a.169). The manufacture of the orifice in osmotically controlled drug release systems may be performed using several different methods including laser drilling, by the use of custom designed tablet punches and by the use of excipients that dissolve to form pores in the semipermeable membrane.

(iv) Physicochemical properties of the semi-permeable membrane

Further consideration of Equation 28 reveals that the rate of drug release from osmotically controlled systems is directly proportional to the rate of fluid entry into the tablet core. A mass transfer process that is controlled by the physicochemical properties of the semi-permeable membrane. Several polymer candidates have been investigated for this application including cellulose esters (acetate, diacetate, triacetate, propionate, acetate butyrate) (a.170), ethylcellulose (a.171) and acrylate/methacrylate copolymers (Eudragits) (a. 172). The earlier osmotically controlled systems used cellulose acetate due to the high water permeability, the extent of which may be readily modified by the degree of acetylation of the polymer. The water permeability of other polymers, e.g., ethylcellulose, may be low thereby resulting in a low drug release rate. Under these conditions hydrophilic polymers may be included within the semi-permeable membrane, which will dissolve upon contact with aqueous fluid thereby generating pores and enhancing permeability (a.173, a.174).

Other factors that influence the aqueous permeability include the thickness of the membrane (as water permeability is inversely proportional to membrane thickness) (a.175), the type and amount of plasticiser (a.176) (due to the effects on polymer mobility and hence drug diffusion) and the degree of crosslinking.

Other designs of osmotically controlled drug delivery systems have been reported (a.159).

3.7 Stimulus Responsive Drug Release

Up to this section the discussion of drug release has been primarily concerned with systems from which drug release is facilitated by simple diffusion. Osmotically controlled systems and the use of biodegradable polymers offer possibilities for the enhancement of drug release through ancillary processes, namely osmotic pressure and polymer degradation. However another aspect of great interest in drug delivery is the ability to engincer dosage forms
to release the drug on demand following the application of an appropriate stimulus, e.g., drug release at a specific location within the gastrointestinal tract. Stimulus responsive polymers are frequently referred to as 'smart' polymers and, following exposure to external signals; these systems will alter their structural and physical properties. Before embarking on a further description of the design and function of these systems it is worth reminding the reader that the design and development of stimuli responsive systems is a large and expanding area within the pharmaceutical and related sciences. Accordingly the systems that are described in this section are presented as exemplars of the various technologies that are either under investigation or have been commercialised.

3.7.1 Ultrasound Responsive Drug Release

The main application of ultrasound in drug delivery has been for the enhancement of drug permeability across biological membranes, e.g., skin. However, in these examples the stimulus does not control drug release from the formulation but affects the barrier properties of the biological membrane onto which the formulation has been located. There have been some papers that have examined the effect of ultrasound on drug release from polymeric systems. For example, following the application of ultrasound, large increases in the release of 5-fluorouracil and insulin from poly(ethylene vinylacetate), which could be manipulated as a function of ultrasound frequency, were reported (a.177, a.178). More recently, systems have been developed as polymeric coatings whose structural properties were altered following the application of ultrasound (164, a.179).

3.7.2 Temperature Responsive Drug Release

There have been several reports concerning the design and application of pulsatile, controlled drug delivery systems using temperature as the external stimulus. The polymers used to obtain such release properties are referred to as thermoresponsive polymeric systems. Typically homo- and *co*-polymers of *N*-substituted acryl and methacryl amides are used for this purpose, e.g., poly(isopropylacrylamide) (pNIPAA) (251) (**Figure 22**). More specifically, there are two types of thermoresponsive polymer systems namely those that exhibit positive and negative temperature dependency. Polymers in the former category display an upper critical solution temperature (UCST) below which polymer contraction occurs upon cooling. Conversely, negative temperature dependent polymers have a lower



Figure 22 Chemical structure of p(NIPAA)

critical solution temperature (LCST) and will contract upon heating above the LCST (a.180). For example, the critical temperature for hydrogels composed of p(NIPAA) is usually around 34 °C, representing a LCST in aqueous solution (a.181). Hydrogels composed of p(NIPAA) exhibit negative temperature dependent swelling in water with a dramatic deswelling transition occurring at temperatures corresponding to the LCST. Below the transition temperature p(NIPAA) hydrogels are swollen but shrink and collapse as the temperature is raised through the LCST, i.e., they exhibit hydrophilic properties below the LCST and a hydrophobic character above Hydrophobic moieties, the LCST. e.g., alkylmethacrylates, lower the LCST, whereas in contrast, the LCST is raised by the inclusion of a hydrophilic copolymer, e.g., acrylic acid (AA_c) or acrylamide (a.182). Furthermore it has been reported that LCST is affected by the composition of solvent/ solute (a.183).

Due to the ability to regulate the physical properties of hydrogels composed, at least in part, of p(NIPAA), there have been several reports of the use of these systems for pulsatile drug release (257, a.183-a.187). These systems are particularly interesting as the phase transition often occurs, or can be designed to occur at temperatures close to physiological conditions. For example, the release of vitamin B₁₂ from p(NIPAA)hydrogels at temperatures above and below the LCST has been reported (a.183). Below this temperature, release rates were linear with the square root of time indicating that drug release was controlled by normal Fickian diffusion. Above the LCST, a pseudo first-order release rate was seen. There was an initial rapid release (5-6 minutes), which may have been due to a type of hydrostatic pumping of the solution from the gel. Thus, drug release in the initial period may occur primarily through movement of bulk solution out of the hydrogel pores as a skin forms and the polymer network collapses. This collapse was followed by a sustained, slower release rate (5-6 hours), which may have been due to closure of large interconnected pores. The authors stated that the release in this second region was more like Fickian diffusion, but now through much smaller pores and more tortuous diffusion pathways. Similarly, Hoffman and co-workers (a.184) studied the use of crosslinked p(NIPPA) gels as drug carriers by loading with vitamin B_{12} and methylene blue dye at temperatures below their LCST. These gels were swollen in the drug solution at low temperatures and then drug release studies were carried out at 50 °C, (i.e., a temperature well above the LCST for those gels). These studies showed an initial rapid burst followed by a slow sustained release rate. It was concluded that this was due to a squeezing effect accompanying the gel deswelling which caused a discharge of dissolved drug with water in addition to diffusion release. The controlled release of indomethacin from hydrogels composed of crosslinked p(NIPAA/butyl methacrylate) was investigated by Bae (257). On-off regulation was achieved by stepwise temperature changes between 20-30 °C. A pulsatile release pattern was reported, with the complete 'off' process observed at 30 °C but release rates increased when the temperature was decreased from 30 to 20 °C. Similarly the diffusion of insulin through a polymeric membrane composed of polyNIPAA-co-butylmethacrylate) membrane was shown to occur below the LCST but was inhibited above this temperature (a.181). More recently Li and D'Emanuele polymerised (and crosslinked) p(NIPAA) within the pore structure of a sintered glass filter to form a membrane and examined the effect of temperature on the diffusion of two model drugs, bovine serum albumin and salicylic acid, across this polymeric barrier. Interestingly, drug diffusion increased as the temperature was increased from 20 to 40 °C and was accredited to polymer collapse (above the LCST) thereby effectively opening the pore structure of the sintered substrate (a.188).

3.7.3 pH Responsive Drug Release

In the design of dosage forms, one specific objective may be to achieve drug release at sites that will ensure maximum therapeutic benefits. Within the gastrointestinal tract a range of pH values exist, ranging from about one in the stomach to neutrality within the intestine. Targeting drug release within certain regions of the gastrointestinal tract as a method to enhance drug stability within acidic fluids or to reduce the irritant effects of certain drugs has been used for several decades. For example enteric polymers have been used as coatings of tablets for this purpose, examples of which include cellulose acetate butyrate and cellulose acetate phthalate. These polymers are insoluble at low pH environments, (e.g., the stomach), however they are soluble in the less acidic regions of the gastrointestinal tract. Following dissolution of the enteric coating, the tablet and hence the drug will dissolve, thereby facilitating drug absorption. Due to this pH dependent solubility, enteric polymers may be described as pH responsive polymers.

In addition to enteric polymers, there is a strong interest in hydrogel polymers that possess the ability to change their swelling/deswelling characteristics in response to a change in the pH of the external environment. Such systems may be used as the basis of a stimulus responsive controlled drug delivery device since variations in pH occur naturally in different areas of the human body. Crosslinked polymers containing ionisable side chains, e.g., acrylic acid, methacrylic acid, diethylaminomethacrylate, may be designed to swell extensively in aqueous media. This swelling transition is dependent upon the pH of the environment and the nature of the side groups. In an aqueous environment, the side chains ionise and swelling occurs due to ionic repulsion between these charged groups thereby facilitating solvent uptake. Negatively or positively charged hydrogels show opposite swelling characteristics in response to the same pH environment. In terms of drug delivery, drug release from such hydrogels is facilitated by polymer swelling and is markedly reduced whenever the pendent chemical groups remain unionised. For example the release of caffeine from copolymers of methylmethacylate and N,N-dimethylaminoethyl methacrylate (a basic monomer) was negligible at neutral pH but was significant in an acidic medium (a.189). Conversely, the release of therapeutic agents from an acidic copolymer, poly(hydroxyethylmethacrylate-comethacrylic acid) was shown to optimally occur whenever the pH of the release medium was greater than the pKa of the polymer (256, a.190). In these systems, drug release was also dependent on the ionic strength of the dissolution medium, in which at higher ionic strengths polymer swelling was reduced (256, a. 191). Therefore, the ability to control drug release by changes in pH of the surrounding biological medium offers a potential method to target drug release to specific regions of the gastrointestinal tract. In light of the constant pH of other body fluids, targeted gastrointestinal drug delivery remains the main application of these systems.

3.7.4 Electric Current Responsive Drug Release

Developments in technologies such as microelectronics and micromachining have aided the development of electronically-assisted drug delivery technologies, including iontophoresis (defined as the delivery of charged drugs across the skin by the use of electric current) (a.192). Electrical stimulus-responsive drug delivery systems based on hydrogels are also being developed and a drug release system using electricallystimulated swelling/deswelling characteristics of polyelectrolyte hydrogels has been developed (a.193). Typically electrically responsive systems may be formulated using pH responsive systems in which application of the current changes the local pH thereby changing the morphology of the polymer or facilitating polymer erosion. Using this approach Kwon and coworkers described the synthesis and formulation of copolymers poly(ethylozazoline) of and poly(methacrylic acid) and poly(ethylozazoline) and poly(acrylic acid), containing insulin. Application of an electrical current facilitated generation of hydroxyl ions, which, in turn raised the pH and resulted in a disruption of interchain hydrogen bonding and hence allowed insulin release (a.194). Insulin release did not occur in the absence of an electrical stimulus. Other examples of electrically stimulated drug delivery include the pulsatile release of insulin from poly(dimethylaminopropylacrylamide) (a.195) and the pulsatile release of theophylline from an interpenetrating polymer network composed of poly(vinyl alcohol) and poly(acrylic acid) (203). The authors of these studies accredited the pulsatile release to the electrical current mediated collapse of the structure of the polymeric hydrogel.

Other stimuli have been examined as mediators of drug release including magnetic field and light, however space restrictions in this review prevent further discussion of these aspects. For further information the reader should consult the review by Serchen and West (a.196).

3.8 Polymer-Drug Conjugates

Polymer-drug conjugates offer an exciting strategy for the improved delivery of therapeutic agents, both in terms of the provision of controlled release but also for the improved targeting of the therapeutic agent to a particular site. As the title suggests, polymer drug conjugates are composed of a drug that is covalently bound to a polymer, which may be either hydrophilic or hydrophobic. The linkage of a drug to a macromolecular carrier will alter its pharmacokinetics, while retaining or preferably enhancing the bioavailability, specificity and duration of action at the target site (254). Prolonged and/or controlled drug delivery from a carrier can also help overcome difficulties with patient compliance in multidose regimes.

The objectives of polymeric carriers have been defined as (254):

- 1. To maximise the bioavailability of a therapeutic agent in a target tissue.
- 2. To optimise the onset, rate and duration of drug delivery.
- 3. To maintain the steady state plasma drug level within a therapeutic range as long as required for an effective treatment.
- 4. To minimise adverse side effects of a therapeutic agent.

There are three basic synthetic routes that have been used to produce polymeric drug carriers, namely:

- 1. Polymerisation of a group already present in the parent drug molecule.
- 2. Modification of the drug molecule to include a polymerisable functionality, then either homo- or co-polymerise with other monomers to form the polymeric drug-containing carrier.
- 3. Covalent linking of the drug molecules to a preformed polymer.

Polymer-drug conjugates are a promising new strategy for drug delivery especially in the field of cancer therapy. This strategy has been refereed to as 'polymer therapeutics'. Chemotherapy involves the use of cytotoxic drugs to eradicate cancer cells, which typically divide more rapidly than non-tumour cells. The problem with the use of such drugs is that the difference in the activity of the drug against the cancer cell and non-cancerous cells is relatively small, leading to the drug having a damaging effect on normal cells in addition to tumour cells. Therefore if the drug could be targeted to the tumour more effectively and the amount of drug reaching the normal tissue could be reduced there would be lesser side effects from chemotherapy and the success of cancer therapy could be greatly improved. Whilst research is ongoing concerning the conjugation of therapeutic agents, e.g., antimicrobial agents, to hydrophobic polymers as a novel strategy for medical device design, the major application involves the conjugation of drugs to hydrophilic polymers. These systems can provide an effective way to prolong the pharmacological activity, stabilise labile drugs from chemical and proteolytic degradation, minimise side effects, increase solubility and target drugs to specific cells or tissues. The high molecular weight of the polymers promotes tumour localisation, as the vascular epithelium is more fenestrated. Conjugation of the drug to the hydrophilic polymer by a covalent (sacrificial) linker provides the opportunity to solubilise poorly water-soluble drugs, which in turn improves tumour targeting and reduces the toxicity of the drug. Polymer conjugation also provides new possibilities for drugs, which have failed in early clinical development due to unsuitable hydrophobic properties and high toxicity.

The essential criteria for the polymer used for such a system is that it is non-immunogenic and non-toxic (a.197). The molecular weight of the polymer must be sufficiently large to avoid rapid elimination via kidney ultrafiltration and low enough to prevent undesirable accumulation within the body. The ideal polymeric carrier should be hydrophilic and must contain a functional group which can form a covalent link with the active ingredient (a.198). Biodegradable polymers are preferable although most of the polymer systems studied are mainly non-biodegradable synthetic polymers such as PEG and poly(hydroxypropylmethacrylamide) (HPMA). Unlike the drug itself the polymer bound drug will not penetrate the cell readily and is restricted to lysosomotropic delivery via the endocytic route. Therefore it is essential that the polymer-drug conjugate can enter the tumour cell via the endocytic route and the active drug is able to pass the lysosomal membrane. The polymer carrier should be able to carry the required amount of the drug while protecting it against premature metabolism in transit. In order to improve cell penetration and cell disposition suitable spacers are introduced. These are usually peptide sequences and should be stable in circulation while being capable of specific enzymic or hydrolytic cleavage. In general drugs such as daunomycin, doxorubicin, melphalan and platinates have been bound to the polymer backbone using peptidyl spacers which can be cleaved by cysteine proteases (a.199). These enzymes have been shown to be present in increased concentration in human tumours.

As already mentioned the macromolecular drug conjugates differ from low molecular weight drugs in how they behave in the body at both tissue and cellular level. Therefore the barriers to be overcome are different and can be exploited to enhance the specificity of the conjugate (a.199). The small drug molecules can partition across the lipoidal membranes and can distribute itself throughout the body including most tissues and cells. The small size of the molecules allows for rapid renal elimination so the residence time of the drug at the active site may be very short. Polymer conjugates on the other hand are generally water soluble and too large to partition across membranes and are therefore retained in different parts of the body and redistributed very slowly. This can allow the macromolecular conjugate to be retained at the targeted site. The macromolecule forces the conjugate to enter the cell through the endocytosis process. Once the polymer conjugate is within the cell the drug is released following lysosomal cleavage of the macromolecule. The tumour cell environment is more acidic than normal tissue and also contains amounts of cathepsins and other proteases, which allow the drug to be released from the conjugate.

The simplest way of attaching the drug to the macromolecule is via direct attachment without the attachment of a spacer molecule (a.199). Peptide and ester bond forming reagents can be used to attach carboxyl-containing drugs. However these simple linkages will release the drug upon simple hydrolytic cleavage. A linker that specifically cleaves via lysosomal enzymic cleavage is therefore necessary to target the conjugate and maintain its stability in the blood. Enzymically degradable linkers are the most preferable linkages as these make the conjugate drug stable in the serum but allow intracellular cleavage by specific enzymes. Various tetra-aminoacid spacers such as Ala-Leu-Ala-Leu, Gly-Phe-Leu-Gly and Leu-Gly-Val-Phe are the most appropriate sequences. HPMA conjugates such as HPMA-doxorubicin (PK1, FCE28068) and HPMA-paclitaxel (PNU 166945) are already undergoing Phase I/II clinical trials (Figure 23). These are composed of HPMA copolymer main chain of molecular weight 30,000 Da and a Gly-Phe-Leu-Gly peptidyl drug linker. Doxorubicin is conjugated to the peptide linker via the peptide bond whereas paclitaxel is conjugated via the terminal ester linkage. The results from the phase I trial for HPMAdoxorubicin have shown reduced toxicity compared to the free doxorubicin, with no polymer related toxicity (a.197, a.198).

In addition to the low molecular weight drugs conjugated to polymers the principle of bioconjugation can be further extended in the delivery of larger molecules such as proteins, peptides and oligonucleotides. The main drawback of biologically active protein therapy is the short body residence time due to rapid renal elimination of such molecules. Once the polymer is attached to the



Figure 23

Chemical structure of HPMA-drug conjugates (a.196, a.197)

protein it is protected from enzymatic and hydrolytic degradation and also directs it to specific organs of the body. Various polymers have been used for conjugating proteins, the most common ones being PEG and dextrans. Streptokinase conjugated to dextran (35-50 kDa) sold under the trade name Streptodekase® was one of the first therapeutic enzymes approved for the treatment of cardio-vascular and ophthalmic pathologies caused by thrombosis (a.200). As a result of conjugation streptokinase can be administered as a single bolus instead of a continuous infusions. PEG-asparaginase (Oncospar®) is commonly used for the treatment of lymphocytic leukaemia. Some patients can develop an immunc-based resistance to asparaginase when used in the free form. However this is reduced when conjugated to PEG. The conjugation with PEG is also accompanied by reduced immunogenicity, antigenicity and proteolytic

susceptibility. Haemoglobin (Hb) has been conjugated to PEG and the PEG-Hb conjugate is undergoing Phase II clinical trial for use for blood transfusion.

The use of oligonucleotides as drugs has similar problems to proteins, namely rapid proteolytic enzyme degradation, chemical degradation and rapid renal elimination. In addition the high charge and polarity of the oligonucleotides leads to poor cellular uptake. PEG has been conjugated to oligonucleotides and although the research is at early stages there have been some promising results.

Conjugation of drugs to polymers offers several advantages for drug delivery. The polymer shields the drug from enzymic and chemical degradation in addition to masking the antigen sites of the drugs and reducing the immunogenic response. The polymer also reduces the rate of renal elimination of the drug, owing to its high molecular weight, thus increases the residence time of the drug. The conjugation of the drug to the polymer promotes targeted drug delivery mainly to the sites in the body with increased capillary permeability such as inflamed tissues and, additionally, allows the exploitation of a completely new pathway for drug delivery based on endocytosis.

4 General Conclusions

This review has described the use of polymers for the controlled release of therapeutic agents. The systems described herein have dramatically improved the treatment of a wide range of disease states and will continuc to do so in the future. The design of controlled release drug delivery systems requires knowledge of the physicochemical properties of both the polymer and drug, in addition to the biological requirements, e.g., pharmacokinetic and pharmacodynamic properties of the drug and knowledge of the disease state. The chemical versatility of polymers and the wide range of designs of controlled release systems offer numerous possibilities for the formulation of therapeutic agents. It is suggested that, due to the versatility of these systems, the ability of polymers to control the delivery of newer therapeutic agents, many of which will be macromolecular (e.g., proteins), will be assured.

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Abbreviations and Acronyms

AA _c	Acrylic acid
Ala	Alanine
BPI	Birmingham Polymers, Inc.
CMC	Carboxymethylcellulose
DL-PLA	Poly(DL-lactide)
DL-PLGA	Poly(DL-lactide-co-glycolide)
D-PLA	Poly(D-lactide)
DS	Degree of substitution
EC	Ethylcellulose
Gly	Glycine
Hb	Haemoglobin
HEC	Hydroxyethylcellulose
HPC	Hydroxypropylcellulose
HPMA	Hydroxypropylmethacrylamide
HPMC	Hydroxypropylmethylcellulose
IUD	Intra-uterine device
LCST	Lower critical solution temperature
Leu	Leucine
L-PLA	Poly(L-lactide)
MC	Mcthylcellulose
mp	Melting point
MS	Molar substitution
MW	Molecular weight
PCL	Poly(<i>ɛ</i> -caprolactone)
PEG	Polyethylene glycol(s)
PEO	Polyethylene oxide
PGA	Polyglycolide
Phe	Phenylalanine
PLA	Polylactide
PLGA	Poly(lactide-co-glycolide)
pNIPAA	Poly(isopropylacrylamide)
PVA	Polyvinyl acetate
PVC	Poly(vinyl chloride)
PVP	Polyvinylpyrrolidone
Т _g	Glass transition temperature
THF	Tetrahydrofuran
Т _m	Melting temperature
UCST	Upper critical solution temperature
Val	Valine

Abstracts from the Polymer Library Database

ltem 1

Journal of Microencapsulation 21, No.2, March 2004, p.137-49 MICROENCAPSULATION OF HYDROPHILIC DRUG SUBSTANCES USING BIODEGRADABLE POLYESTERS. II. IMPLANTS ALLOWING CONTROLLED DRUG RELEASE - A FEASIBILITY STUDY USING BISPHOSPHONATES Weidenauer U; Bodmer D; Kissel T

Marburg, Philipps University; Novartis Pharma Corp.

A pamidronate disodium salt(APD)-containing polymer matrix consisting of a APD-chitosan implant embedded in the biodegradable polymer D,L-poly(lactide-coglycolide-glucose)(PLG-GLU) was compared with a matrix system with the microionised drug distributed in the PLG-GLU. The APD-chitosan matrix system exhibited a triphasic release behaviour at loading levels of 6.86 and 15.54% w/w over 36 days under in-vitro conditions. At higher loading (31.92%), a drug burst was observed within 6 days due to the formation of pores and channels in the polymeric matrix. In contrast, implants containing the micronised drug showed a more continuous release profile over 48 days up to a loading of 31.78% w/ w. At a drug loading of 46.17% w/w, a drug burst was observed. Using micronised drug salts and reducing the surface area available for diffusion, parenteral delivery systems for highly water-soluble drug candidates were shown to be technically feasible at high drug loadings. 25 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; GERMANY; SWITZERLAND; WESTERN EUROPE

Accession no.910426

ltem 2

Journal of Microencapsulation 21, No.2, March 2004, p.175-89 EFFECTS OF THE PERMEABILITY CHARACTERISTICS OF DIFFERENT POLYMETHACRYLATES ON THE PHARMACEUTICAL CHARACTERISTICS OF VERAPAMIL HYDROCHLORIDE-LOADED MICROSPHERES

Kilicarslan M; Baykara T Ankara,University

Microspheres containing verapamil hydrochloride (a calcium antagonist) were prepared with various polymethacrylates with different permeability characteristics (Eudragit RS 100, Eudragit RL 100, Eudragit L 100 and Eudragit L 100-55 from Roehm Pharma) and also with mixtures of these polymers in a 1:1 ratio using the solvent evaporation method. The effects of permeability of the polymers on the drug release rates and the characteristics of the microspheres

were studied. Yield, incorporation efficiency, particle size and the distribution of microspheres were determined and the influence of the inner phase viscosities prepared with different polymer and polymer mixtures on particle size and the distribution of microspheres were evaluated. Surface morphologies of microspheres were observed by SEM. Drug release rates from microspheres were determined by the halfchange method using a flow-through cell. The results indicated that microspheres with different surface morphologies and statistically different yields and incorporation efficiencies could be prepared and their particle size and distribution variances resulted from the viscosity of the inner phase. Dissolution profiles showed that the drug release rate could be modified depending on the permeability characteristics of polymethacrylates. 41 refs.

Rohm Pharma GmbH TURKEY

Accession no.910428

Item 3

Journal of Microencapsulation 21, No.2, March 2004, p.203-11 FLUCONAZOLE ENCAPSULATION IN PLGA MICROSPHERES BY SPRAY-DRYING

Rivera P A; Martinez-Oharriz M C; Rubio M; Irache J M; Espuelas S

Navarra, Universidad; Pamplona, Clinica Universitaria

Poly(D,L-lactide-co-glycolide) microspheres loaded with fluconazole, a drug used for fungal suppressive therapy in AIDS patients, were prepared by spray-drying. The effect of some process parameters on the physical characteristics of the microspheres was evaluated. Neither type nor polymer concentration significantly affected the mean diameter of the microspheres, their size distribution and encapsulation efficiency of the drug. The drug loading, however, markedly affected their size and the physical state in which fluconazole could exist in the matrix of the carriers and thus affected the release rate of the drug. The results obtained by DTA and X-ray powder diffraction revealed that, at low nominal drug loading, fluoconazole was incorporated in an amorphous state or in a molecular dispersion in the matrix of the microspheres and at high nominal drug loading part of the drug was in a crystalline form. Release profiles of fluconazole from the microspheres exhibited a biphasic shape. The duration and extent of each phase was affected mainly by the nature of the polymer, drug loading and physical state in which fluconazole existed in the polymeric matrix. 17 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE Accession no.910429 Item 4

ACS Polymeric Materials Science and Engineering. Spring Meeting 2003. Volume 88. Proceedings of a conference held New Orleans, La., 23rd-27th March 2003.

Washington, D.C., ACS, Div.of Polymeric Materials Science & Engineering, 2003, p.222-3, CD-ROM, 012 ENCAPSULATION OF BIOACTIVE

MOLECULES IN CROSSLINKED MICROGELS

Goh S L; Murthy N; MingCheng Xu; Schuck S M; Lau L; Dubber M; Frechet J M J

California, University at Berkeley

(ACS, Div. of Polymeric Materials Science & Engng.)

Biocompatible microgels for the delivery of protein and DNA biomolecules were developed using acrylamide monomer, a bisacrylamide acetal crosslinker and potassium persulphate initiator. Encapsulation was shown to provide protection from enzymatic degradation of the protein or DNA. These particles demonstrated pH sensitivity such that in an acidic environment, as in the lysosome, the polymeric carrier degraded and released the encapsulated biomolecule. 9 refs.

USA

Accession no.910531

Item 5

European Polymer Journal 40, No.4, April 2004, p.873-81 SYNTHESIS AND CHARACTERIZATION OF THERMOSENSITIVE COPOLYMERS FOR ORAL CONTROLLED DRUG DELIVERY Eeckman F; Moes A J; Amighi K

Bruxelles,Universite

Copolymers of N-isopropylacrylamide with various hydrophilic comonomers were synthesised with the aim of obtaining copolymers with a phase transition temperature slightly higher than the physiological temperature, as required by a drug delivery concept described in a previous paper. The copolymers were characterised and the influence of the type and of the amount of the comonomer used on the phase transition temperature was examined. Among the comonomers studied, acrylamide, N-methyl-Nvinylacetamide, N-vinylacetamide and N-vinyl-2pyrrolidinone were found to be capable of raising the phase transition temperature to a value slightly higher than 37C and to exhibit adequate phase transition behaviour. The four copolymers selected were subjected to an additional purification step which should make them suitable for use as a controlling agent in drug delivery systems. 27 refs. BELGIUM: EU: EUROPEAN COMMUNITY: EUROPEAN UNION; WESTERN EUROPE; WESTERN EUROPE-GENERAL Accession no.910577

ltem 6

Journal of Bioactive and Compatible Polymers 19, No.1, Jan.2004, p.45-53

LINEAR TYPE AZO-CONTAINING POLYURETHANES FOR COLON-SPECIFIC DRUG DELIVERY

Mahkam M; Assadi M G; Zahedifar R; Ramesh M; Davaran S

Tabriz, Azarbaijan University; Tabriz, University

Details are given of the preparation of new biodegradable polyurethanes containing azo-linked polymeric prodrugs of amino salicylic acid in the main chain. Polymers were characterised by FTIR and proton NMR. Hydrolysis measurements were carried out. The hydrolysis product was detected using UV spectroscopy. 30 refs.

IRAN Accession no.910713

ltem 7

Materials World 12, No.4, April 2004, p.9 POLYMER ASSISTS NANOPARTICLE DRUG DELIVERY

A new type of polymer for coating nanoparticle drugs could make treatments for some types of cancer and inflammatory diseases more effective in the future. Nanoparticles are particularly efficient in transporting drugs to diseased sites, but the body can eliminate them if they are recognised as foreign matter. Coating the particles with polyethylene glycol means they can escape recognition, but incorporating and retaining the drug in the particle core is also essential for effective treatment. A team from the University of Nottingham has designed new polymers that interact better with drugs and achieve higher drug loadings and better drug retention within the nanoparticles. The polymers are synthesised from biological monomers. The team has also developed biodegradable polymers for gene therapy by altering the polymer structures to give optimum DNA interaction characteristics.

Nottingham, University EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.909709

Item 8

Biomaterials 25, No.12, 2004, p.2393-8 HYDROGEN-BONDED POLYMER GEL AND ITS APPLICATION AS A TEMPERATURE-SENSITIVE DRUG DELIVERY SYSTEM Oh K S; Han S K; Choi Y W; Lee J H; Lee J Y; Yuk S H

Hannam, University; Kyunggi, University

Details are given of the formation of a complex gel from a mixture of ethylene oxide-propylene oxide-ethylene oxide copolymer and PVAL via hydrogen bonding in water. The formation was verified by DSC. Based on the temperature-sensitivity of hydrogen bonding in the gel, a temperature-sensitive drug delivery system was designed and characterised. The release of acetoaminophen was examined as a model drug. 14 refs. KOREA

Accession no.908189

Item 9

Biomaterials 25, No.14, 2004, p.2843-9 **METHOXY POLYETHYLENE GLYCOL-POLYLACTIDE NANOPARTICLES FOR CONTROLLED DELIVERY OF ANTICANCER DRUGS**

Dong Y; Feng S-S Singapore, National University

Details are given of the synthesis of methoxy ethylene glycol-lactide copolymers nanoparticles by the nanoprecipitation method for the clinical administration of antineoplastic drugs size and size distribution, surface morphology, surface charge and surface chemistry of the drug-loaded nanoparticles were investigated by laser light scattering, atomic force microscopy, zeta-potential analyser and X-ray photoelectron spectroscopy. Drug encapsulation efficiency and in vitro release profile were measured by HPLC. 44 refs.

SINGAPORE

Accession no.908223

Item 10

Journal of Applied Polymer Science 91, No.1, 5th Jan.2004, p.72-7 RELEASE OF DICLOFENAC THROUGH GLUTERALDEHYDE CROSSLINKED POLY(VINYL ALCOHOL)/POLY(ACRYLIC ACID) ALLOY MEMBRANES Sanli O; Asman G

Gazi, University

A controlled release preparation of diclofenac sodium, a non-steroidal anti-inflammatory agent, was developed for transdermal administration. PVAl and PVAl/polyacrylic acid(PAA) alloy membranes were prepared from a solvent-casting technique using different PVAl/PAA v/vratios. The release of the drug from the membrane was evaluated under in vitro conditions at pH 7.4. The delivery system provided linear release without time lag, burst effect and boundary layer resistance. The effects of such variables as film thickness and PVAl/PAA ratio on the permeation behaviour of the polymeric membranes are discussed. The optimal PVAl/PAA was found to be 50/ 50. 48 refs.

TURKEY Accession no.908447

Item 11 Journal of Applied Polymer Science 91, No.1, 5th Jan.2004, p.636-43

PREPARATION OF PH-SENSITIVE POLY(VINYL ALCOHOL-G-METHACRYLIC ACID) AND POLY(VINYL ALCOHOL-G-ACRYLIC ACID) HYDROGELS BY GAMMA RAY IRRADIATION AND THEIR INSULIN RELEASE BEHAVIOR

Sung-Eun Park; Young-Chang Nho; Youn-Mook Lim; Hyung-Il Kim

Chungnam, National University; Korea, Atomic Energy Research Institute; Hanyang, University

A series of pH-responsive hydrogels was studied for use as potential drug carriers for the protection of insulin from the acidic environment of the stomach before release into the small intestine. Hydrogels based on PVAI networks grafted with acrylic acid or methacrylic acid were prepared by a two-step process. PVAI hydrogels were prepared by gamma-irradiation (50 kGy) and either acrylic acid or methacrylic acid was then grafted onto these PVA1 hydrogels with subsequent irradiation (5-20 kGy). The graft hydrogels showed pH-sensitive swelling behaviour and were used as carriers for the controlled release of insulin. The in-vitro release of insulin was observed for the insulin-loaded hydrogels in a simulated intestinal fluid (pH 6.8) but not in a simulated gastric fluid (pH 1.2). The release behaviour of insulin in-vivo in a rat model confirmed the effectiveness of the oral delivery of insulin to control the level of glucose. 11 refs.

SOUTH KOREA

Accession no.908520

Item 12

Polymer Preprints. Volume 44. Number 1. March 2003.
Papers presented at the ACS meeting held New
Orleans,Lo., 23rd-27th March 2003.
Washington, DC, ACS, Div.of Polymer Chemistry,
2003, p.936-7, 28CM, 012
MICROWAVE-ASSISTED SYNTHESIS OF
POLY(E-CAPROLACTONE) WITH ACID AS
INITIATOR AND A NOVEL METHOD IN
PREPARATION OF DRUG RELEASE SYSTEMS
Song Y; Liu L J; Yu X C; Zhuo R X
Wuhan,University
(ACS,Div.of Polymer Chemistry)

Polymerisation of e-caprolactone, by ring opening polymerisation of e-caprolactone using acidic catalysts, such as maleic acid, succinic acid and adipic acid, and enhanced by microwave assistance, was demonstrated. The ability of this polymerisation method to be used in the presence of drugs, for preparation of drug release systems, was demonstrated by carrying out the reaction in the presence of ibuprofen. Drug release was shown to be sustained and steady in In Vitro conditions. Gel permeation chromatography was used to determine molecular weights of polymers, and drug release was monitored by use of ultraviolet visual spectroscopy. 7 refs. CHINA

Accession no.907368

Item 13

Journal of Applied Polymer Science 91, No.3, 5th Feb.2004, p.1576-89 INFLUENCE OF PLASTICISER TYPE AND STORAGE CONDITIONS ON PROPERTIES OF POLY(METHYL VINYL ETHER-CO-MALEIC ANHYDRIDE) BIOADHESIVE FILMS

Hou T H; Costen R C

Belfast, Queens University; Belfast, City Hospital

A comparison between films prepared from copolymers of methylvinyl ether and maleic anhydride incorporating two different plasticisers, glycerol or tripropylene glycol methyl ether (TPME) revealed that the film containing TPME was potentially more suitable for use in bioadhesive films for use in drug delivery systems. Esterification occurred when glycerol was used as plasticiser, resulting in crosslinking which, with time, resulted in brittle films having little adhesive properties and loss of aqueous solubility. These changes occurred no matter what the storage conditions. After seven days, swelling was also observed. Films containing TPME did not undergo these changes. Methods of film preparation were described, and films were characterised using differential scanning calorimetry, bioadhesion measurements, tensile properties, swelling studies, determination of water content and nuclear magnetic resonance spectroscopy. 14 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.907412

Item 14

Industrial and Engineering Chemistry Research 43, No.4, 18th Feb.2004, p.1103-12 INCREASING COPPER INDOMETHACIN SOLUBILITY BY COPRECIPITATION WITH POLY(VINYLPYRROLIDONE) USING THE AEROSOL SOLVENT EXTRACTION SYSTEM Meure L A; Warwick B; Dehghani F; Regtop H L; Foster N R

New South Wales, University

Copper indomethacin(Cu-Indo), a non-steroidal antiinflammatory drug for veterinary use, was coprecipitated with polyvinyl pyrrolidone(PVP) to increase its solubility in biocompatible solvents. The aerosol solvent extraction system was used to produce Cu-Indo/PVP coprecipitates in various ratios. Carbon dioxide was used as an antisolvent to precipitate PVP and Cu-Indo from DMF solutions. Microspheres of PVP and Cu-Indo were formed that ranged in size from 50 nm to 4 micrometres under most conditions studied. A coprecipitate containing 10 wt % Cu-Indo and 90 wt % PVP was found to be at least 93 times more soluble in ethanol than factory-grade Cu-Indo. The significance of these results was that there could be potential for Cu-Indo to be used in parenteral applications. 37 refs.

AUSTRALIA Accession no.908099

Item 15 Biomaterials 25, No.7-8, 2004, p.1365-73 STUDIES ON BONE MARROW STROMAL CELLS AFFINITY OF POLYHYDROXYBUTYRATE-CO-HYDROXYHEXANOATE Yang M: Zhu S: Chen Y: Chang Z: Chen G: Gon

Yang M; Zhu S; Chen Y; Chang Z; Chen G; Gong Y; Zhao N; Zhang X Tsinghua,University

Details are given of the biocompatibility of hydroxybutyrate-hydroxyhexanoate copolymer with bone marrow stromal cells in vitro. The adsorption of fibronectin on the material was studied by enzyme-linked immunosorbent assay. The wettability and thermal properties of copolymer films were also studied by contact angle goniometer, TGA and DSC. Potential applications in bone tissue engineering are mentioned. 37 refs.

Accession no.906922

Item 16

Biomaterials 25, No.5, 2004, p.877-86 ALIGNED BIODEGRADABLE NANOFIBROUS STRUCTURE. A POTENTIAL SCAFFOLD FOR BLOOD VESSEL ENGINEERING Xu C Y; Inai R; Kotaki M; Ramakrishna S Singapore, National University

Details are given of the production of a biodegradable lactide-caprolactone copolymer nanofibrous scaffold by electrospinning. Interactions between the scaffold and human coronary artery smooth muscle cells were demonstrated via MTS assay, phase contrast light microscopy, SEM, immunohistology assay and laser scanning confocal microscopy. 34 refs. SINGAPORE

Accession no.906913

Item 17

Biomaterials 25, No.5, 2004, p.813-21 STUDY OF THE INITIAL STAGES OF DRUG RELEASE FROM A DEGRADABLE MATRIX OF POLYLACTIDE-CO-GLYCOLIDE

Frank A; Rath S K; Boey F; Venkatraman S Nanyang, Technological University

The initial stages of the in vitro degradation of and drug release from a matrix of lactide-glycolide copolymer was carried out in a phosphate buffer saline medium. Mechanisms are proposed for each phase of release, based on results from weight loss, amount of water absorption and SEM. The details of the structural changes and their effects on drug release are discussed. 29 refs. SINGAPORE

Accession no.906910

Item 18

Biomaterials 25, No.6, 2004, p.1059-67 IMMOBILIZATION OF CHITOSAN ONTO POLYLACTIC ACID FILM SURFACE BY PLASMA GRAFT POLYMERIZATION TO CONTROL THE MORPHOLOGY OF FIBROBLAST AND LIVER CELLS

Ding Z; Chen J; Gao S; Chang J; Zhang J; Kang E T Nanjing, University; Singapore, National University

Surface functionalisation of biodegradable polylactic acid was achieved by plasma coupling reaction of chitosan. Surfaces were characterised by contact angle measurements and X-ray photoelectron spectroscopy. Two cell lines were cultured on the modified surface. Potential applications in tissue engineering are mentioned. 36 refs. CHINA; SINGAPORE

Accession no.906871

Item 19

Journal of Microencapsulation 21, No.1, Feb.2004, p.3-13 ENCAPSULATION OF PROLI/NO IN BIODEGRADABLE MICROPARTICLES Jeh H S; Lu S; George S C California,University at Irvine

A small hydrophilic prodrug (PROLI/NO) to be delivered to the alveolar region of the lungs was encapsulated with microparticles of a biodegradable, hydrophilic lactic acidglycolic acid copolymer and an ethylene oxide-lactic acid copolymer and the kinetics of release of nitric oxide characterised using three parameters. These parameters were maximum concentration of nitric oxide per unit weight of microparticles, window of time over which the concentration exceeded 50% of the maximum concentration and the initial rate of release. 18 refs.

USA

Accession no.906556

Item 20

Engineering Elastomers 2003. Proceedings of a conference held in Geneva, Switzerland, 13th-14th Nov.2003.

Shawbury, Rapra Technology Ltd., 2003, Session 8, Paper 26, p207-10, 29cm, 012

EXPANDING THE APPLICATIONS OF EPDM/ EPM ELASTOMERS IN THE PHARMACEUTICAL AND FOOD INDUSTRIES

Ng V S Y; Stevens A Precision Polymer Engineering Ltd. (Rapra Technology Ltd.)

The general properties of EPM and EPDM elastomers are summarised with respect to the food and pharmaceutical industry requirements. The development of high purity inert grades have lead to their approval by regulatory bodies such as the United States Pharmacoepia and Food and Drug Administration and the UK's Water Research Council. Details of specific grades developed for the food and pharmaceutical industry are given with their various regulatory body approvals. The development and testing procedures required to obtain approval are outlined. EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.905493

Item 21

Polymer News 28, No.12, Dec.2003, p.393-6 POLYMERS IN DRUG DELIVERY. STABILIZERS USED TO PREPARE POLYMERIC MICROPARTICLES BY EMULSIFICATION/ SOLVENT EVAPORATION METHOD Aminabhavi T; Kulkarni V; Kulkarni A Karnatak University

Details are given of the use of various stabilisers in the preparation of polymer microparticles and the outcome in terms of particle size and encapsulation efficiency. Data are presented for polylactic acid, polyglycolic acid, lactic acid-glycolic acid copolymer and polyphosphazene microparticles loaded with drugs and prepared by emulsification/solvent evaporation. 18 refs.

INDIA

Accession no.904889

Item 22

Macromolecular Symposia No.203, 2003, p.213-8 NOVEL PH SENSITIVE POROUS MEMBRANE CARRIER FOR VARIOUS BIOMEDICAL APPLICATIONS BASED ON PHEMA/ CHITOSAN. PREPARATION AND ITS DRUG RELEASE CHARACTERISTICS Bayramoglu G; Arica M Y Kirikkale,University

Details are given of the preparation of pH sensitive blends in membrane form using hydroxyethyl methacrylate and chitosan via photopolymerisation in the presence of AIBN initiator. A series of hydrogels were prepared and the equilibrium swelling studies were conducted to investigate swelling behaviours of the membrane according to the pH of the swelling medium. Antibiotic release experiments were performed with amoxicillin loaded membranes. 6 refs.

TURKEY

Accession no.904483

Item 23

Macromolecules 36, No.20, 7th Oct.2003, p.7484-90 NONIONIC NANOPARTICLES BY MINIEMULSION POLYMERIZATION OF VINYL ACETATE WITH OLIGOCAPROLACTONE

MACROMONOMER OR MIGLYOL AS HYDROPHOBE. APPLICATION TO THE ENCAPSULATION OF INDOMETHACIN

Rajot I; Bone S; Graillat C; Hamaide T Laboratoire de Chimie et Procedes de Polymerisation

Miniemulsion polymerisation of vinyl acetate was carried out with non-ionic surfactants and AIBN or hydrogen peroxide-ascorbic acid system as initiator in order to produce non-ionic nanoparticles suitable for the encapsulation of hydrophobic drugs. In addition, oligocaprolactone macromonomers, benzyl benzoate or triglycerides from fatty acids (Miglyol) were used as the hydrophobe in order to prepare biocompatible systems. These oligocaprolactones were obtained by anionic coordinated ring-opening polymerisation in the presence of a transfer agent. Molec.wts. were controlled by using transfer agents. Encapsulation of indomethacin was performed by adding the drug in the miniemulsion recipe. 23 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; FRANCE; WESTERN EUROPE

Accession no.904011

Item 24

Journal of Microencapsulation 20, No.6, Nov.-Dec.2003, p.777-89 OXPRENOLOL-LOADED BIOADHESIVE MICROSPHERES: PREPARATION AND IN VITRO/IN VIVO CHARACTERIZATION Preda M; Leucuta S E

Cluj Napoca, University of Medicine & Pharmacy Iuliu Hatieganu

The preparation of a bioadhesive drug delivery system based upon gelatin/polyacrylic acid microspheres loaded with a model drug (oxprenolol hydrochloride) is described. The effects of preparation and formulation variables on the physicochemical properties and pharmaceutical characteristics of the microspheres are examined and the in-vitro adhesion, bioadhesion, drug release and drug bioavailability behaviour of the drug delivery system evaluated. 15 refs.

EASTERN EUROPE; RUMANIA

Accession no.903855

Item 25

Polymer News 28, No.10, Oct.2003, p.315-20 POLYMERS IN DRUG DELIVERY. METHODS TO ENHANCE SOLUBILITY OF DRUGS USING POLYMERIC DISPERSION TECHNIQUE Aminabhavi T M; Desai K H; Kulkarni A R Karnatak University

The use of the polymeric dispersion technique to develop oral-modified release formulations for easy absorption and bioavailability of poorly water-soluble drugs is discussed. Techniques for preparation of solid polymeric dispersions are described, including the methods of melting, solvent evaporation, coprecipitation and kneading. Information is given on hydrophilic carriers used in the preparation of solid dispersions (cyclodextrins), different polymers used as solubility enhancers (polyethylene glycol, polyvinyl pyrrolidone, cellulose derivatives, urea and mannitol), characterisation of solid dispersions and in vitro release of solid dispersions. 22 refs.

INDIA

Accession no.903598

Item 26

Nature Materials 2, No.11, Nov.2003, p.767-72 MULTI-PULSE DRUG DELIVERY FROM A RESORBABLE POLYMERIC MICROCHIP DEVICE

Grayson A C R; Choi I S; Tyler B M; Wang P P; Brem H; Cima M J; Langer R Massachusetts,Institute of Technology; Korea,Advanced Institute of Science & Technology; Johns Hopkins University

A report is presented on the design, fabrication and testing of biodegradable polymeric microchip devices capable of multi-pulse drug release from a polymeric system over periods of several months without the need for a stimulus to trigger drug release. The devices are made from poly(Llactic acid) and poly(D,L-lactic-co-glycolic acid) membranes, which cover drug-containing reservoirs on the microchips. The microchips are shown to be capable of releasing four pulses of radiolabelled dextran, human growth hormone or heparin in-vitro. 49 refs.

KOREA; USA

Accession no.903096

Item 27

Chemistry of Materials 15, No.21, 21st Oct.2003, p.4132-8 INFLUENCE OF A SIO2-CAO-P2O5 SOL-GEL GLASS ON THE BIOACTIVITY AND CONTROLLED RELEASE OF CERAMIC/ POLYMER/ANTIBIOTIC MIXED MATERIALS Arcos D; Pena J; Vallet-Regi M Madrid,Universidad Complutense

Materials were formed from a hydrophobic polymeric matrix (PMMA), a ceramic component and a drug (gentamicin, a wide spectrum antibiotic). The PMMA allowed the controlled release of the drug and the ceramic component should provide bioactive behaviour for the system. The ceramic phase was composed of two phases, hydroxyapatite and a bioactive sol-gel glass. The role of the glass in the behaviour of the blends was studied in terms of bioactivity and drug release. The results obtained showed that, when synthesising bioactive materials for use as drug delivery systems, consideration should be given to the effect of surface modifications on drug release kinetics. 37 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE

Accession no.902147

Item 28

Journal of Applied Polymer Science 84, No.6, 9th May 2002, 1178-84 PREPARATION OF CHEMICALLY CROSSLINKED GELS WITH MALEATE-DENATURED POLY(VINYL ALCOHOL) AND ITS APPLICATION TO DRUG RELEASE Horiike S; Matsuzawa S; Yamaura K Shinshu,University at Ueda

Maleate-denatured poly(vinyl alcohol) (M-PVA) was crosslinked with heating. The mechanism of crosslinking was studied using titration, Fourier transform infrared, and solubility. The carboxyl groups of M-PVA consisted of carboxylates and a few free carboxyl groups. The crosslink was the ester linkage between hydroxyl and carboxyl groups. Several kinds of M-PVA tablets were prepared under different conditions: pressures of 200-600 kgf/sq. cm and grain sizes of 75 (pass) to 250 micron (on). The swelling behaviour of these chemically crosslinked tablets was studied in a buffer solution of pH 7.4, mainly at 37C. Moreover, the effect of temperature from 5 to 50C and the effect of repeated swell-dry cycles on the behaviour of the tablets in a buffer solution were studied. The release of p-acetamidophenol from those tablets in the pH 7.4 buffer solution was studied. The different release patterns were due to the differences in the swelling behaviour. 12 refs.

JAPAN

Accession no.901865

Item 29

Journal of Applied Polymer Science 84, No.6, 9th May 2002, 1133-45 COLON-SPECIFIC ORAL DELIVERY OF VITAMIN B2 FROM POLY(ACRYLAMIDE-CO-MALEIC ACID) HYDROGELS: AN IN VITRO STUDY

Bajpai S K; Bajpai M; Kalla K G Jabalpur,Government Autonomous Science College

Hydrogels composed of poly(acrylamide-co-maleic acid) were synthesized and the release of vitamin B2 from these gels was studied as a function of the pH of the external media, the initial amount of the drug loaded, and the crosslinking ratio in the polymer matrix. The gels containing 3.8 mg of the drug per gram gel exhibit almost zero-order release behaviour in the external media of pH 7.4 over the time interval of more than their half-life period. The amount of the drug loaded into the hydrogel also affected the dynamic release of the encapsulated drug. As expected, the gels showed a complete swelling-

dependent mechanism, which was further supported by the similar morphology of the swelling and release profiles of the drug-loaded sample. The hydrophilic nature of the drug riboflavin does not contribute toward the zero-order release dynamics of the hydrogel system. On the other hand, the swelling osmotic pressure developed between the gels and the external phase, due to loading of the drug by equilibration of the gels in the alkaline drug solution, plays an effective role in governing the swelling and release profiles. Finally, the maximum release with zeroorder kinetics in the medium of pH 7.4 suggest that the proposed drug-delivery devices have a significant potential to be used as an oral drug-delivery system for colon-specific delivery along the gastrointestinal tract. 19 refs.

INDIA

Accession no.901861

Item 30

Macromolecular Symposia No.201, 2003, p.179-86 NEW BIODEGRADABLE POLYMERS FOR DELIVERY OF BIOACTIVE AGENTS Young Min Kwon; Sung Wan Kim Utah,University

The preparation of drug-loaded microspheres and injectable hydrogels based on biodegradable, thermosensitive PLGA-PEG-PLGA triblock copolymers is described. The drug delivery properties of both microspheres and hydrogels for protein or water-insoluble drugs were investigated by studying the in vitro and in vivo release of insulin over a period of time and the results are discussed. 8 refs.

USA

Accession no.901639

Item 31

Biomaterials 25, No.2, 2004, p.315-25 **PRECIPITATION CASTING OF POLYCAPROLACTONE FOR APPLICATIONS IN TISSUE ENGINEERING AND DRUG DELIVERY**

Coombes A G A; Rizzi S C; Williams M; Barralet J E; Downes S; Wallace W A Nottingham, University; Zurich, University; Aston, University; Birmingham, University

Microparticles of hydroxyapatite and inulin polysaccharide were incorporated in precipitation cast polycaprolactone matrices. Potential applications in hard tissue repair and macromolecular drug release are illustrated. In vitro degradation characteristics were monitored over 45 months. 31 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SWITZERLAND; UK; WESTERN EUROPE Accession no.901304 Item 32 Biomaterials 25, No.1, 2004, p.139-46 BIODEGRADATION AND RELEASE OF GENTAMICIN SULPHATE FROM INTERPENETRATING NETWORK HYDROGELS BASED ON POLYACRYLIC ACID AND GELATIN. IN VITRO AND IN VIVO Changez M; Koul V; Krishna B; Dinda A K;

Choudhary V Indian Institute of Technology

Hydrogel blends based on polyacrylic acid and gelatin were evaluated for in vitro and in vivo biodegradation and in vivo release of gentamicin sulphate. The effect of acrylic acid content on degradation kinetics was investigated. Drug concentration was measured in local skin tissue, blood serum, kidney, liver and spleen. 23 refs. INDIA

Accession no.901221

Item 33

Biomaterials 24, No.28, 2003, p.5163-71 **USE OF BIODEGRADABLE POLYURETHANE SCAFFOLDS FOR CARTILAGE TISSUE ENGINEERING. POTENTIAL AND LIMITATIONS**

Grad S; Kupcsik L; Gorna K; Gogolewski S; Alini M Switzerland, AO Research Institute

Details are given of the capability of biodegradable PU scaffolds to support attachment, growth and maintenance of differentiated chondrocytes in vitro. A progressive increase in glycosaminoglycans and collagen was observed during the culture period. The limitations of the system wer found to be the diffusion of large amounts of matrix molecules into the culture medium and the dedifferentiation of the chondrocytes with prolonged time in culture. Morphologies were examined using SEM. 69 refs.

SWITZERLAND; WESTERN EUROPE

Accession no.900184

Item 34

Journal of Biomaterials Science: Polymer Edition 14, No.10, 2003, p.1043-56 **PENICILLIN V-CONJUGATED PEG-PAMAM STAR POLYMERS**

Yang H; Lopina S T Akron,University

Details are given of the use of a polyethylene glycolpolyamidoamine star polymer to design and build drugdelivery scaffolds. Penicillin V was used as a model carboxylic group containing drug. Characterisation was undertaken using FTIR, UV vis spectroscopy and proton NMR. 28 refs.

USA Acusari

Accession no.899611

ltem 35

Journal of Biomaterials Applications 18, No.2, Oct.2003, p.95-108 EFFECT OF GAMMA-STERILIZATION PROCESS ON PLGA MICROSPHERES LOADED WITH INSULIN-LIKE GROWTH FACTOR-I Carrascosa C; Espejo L; Torrado S; Tarrado J J

Madrid, University

The influence of gamma-sterilisation on the physicochemical properties of a controlled release formulation for insulin-like growth factor-I was investigated. The growth factor was entrapped in lactide-glycolide copolymer microspheres by a waterin-oil-in-water solvent evaporation technique. Microspheres were irradiated and evaluated by SEM and DSC. The stability of the released protein was investigated by circular dichroism and gel electrophoresis. 34 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE

Accession no.898599

ltem 36

Journal of Microencapsulation 20, No.5, Sept.-Oct.2003, p.613-25 PROPERTIES OF DRUG-CONTAINING SPHERICAL PELLETS PRODUCED BY A HOT-MELT EXTRUSION AND SPHERONIZATION PROCESS

Young C R; Koleng J J; McGinity J W Texas, University; Pharmaform LLC

Spherical pellets were produced by hot-melt extrusion without the use of water or other solvents. A powder blend of theophylline, Eudragit Preparation 4135 F (methyl acrylate-methacrylic acid-methyl methacrylate copolymer), microcrystalline cellulose and polyethylene glycol 8000 was hot melt-extruded and the resulting composite rod was cut into cylindrical pellets. The pellets were then spheronised in a traditional spheroniser at elevated temperature. The same powder was processed using conventional wet-mass techniques. Unlike wetmass extruded pellets, pellets prepared from hot-melt extrusion exhibited both a narrow particle size distribution and controlled drug release in dissolution media less than pH 7.4. SEM, X-ray diffraction and porosity measurements were used to explain the differences in drug release rates of theophylline from pellets produced by the two processing techniques. Theophylline release from the hot-melt extruded pellets was described using the Higuchi diffusion model and drug release rates from wet-granulated and meltextruded pellets did not change after post-processing thermal treatment. 35 refs.

ROEHM GMBH

EUROPEAN COMMUNITY; EUROPEAN UNION; GERMANY; USA; WESTERN EUROPE Accession no.898409

Item 37 Engineer 292, No.7637, 10th-23rd Oct.2003, p.18 **SAVING PATIENTS' BREATH** Pierce J

The development by Hanes at Johns Hopkins University of microscopic plastics spheres than can be inhaled into the lungs is briefly discussed. The particles can contain mediation for treatment of lung cancer or be used to deliver DNA directly into the nucleus of cells for use in gene therapy. The particles are made from a combination of three biodegradable plastics monomers.

JOHNS HOPKINS UNIVERSITY USA

Accession no.898269

Item 38

Medical Device Technology 14, No.7, Sept.2003, p.16-9 COMBINED LOCAL DRUG DELIVERY AND IMPLANTABLE MEDICAL DEVICES Anderson A B SurModics Inc.

Details are given of product developments for the targeted, controlled local delivery of a drug by an implant. Potential future device applications and progress with novel techniques employing drug delivery matrices and coating methods are discussed. 6 refs.

USA

Accession no.896563

Item 39

Polymer Preprints. Volume 44. Number 1. March 2003. Papers presented at the ACS meeting held New Orleans, La., 23rd-27th March 2003. Washington, D.C., ACS, Division of Polymer Chemistry, 2003, p.221-2, 28cm, 012 **TRANSDERMAL PATCHES: NOT JUST FOR CONTROL FREAKS?**

Foreman P B; Jacobson S H National Starch & Chemical Co. (ACS,Div.of Polymer Chemistry)

Pressure sensitive adhesives (PSA) used for transdermal patch attachment must meet pharmaceutical standards of safety and stability whilst providing sufficient drug solubility and diffusivity to deliver a constant dose. Acrylic PSA, often random copolymers produced by free radical polymerisation, provide the greatest versatility. Achieving peel and shear strength may require using monomers with active hydrogen functionality. This may compromise drug compatibility, and reinforcement may then be achieved by grafting styrene or methyl methacrylate side chains to create physical crosslinks. Silicone PSA has a two phase morphology, with silicaterich domains in a continuous phase rich in polysiloxane. The composition determines the level of tack. Polyisobutylene PSA is also used. Procedures for the prediction of drug solubility and diffusion in a polymer matrix are described. 16 refs. USA

Accession no.896137

Item 40

Biomaterials 24, No.24, 2003, p.4417-23 **DEVELOPMENT OF A TEMPERATURE SENSITIVE DRUG RELEASE SYSTEM FOR POLYMERIC IMPLANT DEVICES**

Roos A; Klee D; Schuermann K; Hocker H Aachen,RWTH

An LDPE model surface was coated with polyaminoxylene via chemical vapour deposition polymerisation. The functional surface was used to immobilise a polymeric drug release system consisting of isopropyl acrylamide-acrylic acid copolymer. The coupled drug release system was used to incorporate the thrombin inhibitor r-hirudin. 16 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; GERMANY; WESTERN EUROPE

Accession no.894747

Item 41

Journal of Polymer Science: Polymer Chemistry Edition

41, No.15, 1st Aug.2003, p.2404-11 AMINO-FUNCTIONALIZED LATEX PARTICLES OBTAINED BY A MULTISTEP METHOD: DEVELOPMENT OF A NEW IMMUNOREAGENT

Ramos J; Martin-Molina A; Sanz-Izquierdo M P; Rus A; Borque L; Hidalgo-Alvarez R; Galisteo-Gonzalez F; Forcada J

Pais Vasco, Universidad; Granada, University; Logrono, Clinical Analysis Laboratory

Cationic latex particles with surface amino groups were prepared by a multi-step batch emulsion polymerisation. Monodisperse cationic latex particles to be used as the seed were synthesised first. Then the amino-functionalised monomer, aminoethylmethacrylate hydrochloride, was used to synthesise the final functionalised latex particles. Three different azo initiators were used: 2,2'azobisisobutyramidine dihydrochloride, 2,2'azobisdimethyleneisobutyramidine dihydrochloride, and 2,2'-azobisisobutyronitrile. Hexadecyltrimethylammonium bromide was used as the emulsifier. The latices were characterised by photon correlation spectroscopy to study the mean particle diameters, transmission electron microscopy to determine the particle size distributions, and hence the number- and weight-average diameters and the polydispersity index. The conversion was determined gravimetrically, the surface density of the amino groups was determined by conductimetric titrations, and the

electrophoretic mobility was investigated. Activation of the latex particles with glutaraldehyde produced an efficient reagent for immuno-assay. The reagent was used in the measurement of serum ferritin concentration in a new turbidimetric procedure. This method compared favourably with a commercial nephelometric method. 23 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE

Accession no.894257

Item 42

Macromolecular Symposia No.196, 2003, p.145-54 DENDRITIC POLYMERS. FROM EFFICIENT CATALYSIS TO DRUG DELIVERY Kakkar A K McGill University

A detailed investigation is described of dendritic effects in transition metal catalysed organic transformations. Small dye molecules were loaded into the intrinsic cavities of the backbone of dihydroxybenzyl alcohol based dendrimers which led to a change in physical properties of both the dye and the dendrimer. The use of dendrimers as templates to prepare network carriers containing cavities of predetermined size and disposition was also investigated. 21 refs.

CANADA Accession no.893926

Item 43

Biomaterials 24, No.22, 2003, p.4037-43 **BIOACTIVE GLASS-POLYMER MATERIALS FOR CONTROLLED RELEASE OF IBUPROFEN** Ladron de Guevara-Fernandez S; Ragel C V; Vallet-Regi M Madrid,Universidad Complutense

Ibuprofen release from bioactive glass, polylactic acid and PMMA were studied. The analysis of the samples before and after different soaking periods in simulated body fluid demonstrated the growth of an apatite-like layer on the material surface. The drug release rate was correlated with the growth kinetics of this layer. Materials were characterised using X-ray diffraction, DSC and SEM. 36 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE

Accession no.893900

Item 44

Macromolecular Bioscience 3, No.7, 14th July 2003, p.364-72 CONJUGATES OF ANTIBODY-TARGETED PEG MULTIBLOCK POLYMERS WITH DOXORUBICIN IN CANCER THERAPY Pechar M; Ulbrich K; Jelinkova M; Rihova B Czech Republic, Academy of Sciences The synthesis and physico-chemical characterisation of biodegradable multiples polymer drug carriers based on polyethylene glycol are described. The polymer blocks are interconnected by an enzymatically degradable tripeptide derivative. Doxorubicin anticancer drug was attached to the polymer carrier by a tetra peptide spacer which was susceptible to degradation by lysosomal enzymes. A targeting polyclonal antibody was linked to the conjugate and the resulting conjugates were characterised by size exclusion chromatography, UV-vis spectroscopy and amino acid analysis. 35 refs.

CZECH REPUBLIC

Accession no.893893

Item 45

Polymers for Advanced Technologies 14, No.7, July 2003, p.502-7 **ACRYLATE-BASED PRESSURE SENSITIVE ADHESIVE IN FABRICATION OF TRANSDERMAL THERAPEUTIC SYSTEM** Tipre D N; Vavia P R Mumbai, University

An acrylate-based pressure-sensitive adhesive(PSA) was synthesised for incorporation into the design of a drugin-adhesive(DIA) type transdermal therapeutic system(TTS) for nitrendipine and nicorandil in treatment of hypertension and angina pectoris, respectively. Solutions of 2-ethylhexyl acrylate, methyl methacrylate, acrylic acid and vinyl acetate in either ethyl acetate, acetone or methanol were polymerised under free radical conditions to synthesise the PSA. The effects of solvent, reaction time, initiator concentration and reaction temperature on the polymerisation were studied. The PSA was used to develop DIA type patches for delivery of nitrendipine and nicorandil. The TTSs were evaluated for thickness, weight, peel strength, moisture uptake, in vitro release and in vitro skin permeation through guinea-pig skin. The copolymer was found effectively to control the rate of drug release and the corresponding TTSs could be successfully employed in transdermal delivery of nitrendipine and nicorandil. 24 refs. INDIA

Accession no.893101

Item 46

Biomaterials 24, No.21, 2003, p.3707-14 **IMPROVED REVERSE THERMO-RESPONSIVE POLYMERIC SYSTEMS** Cohn D; Sosnik A; Levy A Jerusalem,Hebrew University

Details are given of the synthesis of novel reverse thermoresponsive polymeric systems by the polymerisation of polyethylene oxide and polypropylene oxide segments. Data are presented concerning the size of aggregates formed by these materials in aqueous solution as the release profile of an anti-restenosis model drug. 34 refs. ISRAEL

Accession no.893054

Item 47

Biomedical Polymers and Polymer Therapeutics. Dordrecht, Kluwer Academic Publishers, 2001, Part 2, Chapter 24, p.315-30, 25cm, 6S **DEVELOPMENT OF FUSOGENIC LIPOSOMES AND ITS APPLICATION FOR VACCINE** Hayashi A; Mayumi T

Osaka, University

Edited by: Chiellini E; Sunamoto J; Migliaresi C; Ottenbrite R M; Cohn D

For patients with infectious diseases including AIDS or those with cancer, induction of protective immunity, which can eliminate the cells involved in the respective pathologic conditions, is essential. Induction of cytotoxic T lymphocytes (CTL) becomes is particularly in such patients, as CTL plays a central role in protective immunity. It has been reported that endogenous antigens in the cytoplasm are generally presented to the T cells in conjunction with class I MHC molecules, while exogenous antigens are processed by endocytosis, then presented to the T cells in conjunction with class II MHC molecules. Recently, attention has been focused on component vaccines due to their higher safety. However, since component vaccines are exogenous antigens, most component vaccines are endocytosed after administration, then presented to the T cells in conjunction with class I MHC molecules. It is a major drawback of component vaccines that the efficiency of antigen presentation in conjunction with class I MHC molecules, which is essential for CTL induction, is markedly low. Also, when peptides that bind to the receptors of class I MHC molecules are used as vaccines, there is the risk that these vaccines may undergo degradation in endosomes during the usual pathway of antigen presentation via endocytosis even when antigen molecules extravasate from endosomes into the cytoplasm. Therefore, antigen presentation in conjunction with class I MHC molecules is not expected when such vaccines are administered. To design effective component vaccines, it is essential to develop a novel technique considering intracellular kinetics of antigens. Fusogenic liposomes (FL) whose membrane fusion capacity is identical to that of Sendai virus have been developed. FL facilitates direct and efficient induction of inclusion substances into the cytoplasm by membrane fusion without accompanying cytotoxicity. FL is applied to a component vaccine. FL can deliver the encapsulated soluble protein directly into the cytosol of cultured cells and introduce it into the class I MHC antigenpresentation pathway. Moreover, a single immunisation with ovalbumin (OVA) encapsulated in FLs but not in simple liposomes results in the potent priming of OVA-

specific CTLs. Thus, FLs function as an efficient tool for the delivery of CTL vaccines. 48 refs. JAPAN

Accession no.892779

Item 48

Biomedical Polymers and Polymer Therapeutics. Dordrecht, Kluwer Academic Publishers, 2001, Part 2, Chapter 23, p.297-314, 25cm, 6S

SYNTHETIC PEPTIDE AND THEIR POLYMERS AS VACCINES

Jackson D; Brandt E; Brown L; Deliyannis G; Fitzmaurice C; Ghosh S; Good M; Harling-McNabb L; Dadley-Moore D; Pagnon J; Sadler K; Salvatore D; Zeng W Melbourne,University

Edited by: Chiellini E; Sunamoto J; Migliaresi C; Ottenbrite R M; Cohn D

Vaccines follow the availability of clean water as the most cost effective method of achieving improved public health. Infectious diseases, autoimmune disorders and some cancers are amenable to prophylactic and therapeutic treatment by vaccines and it is the realisation of this fact that is responsible not only for the efforts being made by a large number of groups worldwide in designing new vaccines, but also in the efforts of public health organisations in delivering vaccines to the community. Amongst the latest technologies being applied to the development of vaccines, synthetic peptides offer a versatile approach to the problems of vaccine design. Immunisation with peptides can induce humoral (antibody) and cellular (cytotoxic T cell and helper T cell) immune responses capable of cross-reacting with intact antigen. Because of this ability to stimulate both humoral and cellular arms of the immune response, a great deal of effort has been put into evaluating peptides as vaccines not only in those situations where antibody is an important determinant in immunity but also in cases where cytotoxic T cells are required for the elimination of virus infected cells or cancer cells. 33 refs. AUSTRALIA

Accession no.892778

Item 49

Biomedical Polymers and Polymer Therapeutics. Dordrecht, Kluwer Academic Publishers, 2001, Part 1, Chapter 6, p.63-74, 25cm, 6S **POLYMERIC HYDROGELS IN DRUG RELEASE** Chiellini F; Petrucei F; Ranucci E; Solaro R Pisa,University; Stockholm,Royal Institute of Technology

Edited by: Chiellini E; Sunamoto J; Migliaresi C; Ottenbrite R M; Cohn D

Among the several classes of biomedical materials, increasing attention is being devoted to polymeric hydrogels, which have the ability to swell in water or in

aqueous solutions by forming a swollen gel phase that, in the case of crosslinked systems, will not dissolve regardless of the solvent. An important feature of hydrogels is their biocompatibility, that can be attributed to their ability to simulate living tissue characteristics such as large water content, low interfacial tension with body fluids, permeability to metabolites, nutrients and oxygen. At present, the most investigated hydrogels are those based on 2-hydroxyethyl methacrylate (HEMA), due to their ascertained non-toxicity and widespread use in the production of soft contact lenses. The synthesis and characterisation of polymeric hydrogels based on HEMA for use in the formulation of drug delivery systems are described. In particular, HEMA hydrogels are developed to be used as components of dental implants amenable to the controlled release of antibiotics and in the preparation of polymeric scaffolds for tissue engineering application. Studies are carried out to assess a method for loading methronidasole, an antibiotic drug widely used in dentistry, into the hydrogel matrix. Attention is focused on the characterisation of samples with different degree of crosslinking and of swelling in various aqueous solutions. Diffusion coefficients of water, inorganic salts and methronidasole are also investigated. 12 refs. EUROPEAN UNION; SCANDINAVIA; SWEDEN; WESTERN

EUROPE Accession no.892761

Item 50

Biomedical Polymers and Polymer Therapeutics. Dordrecht, Kluwer Academic Publishers, 2001, Part 1, Chapter 5, p.53-63, 25cm, 6S

CELLULOSE CAPSULES - AN ALTERNATIVE TO GELATIN

Nagata S Shionogi Qualicaps Co.Ltd. Edited by: Chiellini E; Sunamoto J; Migliaresi C; Ottenbrite R M; Cohn D

Hard gelatin capsules have been used in the pharmaceutical fields as an edible container for several decades. The development of mass-production facilities and rapid capsule filling machines have made capsules one of the most popular oral dosage forms. However, gelatin capsules have some drawbacks derived from proteins. Gelatin capsule shells have 13-15% water content, so gelatin capsules may not be suitable for readily hydrolysed drugs. Furthermore, when stored under severe conditions, some drugs react with amino groups of protein and crosslinked gelatin prolongs dissolution of drug. Since gelatin for capsules is mainly derived from bovine sources, there is an implication of a potential risk posed by BSE. In addition, gelatin product from bovine and swine sources are sometimes shunned as a result of religious or vegetarian dietary restrictions. For these reasons, trials to develop capsules free of proteins as an alternative to gelatin capsules are carried out. 8 refs.

JAPAN Accession no.892760

Item 51

Biomedical Polymers and Polymer Therapeutics. Dordrecht, Kluwer Academic Publishers, 2001, Part 1, Chapter 3, p.33-6, 25cm, 6S

APPLICATION TO CANCER CHEMOTHERAPY OF SUPRAMOLECULAR SYSTEM

Ichinose K; Yamamoto M; Taniguchi I; Akiyoshi K; Sunamoto J; Kanematsu T Nagasaki,University; Kyoto,University

Edited by: Chiellini E; Sunamoto J; Migliaresi C; Ottenbrite R M; Cohn D

Numerous studies have reported liposomes and microspheres to be a useful drug carrier in drug delivery systems. There are several problems, including their instabilities and poor selectabilities for targeting. Since 1982, Sunamoto et al. reported that hydrophobised polysaccharides, such as cholesterol conjugated pullulan (CHP), coated liposome showed an increased resistance to enzymatic destruction and CHP also formed hydrogelnanoparticles after self-aggregation with various drugs in water. In addition, recent in vitro studies have demonstrated that polysaccharides recognise lectin on the cell surface. CHP bearing galactose moiety (Gal-CHP) has been synthesised as a cell recognition element. The validity of the Gal-CHP coated liposome (Gal-CHP Lip) enclosing the anticancer drug, and the Gal-CHP selfaggregation complex with the anticancer drug, are evaluated. 4 refs.

JAPAN

Accession no.892758

Item 52

Biomedical Polymers and Polymer Therapeutics. Dordrecht, Kluwer Academic Publishers, 2001, Part 1, Chapter 2, p.19-31, 25cm, 6S **BIODEGRADABLE NANOSPHERES:**

THERAPEUTIC APPLICATIONS

Davda J; De S; Zhou W; Labhasetwar V Edited by: Chiellini E; Sunamoto J; Migliaresi C; Ottenbrite R M; Cohn D (Nebraska,University)

Drug delivery has become an integral part of drug development because it can significantly enhance the therapeutic efficacy of drugs. Furthermore, newer drugs prepared by recombinant technology, though comparatively more potent and specific in their pharmacological action, require efficient drug delivery systems. These drugs are either unstable in the biological environments or are unable to cross the biological barriers effectively. Emphasis is placed on biodegradable nanospheres as a drug carrier system. The drug in the core of nanocapsules is released by diffusion through the polymer coating. Polylactic polyglycolic acid copolymer (PLGA) is mainly used; a FDA approved biodegradable and biocompatible polymer to formulate nanospheres. Nanospheres as a drug delivery system could provide many advantages. Since nanospheres are submicron in

size, they could be taken up more efficiently by the cells than the larger size particles. Furthermore, nanospheres could cross the cell membrane barriers by transcytosis. Drug molecules such as proteins and peptides and also DNA, which have a larger hydrodynamic diameter because of the charge and the bound water, could be entrapped into the nanosphere polymer matrix. Thus, the cellular uptake and transport of such macromolecules across biological membranes could be significantly improved by condensing them into nanospheres. Nanospheres could protect the entrapped agent(s) from enzymatic and hydrolytic degradation. Furthermore, the sustained release characteristics of nanospheres could be useful for many therapeutic agents that require repeated administration for their pharmacologic effects or to cure the disease completely. Nanospheres could offer a solution to many problems related to the delivery of therapeutic agents. The various pathophysiologic conditions where nanospheres could be used as an effective drug delivery system are reviewed. 44 refs.

USA

Accession no.892757

Item 53

Journal of Microencapsulation 20, No.4, July-Aug.2003, p.509-24 MICROENCAPSULATION OF HYDROPHILIC DRUG SUBSTANCES USING BIODEGRADABLE POLYESTERS. PART I: EVALUATION OF DIFFERENT TECHNIQUES FOR THE ENCAPSULATION OF PAMIDRONATE DI-SODIUM SALT

Weidenauer U; Bodmer D; Kissel T Philipps-Universitat; Novartis Pharm Ltd.; Ciba Vision Corp.

A bisphosphonate salt was microencapsulated into a biodegradable star-branched D,L-lactide-glycolide-D-glucose terpolymer using various techniques in an attempt to achieve a drug loading of about 30 wt.%. Techniques employed were a water-in-oil-in-water solvent evaporation microencapsulation technique, solid-in-oil-in-water solvent evaporation microencapsulation technique and a non-aqueous microencapsulation technique based on suspension of the drug in organic solvents. The latter technique was found to provide highly loaded microparticles up to 28 wt.% but unfavourable initial burst release. 36 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; GERMANY; SWITZERLAND; WESTERN EUROPE

Accession no.891547

Item 54

Journal of Microencapsulation 20, No.4, July-Aug.2003, p.489-96 MICROENCAPSULATION OF LIPID NANOPARTICLES CONTAINING LIPOPHILIC DRUG Lee K E; Cho S H; Lee H B; Jeong S Y; Yuk S H Hannam, University; Korea, Research Institute of Chemical Technology; Dae Hwa Pharmaceutical Co.

The preparation of cationic lipid nanoparticles containing a lipophilic drug and its encapsulation into an anionic polymer network by ionic interaction for use as an oral drug delivery system are reported. The lipid nanoparticles serve as the core of a capsule, which is produced from a semi-interpenetrating polymer network of sodium alginate and hydroxypropylmethylcellulose. Satisfactory drug release is achieved through control of the composition of the capsule material and environmental pH. 14 refs.

KOREA

Accession no.891545

Item 55

Journal of Macromolecular Science C C43, No.2, 2003, p.187-221 CONTROLLED DELIVERY OF DRUGS FROM ALGINATE MATRIX

Shilpa A; Agrawal S S; Ray A R New Delhi,College of Pharmacy; Indian Institute of Technology; All India Institute of Medical Sciences

A review is presented on the controlled delivery of drugs from alginate matrices over the period 1948 to 2002. It deals with the sources, extraction, structure and properties of alginate, preparation of alginate particulates and controlled drug delivery from alginate matrices. 166 refs. INDIA

Accession no.891512

Item 56

TECH XXVI: LEARN TO SUCCEED. Proceedings of a conference held Washington, DC, 5th-9th May 2003. Northbrook, 11., 2003, p.267-7, 28cm, 012 EFFECT OF NON-FUNCTIONAL/NON-REACTIVE PRESSURE SENSITIVE ADHESIVES IN TRANSDERMAL DRUG DELIVERY SYSTEMS

Kanios D P; Hartwig R L Noven Pharmaceuticals Inc. (Pressure Sensitive Tape Council)

The results are reported of an investigation into the stability, in-vitro drug delivery and adhesive propertics of drug-in-adhesive transdermal drug delivery systems. These systems are composed of a flexible backing film, a fluoropolymer release liner and "active" adhesives, which vary in their monomeric compositions and functionalities. The adhesives are composed of an acrylic pressure-sensitive adhesive, an amine-compatible silicone pressure-sensitive adhesive and methylphenidate base, as the drug. 4 refs.

USA Accession no.891468

Item 57

Medical Device and Diagnostic Industry 25, No.5, May 2003, p.41/3 CONTACT LENSES USED TO DELIVER EYE DRUGS

A brief report is presented on research being conducted at the University of Florida on the development of contact lenses which could deliver drugs slowly enough to remain in the eye. The delivery mechanism entails encapsulating drugs in nanoparticles that are then mixed into the contact lens matrix during manufacture.

FLORIDA, UNIVERSITY USA Accession no.891194

Item 58

Reactive and Functional Polymers 55, No.2, 2003, p.197-210 DYNAMIC RELEASE OF RIBOFLAVIN FROM A

COLON-TARGETED DELIVERY DEVICE: AN IN VITRO STUDY

Bajpai S K; Sonkusley J Jabalpur,Government Autonomous Science College; Jabalpur,Kalaniketan Polytechnique College

The preparation of a pH-sensitive hydrogel composed of poly(N-vinyl-2-pyrrolidone) and poly(acrylamide-coitaconic acid) is described and the release of vitamin B2 therefrom as a function of release media pH is reported. The effects of the initial loading of the drug, pH, itaconic acid content and sample thickness on drug release are evaluated and the kinetics of swelling are compared with drug release. The mechanism of drug release is also considered. 36 refs.

INDIA

Accession no.889770

Item 59

Biomaterials 24, No.19, 2003, p.3311-31 BIOCOMPATIBILITY OF IMPLANTABLE SYNTHETIC POLYMERIC DRUG CARRIERS. FOCUS ON BRAIN BIOCOMPATIBILITY Fournier E; Passirani C; Montero-Menei C N; Benoit J P INSERM

A review is given of classic foreign body responses to polymeric drug delivery devices with emphasis on the central nervous system response. In vivo biocompatibility studies of implanted drug carriers are summarised to illustrate the behaviour of different classes of polymers and the methodologies used to evaluate their tolerance. 150 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; FRANCE; WESTERN EUROPE

Accession no.889523

Item 60

Journal of Macromolecular Science A A40, No.3, 2003, p.265-92 CONTROLLED RELEASE OF A DIGESTIVE ENZYME FROM A SWELLABLE SEMI-INTERPENETRATING POLYMER NETWORK (IPN)

Bajpai A K; Bhanu S Jabalpur, Government Autonomous Science College

A novel interpenetrating polymer network (IPN) of polyethylene glycol, polyvinyl alcohol and polyacrylamide is prepared and its potential for sorption and delivery of diatase, a digestive enzyme, is evaluated. The effects of experimental parameters such as varying chemical composition of the IPN, percent loading of diatase, pH and temperature of the release medium and molecular weight of PEG are investigated on the release dynamics of the diatase. On the basis of Fick's equation, the diffusional exponent (n) and diffusion (D) are evaluated for different IPN compositions. From the kinetic parameters data, an attempt is made to explore the nature of the mechanism of the release process of diastase. The IPNs are characterised by IR and examined for zero-order release behaviour of loaded enzyme. 39 refs. INDIA

Accession no.889264

Item 61

Polymer Preprints. Volume 43. Number 2. Fall 2002.
Papers presented at the ACS meeting held Boston, Ma., 18th-22nd Aug.2002.
Washington, DC, ACS, Div.of Polymer Chemistry, 2002, p.675-6, 28cm, 012
DRUG-ELUTING POLYMER COATINGS FOR CARDIAC STENTS
Callistri-Yeh M; Rosebrough S; Chamberlain A; Donish W; Whitbourne R
STS Biopolymers Inc.
(ACS,Div.of Polymer Chemistry)

A commercial hybrid polymer coating system is described which may be applied to most materials currently used in medical devices. The coating may contain several components, including cellulose esters, polyurethanes, poly(vinyl pyrrolidone)s, poly(methyl methacrylate)s and poly(hydroxyethyl methacrylate)s. The coatings are non-crosslinked and are used to passively entrap drugs, so providing a controlled, localised drug delivery system. Elution profiles for different drugs from the same coating formulation are given. It is shown that the elution time for a given drug is dependent upon the hydrophilicity of the polymer. The time for Paclitaxel was varied between 3 and 10 days in this way. 5 refs.

USA Accession no.889158

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Item 62

Polymer Preprints. Volume 43. Number 2. Fall 2002. Papers presented at the ACS meeting held Boston, Ma., 18th-22nd Aug.2002.

Washington, DC, ACS, Div. of Polymer Chemistry, 2002, p.661-2, 27cm, 012

POLYMERIC VEHICLES FOR POTENTIAL NERVE REGENERATION THERAPIES

Marra K G; Waddell R; Collins K; Doctor J S Carnegie-Mellon University (ACS,Div.of Polymer Chemistry)

A method for encapsulation of nerve growth factor in microspheres of a copolymer of lactic and glycolic acids, and incorporation of these into a polyvinyl alcohol coating to produce tissue engineered scaffolds, is presented. Adherence to, and proliferation on, porous collagen microcarriers, and extension of neurites from the cells were examined using scanning electron microscopy. 11 refs.

USA Accession no.888851

Item 63 Polymer News 28, No.5, May 2003, p.150-3 POLYMERS IN DRUG DELIVERY Aminabhavi T M; Yenkar P S; Kulkarni A R Karnatak University

Stimuli-responsive polymers and blends thereof for ophthalmic drug delivery systems are reviewed. These include polyacrylic acid, temperature sensitive polymers, which are convertible into gels at body temperature, dual responsive polymers, ion-sensitive polymers, such as alginates, and enzyme-sensitive polymers, such as xanthan gum. 26 refs.

INDIA

Accession no.888762

ltem 64

Dordrecht, Kluwer Academic Publishers, 2001, pp.xviii, 451, ISBN 0306464721, 25cm, 6S BIOMEDICAL POLYMERS AND POLYMER THERAPEUTICS

Pisa, University; Niihama, Technical College; Trento, University; Virginia, Commonwealth University; Hebrew University of Jerusalem Edited by: Chiellini E; Sunamoto J; Migliaresi C; Ottenbrite R M; Cohn D

The chapters in this book are based on presentations made at the Third International Symposium on Frontiers in Biomedical Applications in conjunction with the Polymer Therapeutics Symposium (1999). Topics are divided into the following three parts: Part 1: Biomedical Polymers and Polymer Therapeutics; Part 2: Polymers in Diagnosis and Vaccination; Part 3: Polymers in Gene Therapy. Topics within individual chapters include: DDS in cancer chemotherapy; Polymeric hydrogels in drug release; composite materials as scaffolds for tissue engineering, Synthetic peptide and their polymers as vaccines. EUROPE-GENERAL; EUROPEAN COMMUNITY; EUROPEAN UNION; NETHERLANDS; WESTERN EUROPE; WORLD Accession no.888358

Item 65

Polymer Degradation and Stability 80, No.2, 2003, p.199-202 **PREPARATION OF NEW BIODEGRADABLE POLYURETHANES AS A THERAPEUTIC AGENT**

Mahkam M; Sharifi-Sanjani N Tabriz, Azarbaijan University; Tehran, University

Biodegradable PUs and polyether-urethanes having hydrolytically labile morphine groups as therapeutic agent were prepared by reacting 1,4-diisocyanatocubane(DICC) with morphine. Cubylamines and cubylmethylamines are of interest as antiviral agents. Polyether-urethanes containing morphine were prepared by reacting polyethylene glycol with an excess of DICC to give a prepolymer which was reacted with morphine, which contained two hydroxyl groups. The structure of the polymers was confirmed by FTIR and PMR spectroscopies. The hydrolysis of drug-polymer conjugates was carried out in cellophane membrane dialysis bags containing aqueous buffer solution of pH 8 at 37C. UV spectroscopy was used to show that both 1,4-diaminocubane(DAC) and morphine were released by hydrolysis of the PU segments. The PU drug conjugates had longer duration of activity, due to slow release of DAC and morphine. 18 refs.

IRAN

Accession no.887503

Item 66

Journal of Microencapsulation 20, No.3, May-June 2003, p.361-74 BRIMONIDINE FORMULATION IN POLYACRYLIC ACID NANOPARTICLES FOR OPHTHALMIC DELIVERY De T.K.: Rodman D.I.: Holm B.A.: Prasad P.N.: Bergey F

De T K; Rodman D J; Holm B A; Prasad P N; Bergey E J New York, University

A formulation of brimonidine loaded in polyacrylic acid nanoparticles was prepared for potential delivery in ophthalmic therapy. The polymers were subjected to biocompatibility tests using cell culture techniques. Drug release studies are described. 58 refs.

Accession no.886797

Item 67 Journal of Microencapsulation 20, No.3, May-June 2003, p.289-302

IBUPROFEN-LOADED ETHYLCELLULOSE/ POLYSTYRENE MICROSPHERES. AN APPROACH TO GET PROLONGED DRUG RELEASE WITH REDUCED BURST EFFECT AND LOW ETHYLCELLULOSE CONTENT Saravanan M; Bhaskar K; Rao G S; Dhanaraju M D

Chennai, Vel's College of Pharmacy

Details are given of the development of ethyl cellulose microspheres for prolonged drug delivery with reduced burst effect. Ethyl cellulose microspheres loaded with ibuprofen were prepared with and without PS. Characterisation was undertaken using drug loading measurements, FTIR, DSC and SEM. In vitro release studies were performed to determine the influence of PS on ibuprofen release. 15 refs.

INDIA

Accession no.886793

Item 68

Journal of Materials Science:Materials in Medicine 14, No.2, Feb.2003, p.109-12

DEVELOPMENT OF A POLYMER STENT WITH SHAPE MEMORY EFFECT AS A DRUG DELIVERY SYSTEM

Wache H M; Tartakowska D J; Hentrich A; Wagner M H

Berlin, Technical University

Details are given of the use of the shape memory properties of PU in the design of a fully polymeric vascular endoprosthesis. The possibility of using the stent as a drug delivery system is discussed. 15 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; GERMANY; WESTERN EUROPE

Accession no.885929

Item 69

Biomaterials 24, No.12, 2003, p.2053-9 NEW MICELLE-LIKE POLYMER AGGREGATES MADE FROM PEI-PLGA DIBLOCK COPOLYMERS. MICELLAR CHARACTERISTICS AND CELLULAR UPTAKE Nam Y S; Kang H S; Park J Y; Park T G; Han S-H; Chang I-S

Korea, Advanced Institute of Science & Technology

Details are given of the preparation of new amphiphilic block copolymers based on oligomeric polyethyleneimine and lactide-glycolide copolymers. The formation of micelle-like aggregates was examined. The cellular uptake of the aggregates was compared with that of plain lactideglycolide copolymer nanoparticles by using confocal microscopy. Potential applications for new drug carriers are mentioned. 22 refs.

KOREA Accession no.885865

Item 70 Biomaterials 24, No.13, 2003, p.2287-93 NEW SYNTHETIC BIODEGRADABLE POLYMERS AS BMP CARRIERS FOR BONE TISSUE ENGINEERING Saito N; Takaoka K

Shinshu, University; Osaka, City University

Details are given of the synthesis of polylactic acid and its derivatives as carriers for bone morphogenetic proteins. The carrier materials secured the proteins in the local areas, diffused them and also provided scaffolding for the newly formed bone. Control of the induced bone mass was determined. 52 refs.

JAPAN

Accession no.885838

Item 71

Polymer Preprints. Volume 43. Number 2. Fall 2002. Papers presented at the ACS meeting held Boston, Ma., 18th-22nd Aug.2002.

Washington, DC. ACS, Div. of Polymer Chemistry, 2002, p.808-9, 28cm, 012

HYDROGEL/ENZYME DRUG DELIVERY OSCILLATOR

Dhanarajan A P; Misra G P; Siegel R A Minnesota,University (ACS,Div.of Polymer Chemistry)

Details are given of the preparation of an isopropyl acrylamide-methacrylic acid copolymer hydrogel membrane for the pulsatile release of gonadotropin releasing hormone. Factors affecting the prevention of oscillations from occurring are presented. Preliminary results regarding pH-sensitive swelling of the membranes are discussed. 7 refs.

USA

Accession no.884165

Item 72

Polymers for Advanced Technologies 13, No.10-12, Oct.-Dec.2002, p.1006-18 ENZYMATICALLY CONTROLLED RESPONSIVE DRUG DELIVERY SYSTEMS Goldbart R; Traitel T; Lapidot S A; Kost J Ben-Gurion University of the Negev

Two approaches are discussed for the preparation of enzymatically controlled drug delivery systems: a calciumresponsive biodegradable drug delivery system based on a mixture of starch with HPMC (hydroxypropyl methyl cellulose ether) (biodegradable) and the starch hydrolytic enzyme, alpha-amylase, in its non-active form; and a glucose responsive insulin delivery system based on the hydrogel poly(2-hydroxyethyl methacrylate-co-N,Ndimethylaminoethyl methacrylate), with entrapped glucose oxidase, catalase and insulin. In both systems, the sensitivity to a trigger molecule (calcium or glucose) is achieved by incorporation of a specific enzyme that reacts with the trigger molecule. Based on these interactions, two different enzyme-controlled drug release mechanisms are proposed for responsive drug delivery systems. 42 refs.

ISRAEL

Accession no.882556

Item 73

Polymers for Advanced Technologies 13, No.10-12, Oct.-Dec.2002, p.992-9 **DESIGN OF 'SMART' POLYMERS THAT CAN DIRECT INTRACELLULAR DRUG DELIVERY** Hoffman A S; Stayton P S; Press O; Murthy N; Lackey C A; Cheung C; Black F; Campbell J; Fausto N; Kyriakides T R; Bornstein P Washington,University

One of the important characteristics of biological systems is their ability to change important properties in response to small signals. The molecular mechanisms that biological molecule utilise to sense and respond provide interesting models for the development of 'smart' polymeric biomaterials with biomimetic properties. An important example of this is the protein coat of viruses, which contains peptide units that facilitate the trafficking of the virus into the cell via endocytosis, followed by delivery of the genetic material out of the endosome in to the cytoplasm and from there into the nucleus. Several new types of synthetic polymers have been designed to facilitate intracellular trafficking of drugs. One of these has been to designed to mimic the specific peptides on viral coats that facilitate endosomal escape. Another has been designed to contain pH degradable bonds, facilitating endosomal escape of the drug only after the bonds are degraded at the acidic pHs of the endosomes. Both types of polymer are responsive to the lowered pH within endosomes, leading to disruption of the endosomal membrane and release of important biomolecular drugs such as DNA, RNA, peptides and proteins to the cytoplasm before they are trafficked to lysosomes and degraded by lysosomal enzymes. Work on the design, synthesis and action of such smart, pH-sensitive polymers is reviewed. 25 refs.

USA

Accession no.882554

Item 74

Reactive and Functional Polymers 54, No.1-3, 2003, p.5-16 FUNCTIONALIZED POLYSULFONE AS A NOVEL AND USEFUL CARRIER FOR IMMUNIZATION AND ANTIBODY DETECTION Arad-Yellin R; Firer M; Kahana N; Green B S Weizmann Institute of Science; Israel,College of Judea & Samaria

Polysulphone was used, via its carboxylated derivative, as a carrier vehicle for low molec.wt. compounds

(haptens). The synthesis and characterisation of conjugates of carboxylated polysulphone(I) coupled to a relatively non-immunogenic aliphatic hapten(II, an analogue of sulphur mustard) or an aromatic hapten(III) and various intermediates in their syntheses were studied. Immunisation with I, II and III gave anti-hapten antibodies and provided evidence for significant adjuvant activity by I and related compounds. 46 refs.

ISRAEL

Accession no.882271

Item 75

Journal of Biomedical Materials Research 64A, No.4, 15th March 2003, p.638-47 POLYMERIC MATRICES BASED ON GRAFT COPOLYMERS OF PCL ONTO ACRYLIC BACKBONES FOR RELEASING ANTITUMORAL DRUGS

Abraham G A; Gallardo A; San Roman J; Fernandez-Mayoralas A; Zurita M; Vaquero J CSIC

Graft copolymers of polycaprolactone on polydimethyl acrylamide, PMMA or on their copolymers were synthesised and characterised by proton NMR, DSC, and size exclusion chromatography. The copolymers were examined for use as drug delivery systems for the release of low molecular weight glycosides. Data are presented for swelling, degradation and drug release experiments. 23 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE

Accession no.882047

Item 76

Journal of Biomaterials Science: Polymer Edition 14, No.1, 2003, p.87-102 MOLECULAR WEIGHT DISTRIBUTION CHANGES DURING DEGRADATION AND RELEASE OF PLGA NANOPARTICLES CONTAINING EPIRUBICIN HCL Birnbaum D T; Brannon-Peppas L Biogel Technology Inc.; Texas, University

The molecular dynamics of the degradation process of lactic acid-glycolic acid copolymer nanospheres were investigated. The MWD of the copolymers was determined as a function of time as degradation progressed. The degradation of nanospheres containing epirubicin was also analysed. 18 refs.

USA

Accession no.882026

ltem 77

PIMS 2000. Proceedings of the Ninth International Conference on Polymers in Medicine and Surgery, held Krems, Austria, 11th-13th Sept.2000. London, IOM Communications Ltd., 2000, Paper 46, p.417-24, 21cm, 012

VESICLES WITH HYDROPHILIC SURFACE POLYMERS FOR DRUG DELIVERY

Einzmann M; Binder W H; Gruber H Vienna, University of Technology (Institute of Materials)

Details are given of the synthesis of telechelic lipidpolyacetylethylene imine conjugates for potential applications in drug delivery. Emphasis was placed on the preparation of polymers with defined chain length. 17 refs. AUSTRIA; EUROPEAN UNION; WESTERN EUROPE

Accession no.882001

Item 78

PIMS 2000. Proceedings of the Ninth International Conference on Polymers in Medicine and Surgery, held Krems, Austria, 11th-13th Sept.2000.

London, IOM Communications Ltd., 2000, Paper 45, p.410-6, 21cm, 012

NOVEL IMPLANTABLE DRUG DELIVERY SYSTEM FOR CANCER THERAPY

Batyrbekov E; Iskakov R; Zhubanov B Almaty,Chemical Sciences Institute (Institute of Materials)

Details are given of the development of novel implantable drug delivery systems based on segmented polyurethanes for the treatment of cancer diseases. Correlations between polymer molecular structure and release rate of vincristine are discussed. 7 refs.

KAZAKHSTAN

Accession no.882000

Item 79

PIMS 2000. Proceedings of the Ninth International Conference on Polymers in Medicine and Surgery, held Krems, Austria, 11th-13th Sept.2000.

London, IOM Communications Ltd., 2000, Paper 36, p.340-8, 21cm, 012

BONE REGENERATION IN THE PRESENCE OF ALLOPLASTIC VINYL STYRENE BEADS

Sharawy M; Mailhot J; Larke V; Pennington C Georgia, University (Institute of Materials)

Details are given of the use of polyvinyl styrene microspheres as a carrier for local growth factors and other drugs in order to enhance bone regeneration. The fate of the microspheres after implantation was followed. Stained calcified and decalcified sections were studied qualitatively and histomorphometrically. 6 refs.

USA

Accession no.881992

ltem 80

PIMS 2000. Proceedings of the Ninth International Conference on Polymers in Medicine and Surgery, held Krems, Austria, 11th-13th Sept.2000. London, IOM Communications Ltd., 2000, Paper 10, p.89-93, 21cm, 012 CONTROLLED DELIVERY AND PRESENTATION OF BIOACTIVE MOLECULES USING BIODEGRADABLE SYNTHETIC

USING BIODEGRADABLE SYNTHETIC POLYMERS Coombes A G A

Aston,University (Institute of Materials)

Details are given of the design and formulation strategies for polypeptide drug delivery systems. Mention is made of immobilisation of growth factors and cell adhesion using lactide-glycolide copolymer microspheres and also the use of microporous polycaprolactone in wound healing. 7 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.881976

Item 81

Journal of Materials Science:Materials in Medicine 13, No.12, Dec.2002, p.1259-63 IN VITRO MECHANICAL AND DRUG RELEASE PROPERTIES OF BIOABSORBABLE CIPROFLOXACIN CONTAINING AND NEAT SELF-REINFORCED P(L/DL)LA 70/30 FIXATION SCREWS

Veiranto M; Tormala P; Suokas E Tampere, University of Technology; Bionx Implants Ltd.

Osteomyelitis is inflammation of the bone caused by a pathogenic organism. Both its acute and chronic forms are difficult to heal. Antibiotics are still the basic treatment for osteomyelitis. Bioabsorbable ciprofloxacin containing bone fixation screws based on self reinforced (SR) copolylactide P(L/DL)LA 70/30 are developed for local treatment of bone infections. These screws gradually release ciprofloxacin during the in vitro bulk degradation of the matrix polymer and at the same time have sufficient mechanical strength. All the loaded ciprofloxacin is released from the gamma-sterilised screws during 44 in vitro weeks and concentration of the released drug per day remains between 0.06 and 8.7 mu g/ml after the start-up burst peak. 28 refs.

EUROPEAN UNION; FINLAND; SCANDINAVIA; WESTERN EUROPE

Accession no.880579

1tem 82

Journal of Materials Science:Materials in Medicine 13, No.12, Dec.2002, p.1251-7 ACRYLIC-PHOSPHATE GLASSES COMPOSITES AS SELF-CURING CONTROLLED DELIVERY SYSTEMS OF ANTIBIOTICS

Ferndandez M; Mendez J A; Vazquwz B; Roman J S; Ginebra M P; Gil F J; Manero J M; Planell J A CSIC; Barcelona, Universidad Politecnica de Catalunya

New antibiotic delivery systems based on self-hardening methyl methacrylate (MMA)/PMMA systems and phosphate glasses (PG) in the system P2O5-CaO-Na2O are developed. Self-curing formulations are prepared by mixing the solid component containing PMMA beads, different proportions of PG (30-70 wt.%) and vancomycin (5 wt.%) as antibiotic, with the liquid component made of MMA monomer. Dough and setting times increase with content of PG but peak temperature decreases to values well below to guarantee the chemical stability of the antibiotic drug, gentamicin or vancomycin. Mechanical properties of the PMMA/PG composites are evaluated in compression tests, giving rise to values of compressive strength in the range of 100 MPa. The release of vancomycin is analysed in vitro by immersion of samples in phosphate buffer of pH = 7.4. Release profiles are influenced by the content of PG present in the cement. An initial burst of drug release is observed in all cases. The composites with 70 wt.% PG release nearly the total amount of drug loaded in a period of 45 days, and those containing 60 wt.% PG released 70% of the vancomycin in the same period of time. However, either the control of the composite with 30 wt.% PG releases only the 30% of the drug in 10-15 days. The surface of the drug-loaded composites before and after release experiments is analysed by ESEM. The deposition of some aggregates at certain points of the surface is detected for the specimens immersed in buffer phosphate after 45 days. This material is characterised by FTIR and Raman spectroscopy as an amorphous phosphate formed by calcium ortho and pyrophosphates, and indicates an interaction between the hydrated layer at the place of the glass and the surrounding medium. 28 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE

Accession no.880578

Item 83

ACS Polymeric Materials: Science and Engineering. Spring Meeting. Volume 84. Proceedings of a conference held San Diego, Ca., 1st-5th April 2001. Washington, D.C., ACS, Div.of Polymeric Materials Science & Engng., 2001, Paper 450, p.815, 27 cm, 012 **ORAL DELIVERY OF LOW MOLECULAR WEIGHT HEPARIN**

O'Shaughnessy C; Leone-Bay A; Baughman R; Dinh S M Emisphere Technologies Inc.

(ACS, Div.of Polymeric Materials Science & Engng.)

Parenteral low molecular weight heparin (LMWH) is the standard of care for the prevention of deep vein thrombosis in patients undergoing joint replacement surgery. LMWH is administered by injection because it is not absorbed following oral dosing. A group of compounds, called delivery agents, which promote oral absorption when administered individually with LMWH, has been discovered. As part of this programme, the Caco-2 cell model is evaluated as a potential screen for new delivery agents that can increase the oral absorption of therapeutic drugs having low oral bioavailability. A statistically significant correlation is found between Caco-2 results and LMWH plasma levels following dosing in rats. Following identification of lead delivery agents, oral LMWH absorption in rats and monkeys is achieved upon administration of an aqueous solution of the drug in combination with delivery agent. The feasibility of oral LMWH delivery from a solid dose form in dogs has been evaluated. This abstract includes all the information contained in the original article.

USA

Accession no.880239

Item 84

ACS Polymeric Materials: Science and Engineering. Spring Meeting. Volume 84. Proceedings of a conference held San Diego, Ca., 1st-5th April 2001. Washington, D.C., ACS, Div.of Polymeric Materials Science & Engng., 2001, Paper448, p.812-3, 27 cm, 012

DESIGN OF NOVEL PROTEIN HYDROGELS Sakata J K; Shen W; Tirrell D A Amherst,Massachusetts University

(ACS, Div. of Polymeric Materials Science & Engng.)

The capacity of genetic engineering to create new polymeric materials with precisely controlled molecular weight, sequence and structure is explored. Within this context, a group of protein polymers which display characteristics of thermo and pH reversible networks is examined. These triblock protein-polymers are characterised by a water-soluble polyelectrolyte midregion, flanked by two associating leucine zipper domains. A transition between a viscous liquid and an elastic hydrogel can be induced by changing pH or temperature - the associated leucine zipper domains serve as physical crosslinks between individual polymer chains, while the polyelectrolyte mid-block solubilises the aggregates. The macroscopic changes in such hydrogels that result from microscopic changes in the protein architecture are studied, with emphasis on the relation between the length of the polyelectrolyte mid-block and the rheological behaviour of the resulting materials. The mild conditions required for hydrogel formation and the reversibility of the gel-liquid transition make these materials attractive candidates for encapsulation or delivery of molecular and cellular species. 9 refs.

USA

Accession no.880237

Item 85

Polymer Preprints. Volume 43, Number 2. Fall 2002. Papers presented at the ACS Meeting held Boston, Ma., 18th-22nd Aug.2002. Washington, DC, ACS,Div.of Polymer Chemistry, 2002, p.717-8, 28cm, 012

STAR-SHAPED POLY(ETHYLENE GLYCOL MONOMETHACRYLATE) AND POLYGLYCEROL DENDRIMERS AS NEW DRUG DELIVERY SYSTEMS

Ooya T; Lee J; Park K Purdue,University; Japan,Advanced Institute of Science & Technology (ACS,Div.of Polymer Chemistry)

Oligo(ethylene glycol)methacrylate was subjected to atom transfer radical polymerisation using, as macroinitiators, O-isobutyl bromide-monomethoxy-capped oligoethylene glycol and 1,2,3,4,6-penta-O-isobutyryl bromide-alpha-D-glucose, and the resulting polymers, star-shaped polymers and dendrimers characterised by NMR spectroscopy and GPC. An investigation of the effect of monomer unit density on the solubility of paclitaxel, a model poorly water-soluble drug, revealed that both the star and dendritic architectures increased the water solubility of the drug probably as a result of the increased local density of ethylene glycol units in the polymer structures. 6 refs.

JAPAN; USA

Accession no.880071

Item 86

Biomaterials 24, No.8, April 2003, p.1499-506 **RELEASE OF AMOXICILLIN FROM POLYIONIC COMPLEXES OF CHITOSAN AND POLYACRYLIC ACID. STUDY OF POLYMER/ POLYMER AND POLYMER/DRUG INTERACTIONS WITHIN THE NETWORK STRUCTURE**

de la Torre P M; Enobakhare Y; Torrado G; Torrado S Madrid,Universidad Complutense; Madrid,Universidad de alcala

Polyionic complexes of chitosan and polyacrylic acid were prepared in a wide range of copolymer composition and with two kinds of drugs. Release of amoxicillin trihydrate and sodium amoxicillin from these complexes were studied. The swelling behaviour of and solute transport in swellable hydrogels were investigated. 23 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE

Accession no.879733

Item 87

Medical Device Technology 14, No.1, Jan.-Feb.2003, p.12-4 POLYMER COATING TECHNIQUES FOR DRUG-ELUTING STENTS Al-Lamee K; Cook D PolyBioMed Ltd.

It is explained here that a number of approaches are being taken to treat in-stent restenosis, a significant clinical problem. This article is an overview of currently-available methods of delivering drugs from stents and, in particular, reports on a novel polymer coating that can be tailored for the individual drug, and the desired drug-release kinetics. 6 refs.

LOMBARD MEDICAL PLC

EUROPE-GENERAL; EUROPEAN COMMUNITY; EUROPEAN UNION; UK; USA; WESTERN EUROPE Accession no.879592

Accession no.8/9.

Item 88

ACS Polymeric Materials: Science and Engineering. Spring Meeting. Volume 84. Proceedings of a conference held San Diego, Ca., 1st-5th April 2001. Washington D.C., ACS, Div.of Polymeric Materials Science & Engng., 2001, Paper 500, p.897-8, 27cm, 012 SUGAR-INSTALLED POLYMERIC MICELLE FOR A VEHICLE OF AN ACTIVE TARGETING DRUG DELIVERY SYSTEM

Yukio Nagasaki; Kenji Yasugi; Yuji Yamamoto; Atsushi Harada; Kazunori Kataoka Tokyo,Science University; Tokyo,University (ACS,Div.of Polymeric Materials Science & Engng.)

Core-shell micelles made from polylactic acidpolyethylene glycol block copolymer were functionalised at the surface with sugar groups, including glucose, galactose, lactose and mannose moieties. These micelles were investigated as potential vehicles for targeted drug delivery. Simple turbidity investigations were carried out by mixing solutions of the functionalised micelles, and control micelles functionalised with methoxy groups, with the lectins Con A and RCA-1. The Con A lectin was found to interact only with the mannose-functionalised micelles and the RCA-I lectin only with the galactose- or lactosefunctionalised micelles. More detailed investigations were carried out using an affinity column loaded with immobilised RCA-1. Again, the lectin was shown to interact specifically with lactose- or galactosefunctionalised micelles. The interaction of the micelles with the column was inhibited and the micelles released by addition of free galactose, but much larger quantities of free galactose were required for the disaccharide lactose than for the monosaccharide galactose. A very sharp critical inhibition concentration was observed in both cases. This was attributed to a cluster effect of sugar molecules on the micelle surface. A cluster effect was confirmed by the discovery that no interaction was observed when the proportion of functionalised polymer chains was less than 20%, but a very sharp initiation of activity was observed as the functionalisation level was increased between 20% and 30%. 8 refs.

JAPAN

Accession no.879184

Item 89 Macromolecules 35, No.27, 31st Dec.2002, p.9861-7

POLYSACCHARIDES GRAFTED WITH POLYESTERS: NOVEL AMPHIPHILIC COPOLYMERS FOR BIOMEDICAL APPLICATIONS

Gref R; Rodrigues J; Couvreur P Chatenay-Malabry,Centre d'Etudes Pharmaceutiques; Pernambuco,Federal University

Amphiphilic polysaccharides with controlled structure were synthesised by coupling between a carboxylic function present on preformed polyester chains and a hydroxyl group naturally present on polysaccharides. The synthesis of poly(epsilon-caprolactone) monocarboxylic acid (R-PCL-CO2H) was firstly carried out by ring-opening uncatalysed polymerisation of monomer in the presence of a carboxylic acid. R-PCL-CO2H was then reacted with carbonyl diimidazole and the resulting activated intermediate was further reacted with dextran at different molar ratios to obtain amphiphilic copolymers with various hydrophiliclipophilic balance. The coupling reaction was followed by GPC, indicating total conversion. The copolymers were further characterised by GPC, proton NMR and FTIR. Nanoparticles of less than 200 nm, with potential interest for controlled release of bioactive compounds, were prepared using these new materials. 21 refs. BRAZIL; EUROPEAN COMMUNITY; EUROPEAN UNION; FRANCE; WESTERN EUROPE

Accession no.878982

Item 90

Polymer International 51, No.12, Dec.2002, p.1464-72 **BIODEGRADABLE HOLLOW FIBRES CONTAINING DRUG-LOADED NANOPARTICLES AS CONTROLLED RELEASE** SYSTEMS

Polacco G; Cascone M G; Lazzeri L; Ferrara S; Giusti P Pisa, University

A 'multiple' drug delivery system which consisted of hollow microfibres containing drug-loaded nanoparticles was studied. Both fibres and nanoparticles were made of biodegradable polymers, so that the system did not need any surgical operation to be removed. Copolymers of polylactic acid and epsilon-caprolactone were used for the preparation of the fibres through both wet and drywet spinning procedures. Two types of nanoparticles, gelatin and poly(DL-lactide-co-glycolide) nanoparticles, were prepared by simple water-in-oil and oil-in-water emulsions, respectively. The technique used for the preparation of the nanoparticle-filled fibres is described and results of studies of the drug release characteristics of this system are presented and compared with those of the free nanoparticles. 11 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; ITALY; WESTERN EUROPE Accession no.878970

ltem 91

ACS Polymeric Materials:Science and Engineering. Spring Meeting. Volume 84. Proceedings of a conference held San Diego, Ca., 1st-5th April 2001. Washington, D.C., ACS,Div.of Polymeric Materials Science & Engng., 2001, Paper 540, p.970-1, 27cm, 012

MICELLAR DRUG DELIVERY TO DRUG RESISTANT CELLS USING ULTRASONIC ACTIVATION

Rapoport N; Marin A; Muniruzzanian M Utah, University

(ACS, Div. of Polymeric Materials Science & Engng.)

Details are given of the effect of the combination of micellar delivery and ultrasound on drug uptake by drug-resistant ovarian cancer cells. The micelles were formed using ethylene oxide-propylene oxide copolymers loaded with doxorubicin. 11 refs.

Accession no.878865

ltem 92

Journal of Microencapsulation 19, No.6, Nov.-Dec.2002, p.761-5 MICROSPHERE ENTRAPPED BEE-VENOM PHOSPHOLIPASE A2 RETAINS SPECIFIC IGE BINDING CAPACITY: A POSSIBLE USE FOR ORAL SPECIFIC IMMUNOTHERAPY

Guerin V; Dubarry M; Robic D; Brachet F; Rautureau M; Andre C; Bourbouze R; Tome D Paris-Grignon,Institut National d'Agronomie; CNRS; Laboratoire Stallergenes SA

The feasibility of using biodegradable poly(D,L-lactideco-glycolide) microspheres produced by double emulsion solvent evaporation as an oral delivery system for bee venom phospholipase A2 was evaluated. It was found that the microspheres displayed optimal particle size for Peyer's patches uptake and that the integrity of the entrapped bee venom phospholipase A2 retained its specific IgE binding capacity, indicating the suitability of the microspheres as a potential delivery system for this application. 8 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; FRANCE; WESTERN EUROPE

Accession no.878428

Item 93

Journal of Applied Polymer Science 87, No.6, 7th Feb.2003, p.1016-26 SOLUTE AND SOLVENT EFFECTS ON THE THERMORHEOLOGICAL PROPERTIES OF POLYOXYETHYLENE-POLYOXYPROPYLENE BLOCK COPOLYMERS. IMPLICATIONS FOR PHARMACEUTICAL DOSAGE FORM DESIGN Jones D S; Brown A F; Woolfson A D Belfast, Queen's University Details are given of the equilibrium thermorheological properties of oxyethylene-oxypropylene copolymers. The effect of molecular weight, solute and solvent composition on the structural properties was investigated. The efficacy of these copolymers in drug delivery systems is discussed. 32 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.877003

Item 94

Polymer Science Series A 44, No.10, Oct.2002, p.1094-8 POLYCOMPLEXES AND FILM COMPOSITIONS BASED ON HYDROXYETHYLCELLULOSE AND POLY(ACRYLIC ACID) AS SYSTEMS FOR THE CONTROLLED RELEASE OF LEVOMYCETIN Yin Jing Bo; Khutoryanskiy V V; Mun G A; Nurkeeva Z S

Jilin,Institute of Technology; Kazakh,State University

Complex formation between polyacrylic acid and hydroxyethylcellulose in aqueous solutions was studied by turbidimetric and viscometric measurements. It was shown that the process under examination afforded nonstoichiometric and stoichiometric complexes. The critical pH values of complex formation were determined over a wide range of molec.wts. of polyacrylic acid. It was shown that, in principle, multilayer polymer films based on polyacrylic acid and hydroxyethylcellulose could be useful for the controlled release of an antibiotic, levomycetin. 21 refs. (Full translation of Vys.Soed.A, 44, No.10, 2002, p.1826-32)

CHINA; KAZAKHSTAN Accession no.876808

Item 95

Popular Plastics and Packaging 47, No.12, Dec.2002, p.74-9 MEDICAL USE OF POLYMERS - USE OF POLYMERS IN TABLET COATINGS Kalaskar D M

Nagpur,Laxminarayan Institute of Technology

The use of polymers in tablet coatings is discussed. Earlier sugar, gelatin and other natural products were used for tablet coatings, but due to tedious and highly skilled manpower requirements, there is a need for simple, but more efficient coating methods. Film coating has overcome most of the disadvantages of previous techniques and also adds to aesthetics of the tablet. Controlled drug release is possible due to use of polymers and with the use of water soluble polymers. This paper discusses briefly the older and recent techniques of tablet coatings and gives details of various polymers and coating raw materials. 12 refs.

INDIA Accession no.874779

Item 96

Polymer Preprints. Volume 41, Number 1. Proceedings of a conference held San Fracisco, Ca., March 2000. Washington D.C., ACS, Div.of Polymer Chemistry, 2000, p.1012-3, 28cm, 012

FACTORS WITH IMPACT ON THE SUCCESS OF PROTEIN AND VIRUS PEGYLATION

Fisher D; Buckley B; Delgado C; Francis G; Goodwin C; Kippen A; Malik F; Marlow S PolyMASC Pharmaceuticals plc (ACS,Div.of Polymer Chemistry)

PEGylation, the covalent attachment of polyethylene glycol to other molecules, is becoming mainstream technology for the delivery of protein and peptide pharmaceuticals. Increased circulation time and bioavailability, reduced immunogenicity and antigenicity, increased resistance to proteolysis are well known benefits. However, the full potential of PEGylation has been severely limited by a substantial loss of biological activity observed for many targets, especially small delicated proteins. Such loss of bioactivity was initially attributed to the presence of the attached PEG chains. However, it has been shown that this is not necessarily the case and that it is related to the chemistry used. A mild PEGylation method is applied using tresyl monomethoxy PEG (TMPEG) to couple PEG to the target via a stable secondary amine bond, without intervening linker. 'Linkerless' mild coupling and/or this chemistry are demonstrably of advantage. Surprisingly, significant additional improvements in retained bioactivity and other features of the PEGylation reaction are achieved by making a series of changes in the manufacturing process for TMPEG ('biological optimisation'). This technology allows the preparation of PEGylated cytokines and PEGylated viruses with full retention of biological activity/infectivity. This cannot be achieved by using different chemistry or non-biologically optimised TMPEG methods. 8 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE Accession no.873742

Item 97

Polymer Preprints. Volume 41, Number 1. Proceedings of a conference held San Fracisco, Ca., March 2000. Washington D.C., ACS, Div.of Polymer Chemistry, 2000, p.1002-3, 28cm, 012

SYNTHESIS OF A POLYMERIC PRECURSOR BY ATRP FOR CONVERSION TO POLYMER-DRUG CONJUGATES

Godwin A; Muller A H E; Brocchin S London, University; Bayreuth, University (ACS, Div. of Polymer Chemistry)

Covalent conjugation of a cytotoxic drug to a soluble, biocompatible polymer can improve the efficacy of the drug. The three main parts of a polymer-drug conjugate are polymer, pendent chain linker and conjugated drug.
Taken together these components produce a distinct profile of properties typical of polymer-drug conjugates. The polymer is not a mere carrier for the pharmacologically active drug since its properties are directly responsible for altering the biodistribution of the pharmacologically active molecule (e.g. doxorubicin). Unlike most low molecular weight drugs, polymer-drug conjugates exhibit prolonged blood circulation. This can alter the biodistribution and the conjugate can preferentially permeate into diseased tissue, which tends to be more permeable and able to retain large molecules than healthy tissue. While the concept entailing the appropriate conjugation of a drug to a polymer for treatment of cancer is tangible and been proven viable in a clinical environment, future widespread use of polymer conjugates will depend on therapeutic agents fulfilling stringent requirements considered by regulatory authorities for any new drug entity. As polymer drug conjugates tend to be structurally non-uniform with respect to molecular weight distribution, obtaining knowledge of all chemical species required during regulatory approval is difficult. Polymers with narrow molecular weight distribution are needed for study. Also, for a given therapeutic candidate during pre-clinical development, it is necessary to study many analogues to optimise properties. Future development of polymer-drug conjugates will thus depend on practical synthetic routes using appropriate common polymer precursors. The synthesis of polymer to be used as a polymeric precursor to prepare polymer-drug conjugates is described. 16 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; GERMANY; UK; WESTERN EUROPE

Accession no.873737

Item 98

Polymer Preprints. Volume 41, Number 1. Proceedings of a conference held San Fracisco, Ca., March 2000. Washington D.C., ACS, Div.of Polymer Chemistry, 2000, p.992-3, 28cm, 012

IN VITRO AND IN VIVO ANTI-TUMOUR ACTIVITIES OF NANOPARTICLES BASED ON DOXORUBICIN-PLGA CONJUGATES

Yoo H S; Park T G

Korea, Advanced Institute of Science & Technology (ACS, Div. of Polymer Chemistry)

It has previously been reported that various drug molecules can be conjugated to the terminal end group of poly(D,L-lactic-co-glycolic acid) PLGA and they can be formulated into microspheres or nanoparticles. The drug-PLGA conjugation approach has several advantages. However, the conjugation is accomplished by noncleavable, carbamate linkage, which cannot easily be broken under physiological condition. Doxorubicin is conjugated to PLGA by an ester linkage that can be cleavable under physiological condition. The nanoparticles containing doxorubicin-PLGA conjugates are characterised in terms of size, zeta potential and drug loading. In vitro sustained release profiles of doxorubicin from nanoparticles are examined by conjugating two different molecular weights of PLGA. In vitro anti-cancer activity of doxorubicin nanoparticles is determined using a HepG2 cell line. Uptake of nanoparticles into HepG2 cells is quantitated by a flow cytometry method and visualised by using confocal microscopy. In vivo antitumour activity is also studied. 6 refs. KOREA

Accession no.873732

Item 99

Biomaterials 24, No.1, Jan.2003, p.79-87 GENTAMICIN RELEASE FROM MODIFIED ACRYLIC BONE CEMENTS WITH LACTOSE AND HYDROXYPROPYLMETHYLCELLULOSE Virto M R; Frutos P; Torrado S; Frutos G Madrid,Universidad Complutense

Modified PMMA bone cement formulations were prepared by including different proportions of gentamicin and release modulators such as lactose or hydroxypropylmethylcellulose. Surface aspect, gentamicin release and porosity of these modified formulations were studied by SEM, dissolution studies and mercury intrusion porosimetry. 21 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE

Accession no.873562

Item 100

Biomaterials 24, No.1, Jan.2003, p.11-8 HYDROGEL PREPARED BY IN SITU CROSSLINKING OF A THIOL-CONTAINING POLYETHYLENE GLYCOL-BASED COPOLYMER. A NEW BIOMATERIAL FOR PROTEIN DRUG DELIVERY Qiu B; Stefanos S; Ma J; Lalloo A; Perry B A; Leibowitz M I: Sinko P I: Stein S

Leibowitz M J; Sinko P J; Stein S Rutgers, University; New Jersey, State University; TheraPort BioSciences Inc.; New Jersey, University of Medicine and Dentistry

A new polyethylene glycol-based copolymer containing multiple thiol groups was crosslinked to form a hydrogel. The possibilities of using this hydrogel for sustained protein drug delivery are reported. Data are given for the in vitro release of fluorescein-labelled bovine serum albumin and erythropoietin. 23 refs.

USA

Accession no.873559

Item 101

Polymer Preprints. Vol.41, Number 1. Proceedings of a conference held San Francisco, Ca., March 2000. Washington D.C., ACS, Div.of Polymer Chemistry, 2000, p.766-7, 28 cm, 012

VARIOUS INTERACTION OF DRUGS WITH THE CROSS-LINKED HYALURONATE GEL

Yomota C; Okada S

Japan, National Institute of Health Sciences (ACS, Div.of Polymer Chemistry)

Hyaluronate (HA) is a glycosaminoglycan polysaccharide composed of N-acetyl-D-glucosamine and D glucuronate, which possesses a carboxyl group per disaccharides. HA is extensively distributed in the connective tissues, the synovial fluid of joints and the vitreous humour of the eye. It is well known that hyaluronate (HA) plays an important role as a molecular filter, shock absorber and support structure for collagen fibrils. HA has been used as a biomedical polymer for treatment of osteoarthritis by intraarticular administration and in ophthalmic surgery, such as anterior segment surgery. Against this background, hyaluronate is one of the polysaccharides most successfully applied to biomedical applications. It was previously reported that crosslinked HA gel's ability to contain other substances is not strong enough to use a pharmaceutical reservoir. However, it has also been reported that some anionic polymer gels bind cationic surfactants, and some kinds of drugs are known to have properties similar to cationic surfactants. The interaction of the crosslinked HA gel and cationic drugs is studied, and the release of incorporated substances is further investigated. 11 refs.

JAPAN

Accession no.870640

Item 102

Polymer Preprints. Vol.41, Number 1. Proceedings of a conference held San Francisco, Ca., March 2000. Washington D.C., ACS, Div. of Polymer Chemistry, 2000, p.735-6, 28 cm, 012

COLESEVELAM HYDROCHLORIDE: SYNTHESIS AND TESTING OF A NOVEL POLYMER GEL PHARMACEUTICAL

Holmes-Farley S R; Mandeville W H; Miller K L; Ward J P J; Sacchiero B; Maloney C; Brochu S; Rosenbaum D; Goldberg D; Norton K A; Chen X; Mazzeo J R

GelTex Pharmaceuticals Inc. (ACS,Div.of Polymer Chemistry)

Colesevelam hydrochloride (Cholestagel) is a novel polymeric gel designed to treat high cholesterol by binding to bile acids in the gastrointestinal tract. The gel itself contains both cationic and hydrophobic sites, making it ideally suited to bind to anionic, hydrophobic bile acids. The bile acids bound to the polymer gel are subsequently excreted in the faeces. Like previous bile acid sequestrants, its cholesterol lowering action is derived from the body's use of cholesterol in the biosynthesis of bile acids to replace those that are excreted. These previous sequestrants, however, have suffered from poor potency, requiring large doses of 12-24 g/day to achieve their actions. Colesevelam has successfully completed eight human clinical trials, both in monotherapy and in conjunction with statins, currently the standard in cholesterol lowering medications. These trials show that colesevelam is a highly potent bile acid sequestrant. A new drug application has been filed with the US FDA, and a decision is anticipated in the second half of 2000. During the discovery efforts that resulted in colesevelam, a wide range of polymers were examined for bile acid binding in vitro and in vivo. The synthesis of the polymer, and the in vivo testing that resulted in its selection for drug development, are described. 2 refs.

USA

Accession no.870624

Item 103

Journal of Microencapsulation 19, No.5, Sept.-Oct. 2002, p.603-14 ALGINATE-POLYLYSINE-ALGINATE MICROCAPSULES: EFFECT OF SIZE REDUCTION ON CAPSULE PROPERTIES

Strand B L; Gaserods O; Kulseng B; Espevik T; Skjak-Braek G

Norwegian University of Science & Technology; FMC Biopolymers AS

An investigation was carried out into factors governing the size of alginate beads produced by a high voltage electrostatic system and the influence of the size of the beads on the stability and permeability of alginatepolylysine-alginate capsules used as a bio-artificial pancreas in the treatment of diabetes mellitus. The effect of the encapsulation process on the islets of Langerhans was also examined by an investigation of insulin release from the microcapsules and measurement of the protruding islets. 38 refs.

NORWAY; SCANDINAVIA; WESTERN EUROPE *Accession no.870435*

Item 104

Polymer Preprints. Volume 41, Number 1. Proceedings of a conference held San Francisco, Ca., March 2000. Washington D.C., ACS, Div.of Polymer Chemistry, 2000, p.6-7, 28cm, 012

SYNTHESIS AND CHARACTERISATION OF PEG-EDTA BIDENTATES AS ORAL DRUG SYSTEMS

Ottenbrite R M; Hu B

Virginia,Commonwealth University (ACS,Div.of Polymer Chemistry)

Bidentates of di(alkylsalicoyl) (DAS) and ethylenediaminetetraacetic acid, with different alkyl chain lengths in the DAS were prepared and conjugated with polyethylene glycol. The materials were structurally characterised using nuclear magnetic resonance spectroscopy and were submitted for evaluation as oral drug delivery systems in vitro and in vivo. 14 refs.

USA

ltem 105

Journal of Microencapsulation 19, No.4, July-Aug.2002, p.473-84 BIODEGRADABLE BROMOCRYPTINE MESYLATE MICROSPHERES PREPARED BY A SOLVENT EVAPORATION TECHNIQUE. I. EVALUATION OF FORMULATION VARIABLES ON MICROSPHERES CHARACTERISTICS FOR BRAIN DELIVERY

Arica B; Kas H S; Orman M N; Hincal A A Hacettepe,University; Ankara,University

Microspheres of bromocryptine mesylate (an anti-Parkinsonian agent) were prepared using the biodegradable polymers poly-L-lactide, poly-D,L-lactide and poly(D,L-lactide-co-glycolide) using the solvent evaporation technique. The formulation study using a 3(2) factorial design allowed development of the optimum formulation in order to proceed to in vivo animal experiments. The microspheres prepared from all three polymers at a polymer concentration of 10% v/v and an emulsifying agent concentration of 0.75% w/v with sodium carboxymethylcellulose:sodium oleate (4:1 w/v) mixture was the optimum formulation, following the evaluation of the response surface diagrams and counter plots. 24 refs.

TURKEY Accession no.868580

Item 106

Journal of Microencapsulation 19, No.4, July-Aug.2002, p.407-13 NOVEL METHOD FOR PREPARATION OF EUDRAGIT RL MICROCAPSULES Satturwar P M; Mandaogade P M; Dorle A K Nagpur,University

A technique for the preparation of Eudragit RL-100 acrylic resin microcapsules was developed, which was based on the principle of solvent evaporation. Diclofenac sodium was used as a model drug for encapsulation. A solution of drug and Eudragit dissolved in acetone-isopropyl alcohol was sprayed in liquid paraffin. The microcapsules obtained were uniform and free flowing particles. The release rate was more sustained by increasing the polymer concentration. The experimental procedure provided a rapid and convenient method for the preparation of Eudragit microcapsules. 8 refs.

ROHM PHARMA GMBH

EUROPEAN COMMUNITY; EUROPEAN UNION; GERMANY; INDIA; WESTERN EUROPE

Accession no.868576

ltem 107

Biomaterials 23, No.23, Dec.2002, p.4449-58 POLYCAPROLACTONE AND POLYCAPROLACTONE-POLYVINYLPYRROLIDONE-IODINE BLENDS

AS URETERAL BIOMATERIALS. CHARACTERISATION OF MECHANICAL AND SURFACE PROPERTIES, DEGRADATION AND RESISTANCE TO ENCRUSTATION IN VITRO Jones D S; Djokic J; McCoy C P; Gorman S P

Belfast,Queen's University

Details are given of the physicochemical properties and in vitro resistance to encrustation of films of polycaprolactone or blends of polycaprolactone with a polyvinylpyrrolidoneiodine mixture. Films were characterised in terms of tensile properties, dynamic mechanical thermal analysis, dynamic contact angle, and SEM. 29 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.868383

Item 108

Macromolecular Symposia No.186, 2002, p.123-8 SYNTHESIS, ELECTROCHEMISTRY AND CYTOTOXICITY OF FERROCENE-CONTAINING POLYASPARTAMIDES AS WATER-SOLUBLE POLYMERIC DRUG CARRIER/DRUG CONJUGATES

Swarts J C

South Africa, University of the Free State

A general strategy towards the syntheses of water-soluble polymeric drug carriers and their drug conjugates is described. Methods of drug uptake by cells, drug release from the polymeric carrier and the relevance of electrochemistry to drug activity of the ferrocenyl group are highlighted. The advantages of these polymeric systems are demonstrated utilising cytotoxicity results of a polyaspartamide-ferrocenyl conjugate. 19 refs. SOUTH AFRICA

Accession no.867464

Item 109

Journal of Biomedical Materials Research 62, No.2, Nov.2002, p.244-53 NOVEL GRAFT PLLA-BASED COPOLYMERS. POTENTIAL OF THEIR APPLICATION TO PARTICLE TECHNOLOGY

Calandrelli L; De Rosa G; Errico M E; La Rotonda M I; Laurienzo P; Malinconico M; Oliva A; Quaglia F CNR; Napoli,Universita

Details are given of the synthesis of biodegradable graft copolymers based on a backbone of polylactic acid grafted with short blocks of polyacrylamide. Emulsion and solution polymerisations were examined. Molecular structures were determined by proton NMR and FTIR and by DSC. Cytotoxicity tests were conducted to assess their biocompatibility. Preliminary results of their potential in controlled release technologies are reported. 17 refs. EUROPEAN COMMUNITY; EUROPEAN UNION; ITALY; WESTERN EUROPE

Item 110 Biomaterials 23, No.22, Nov.2002, p.4425-33 NEW POLYMERIC CARRIERS FOR CONTROLLED DRUG DELIVERY FOLLOWING INHALATION OR INJECTION

Fu J; Fiegel J; Krauland E; Hanes J Johns Hopkins University

Details are given of the synthesis of a new family of etheranhydride copolymers for use in controlled release drug formulations for inhalation. Microparticles containing model drugs were made with sizes suitable for deposition in various regions of the lung following inhalation as a dry powder. 50 refs.

USA

Accession no.866745

Item 111

Biomaterials 23, No.22, Nov.2002, p.4397-404 **DEVELOPMENT AND APPLICATIONS OF INJECTABLE POLYORTHO ESTERS FOR PAIN CONTROL AND PERIODONTAL TREATMENT** Heller J; Barr J; Ng S Y; Shen H-R; Schwach-Abdellaoui K; Gurny R; Vivien-Castioni N; Loup P J;

Baehni P; Mombelli A

AP Pharma; Geneva, University

Details are given of the incorporation of therapeutic agents in polyorthoesters by a mixing procedure. Erosion rates were controlled by varying the amount of latent acid incorporation into the polymer backbone. Toxicology studies are presented. Mention is made of development studies for the controlled release of analgesic agent and for the treatment of periodontitis. 13 refs.

SWITZERLAND; USA; WESTERN EUROPE *Accession no.866742*

Item 112 Advanced Materials 14, No.15, 5th Aug.2002, p.1090-2 MONODISPERSE TEMPERATURE-SENSITIVE MICROCONTAINERS Zha L S; Zhang Y; Yang W L; Fu S K Fudan,University

Hollow microspheres with well-defined structure in the sub-micrometer-range attract increasing interest due to their broad perspectives in confined reaction vessels, drug carriers, protective shells for cells and enzymes, transfection vectors in gene therapy, etc. For such size and shape-invariant microcontainers, however, their permeability is limited and it is difficult to load or to release substances from their interior in a controlled way at the desired target. One promising strategy to solve this problem is to design intelligent microcontainers that can undergo reversible structural transitions with the help of external stimuli. A convenient way to prepare new, thermoresponsive microcontainers based on crosslinked PNIPAM shells. These particles undergo a reversible swelling transition upon changing the temperature of the system. It is expected that this swelling will have considerable influence on the permeability of the shells of these microcontainers, which makes these systems highly attractive for encapsulation and release of biomolecules such as enzymes, proteins or DNA. 12 refs. CHINA

Accession no.866727

Item 113

Polymer 43, No.21, 2002, p.5623-8 A THERMORHEOLOGICAL INVESTIGATION

INTO THE GELATION AND PHASE SEPARATION OF HYDROXYPROPYL METHYLCELLULOSE AQUEOUS SYSTEMS Hussain S; Keary C; Craig D Q M

Queen's University of Belfast; Dow Chemical Co.

Thermal transitions of a range of hydroxypropyl methylcellulose solutions were investigated using thermorheology. Temperature sweeps were performed at a rate of 2C/min between 20 and 90C at 1.0 Hz and at 4.7 Pa and frequency sweeps were carried out at 4.7 Pa. The effects of temperature on solutions containing up to 20% w/v hydroxypropyl methylcellulose were examined and the influence of concentration and substitution on gelation assessed. The data obtained indicated a relationship between thermal transitions and phase separation, resulting in a decrease in moduli followed by an increase in moduli possibly corresponding to gelation of the polymer rich phase. 15 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; USA; WESTERN EUROPE

Accession no.866397

ltem 114

Biomaterials 23, No.18, Sept.2002, p.3787-97 **RELEASE OF GENTAMICIN SULPHATE FROM A MODIFIED COMMERCIAL BONE CEMENT. EFFECT OF HYDROXYETHYL METHACRYLATE COMONOMER AND POLYVINYLPYRROLIDONE ADDITIVE ON RELEASE MECHANISM AND KINETICS**

Frutos P; Diez-Pena E; Frutos G; Barrales-Rienda J M CSIC; Madrid,Universidad Complutense

The influence of hydroxyethyl methacrylate monomer addition to a PMMA bone cement liquid component and of a polyvinyl pyrrolidone to the solid component on the release of gentamicin sulphate is discussed. The possibility of calculating the desired released amount and composition of devices to achieve very defined drug release profiles were investigated. 42 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE

1tem 115

Biomaterials 23, No.21, Nov.2002, p.4241-8 STABILITY OF POLYETHYLENE OXIDE IN MATRIX TABLETS PREPARED BY HOT-MELT EXTRUSION

Crowley M M; Zhang F; Koleng J J; McGinty J W Texas, University; PharmaForm LLC

The thermal stability of polyethylene oxide in sustained release tablets prepared by hot-melt extrusion was investigated. The weight average molecular weight of the polymer was studied using GPC. The influence of processing parameters and incorporation of a plasticiser and antioxidants on the drug release properties were also investigated. The chemical stability of the polymer under accelerated storage conditions was determined. 22 refs.

USA

Accession no.863984

ltem 116

Biomaterials 23, No.17, Sept.2002, p.3589-94 DYNAMIC MECHANICAL METHOD FOR DETERMINING THE SILICONE ELASTOMER SOLUBILITY OF DRUGS AND PHARMACEUTICAL EXCIPIENTS IN SILICONE INTRAVAGINAL DRUG DELIVERY RINGS

Malcolm R K; McCullagh S; Woolfson A D; Catney M; Tallon P

Belfast, Queen's University

The silicone elastomer solubilities of a range of drugs and pharmaceutical excipients used in the development of silicone intravaginal drug delivery rings were determined using dynamic mechanical analysis. The concentration-dependent decrease in the storage modulus associated with the melting of the incorporated drug/ excipient was measured. The effect of drug/excipient concentrations on the mechanical stiffness of the silicone devices was determined. 21 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.862447

ltem 117

Journal of Applied Polymer Science 85, No.8, 22nd Aug.2002, p.1644-51 INVESTIGATION OF LOADING AND RELEASE IN PVA-BASED HYDROGELS Ruiz J; Mantecon A; Cadiz V Rovira i Virgili,Universitat

Methylene blue(MB) and methyl orange(MO) were used as model drugs to investigate the controlled release behaviour of hydrogels from PVAl crosslinked with ethylene diamine tetraacetic dianhydride. The cationic or anionic nature of these compounds, the molec.wt. between crosslinks of the hydrogel and the concentration of ionisable groups in the hydrogel markedly affected the loading and release of the drugs. MB loading was favoured, therefore, by a higher content of negative charges in the hydrogel, although this implied a greater degree of crosslinking and, therefore, a lower mesh size. The overall loading of negative MO, on the other hand, favoured by a higher mesh size, was very low because of unfavourable interactions with the electrolyte charges. Release studies showed that one of the parameters that most affected the drug release behaviour of these hydrogels was the pH of the solution. MB and MO were not completely released, even at pH 1. 24 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE

Accession no.860005

ltem 118

Journal of Membrane Science 204, No.1-2, 2002, p.237-46 AMINOSALICYLIC ACID PERMEABILITY ENHANCEMENT BY A PH-SENSITIVE EVAL MEMBRANE

Shieh M-J; Lai P-S; Young T-H Taiwan, National University

A pH-sensitive membrane for colon-specific drug delivery was synthesised by the covalent bonding of glycine on EVAL membranes. The processes of surface modification of the membrane structure were observed by SEM. Permeation of aminosalicylic acid through the membranes was studied. 18 refs.

CHINA

Accession no.859457

ltem 119

Biomaterials 23, No.15, Aug.2002, p.3247-55 FLURBIPROFEN-LOADED ACRYLATE POLYMER NANOSUSPENSIONS FOR OPHTHALMIC APPLICATION

Pignatello R; Bucolo C; Spedalieri G; Maltese A; Puglisi G

Catania, University; Bausch & Lomb-Fidia Oftal Pharmaceuticals

Details are given of the preparation of nanoparticle suspensions of ethyl acrylate-methyl methacrylate copolymers and loaded with flurbiprofen. The availability of the drug at an intra-ocular level for the prevention of the myosis induced during extracapsular cataract surgery was investigated. Nanosuspensions were prepared by a quasi-emulsion solvent diffusion technique using different formulation parameters. 34 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; ITALY; WESTERN EUROPE Accession no.859397

Item 120 Polymer News 27, No.1, Jan.2002, p.13-5 **POLYMERS IN CONTROLLED RELEASE. DELIVERY OF ANTI-CANCER AGENTS FROM BIODEGRADABLE NANOPARTICLES** Birnbaum D T; Brannon-Peppas L

Biogel Technology Inc.

The reasons why it is much more difficult to control the release of drugs from nanoparticle systems are discussed and possible alternative methods for formulation of nanoparticles for the sustained release of drugs are described. The experimental work uses nanoparticles of poly(lactic-co-glycolic) acids(PLGA) and the anti-cancer agents 5-fluorouracil and epirubicin. A general scheme for preparation of PLGA microparticles and nanoparticles is presented and data given on the in-vitro release of the two anti-cancer agents from PLGA nanoparticles. 11 refs. USA

Accession no.858359

Item 121

Plastics in Healthcare. Proceedings of a conference held Mumbai, India, 7th-8th Feb.2002. Brookfield, Ct., SPE, Paper 12, pp.3, 28cm, 012 **PLASTICS IN MODERN PHARMACEUTICAL PACKAGING** Banerjee M K

Essel Propack Ltd. (SPE,India Section)

The use of plastics in modern pharmaceutical packaging products is described. Aspects covered include the continual quest for an ideal material and process, properties, machinery and selection criteria (FDA approval, tamper-evident packaging, product-package compatibility, sterilisation, polymer additives, smart design and environmentally-friendly packaging). INDIA

Accession no.857624

Item 122

Brookfield, Ct., SPE, 2002, 15 papers, pp. xxii, 63, 28cm, 012

PLASTICS IN HEALTHCARE. PROCEEDINGS OF A CONFERENCE HELD MUMBAI, INDIA, 7TH-8TH FEB.2002

(SPE,India Section)

Fifteen papers are published following this two day international technical conference concerning plastics in medical and pharma applications. Papers include: plastics in modern pharma packaging; smart syringes; bio-medical waste management; PVC in medical application; prefilled syringes.

ASIA; INDIA; WORLD Accession no.855932

ltem 123

Journal of Biomaterials Science: Polymer Edition 13, No.2, 2002, p.111-26 IN VITRO RELEASE OF IBUPROFEN AND GENTAMICIN FROM PMMA FUNCTIONAL MICROSPHERES Sivakumar M; Rao K P India,Central Leather Research Institute

Ibuprofen- and gentamicin-containing PMMA and PMMA-F functional microspheres were prepared. Fourier transform NMR data clearly indicated that the ibuprofen and gentamicin were entrapped in both the microspheres and confirmed the coupling of carboxylic groups of PMMA-F microspheres with amino groups of gentamicin. Optical micrographs showed the hydrophilic nature and higher swelling of PMMA-F microspheres compared with PMMA microspheres. These PMMA-F functional microspheres floated in the pH range of 1.2 to 7.4, whereas conventional PMMA microspheres settled in the above pH ranges. SEM micrographs revealed that the PMMA-F microspheres were more porous compared with PMMA microspheres. As expected, the large amount of gentamicin was incorporated in the PMMA-F microspheres and the release was prolonged over longer periods of time compared with PMMA microspheres. These carboxyl functional groups could be used advantageously to couple therapeutic bioactive molecules (growth hormone) and also in bone tissue repair and regeneration. 37 refs.

INDIA

Accession no.854703

Item 124

Iranian Polymer Journal 11, No.1, Jan./Feb.2002, p.47-55 USE OF POLYGLYCOL SUCCINATES FOR THE MICROENCAPSULATION OF INSULIN Sariri R; Ghannadzedeh A Gilan,University

Since the discovery of insulin and establishment of its value in the treatment of diabetes mellitus, many investigators have explored the possibility of developing an effective method for its administration other than by injection. The reason is that the necessary injections of the hormone are not only inconvenient but also result in physiological complications as well. The possibility of an oral administration of insulin is investigated. A group of biodegradable polymers from the polyglycol succinate family is synthesised by bulk polycondensation reaction of glycols with diethyl succinate. The polymers are purified and used for microencapsulation of insulin. The size and shape of microcapsules are studied by optical and scanning electron microscopy. The rate of release of core material from the microcapsules is measured by a direct UV absorption method. It is found that pH of the environment, microcapsule wall thickness and the type

of glycol used in polymerisation are the most important factors affecting controlled release. 31 refs. IRAN

Accession no.852971

ltem 125

Advances in Polymer Science Vol.160, 2002, p.45-117 PHARMACEUTICAL POLYMERIC CONTROLLED DRUG DELIVERY SYSTEMS Kumar M N V R; Kumar N; Domb A J; Arora M

Kentucky,University; Jerusalem,Hebrew University; Indian Institute of Technology

Drug delivery systems have taken a great impetus to deliver a drug to the diseased lesions. Although this concept is not new, great progress has recently been made in the treatment of a variety of diseases. A suitable carrier is needed to deliver a suitable and sufficient amount of the drug to a targeted point, hence, various kinds of formulations are being constantly developed. The present state of the art is reviewed regarding synthetic methods and characterisation of nanoparticles, the suitability of polymeric systems for various drugs, drug loading and drug release properties of various systems such as nanoparticles, hydrogels, microspheres, film and membranes, tablets, etc. The available information is summarised so that it will be helpful to beginners and serve as a useful tool for active researchers involved in this area. 420 refs.

INDIA; ISRAEL; USA

Accession no.852951

Item 126

Journal of Biomaterials Science: Polymer Edition 13, No.1, 2002, p.1-15

ASSESSMENT OF BIODEGRADABLE CONTROLLED RELEASE ROD SYSTEMS FOR PAIN RELIEF APPLICATIONS

Sendil D; Wise D L; Hasirci V Ankara,Middle East Technical University; Cambridge Scientific Inc.

Two lactide-glycolide copolymers were used to prepare an implantable rod type drug delivery system containing either an analgesic or an anaesthetic. In vitro drug release kinetics were studied. The influence of drug solubility on release rate was also examined. Rod erosion was investigated using SEM. 27 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; TURKEY; UK; WESTERN EUROPE

Accession no.851692

Item 127

Biomaterials 23, No.10, May 2002, p.2167-77 CHARACTERIZATION OF BIODEGRADABLE DRUG DELIVERY VEHICLES WITH THE ADHESIVE PROPERTIES OF LEUKOCYTES Eniola A O; Rodgers S D; Hammer D A Pennsylvania,University

Details are given of the targeted delivery of antiinflammatory drugs to inflammatory sites using biodegradable lactic acid-glycolic acid copolymer microspheres. A carbohydrate that serves as a ligand to selectins was attached to the surface of the microspheres to mimic the adhesive behaviour of leukocytes on selectins. 47 refs.

USA

Accession no.851237

Item 128

Journal of Applied Polymer Science 84, No.1, 4th April 2002, p.44-9 PERMEATION OF DRUGS IN CHITOSAN MEMBRANES Rocha A N L; Dantas T N C; Fonseca J L C; Pereira M R Rio Grande do Norte,Universidade Federal

Variations in drug concentration from 0.1 to 1 percent, and chitosan membrane thicknesses of 40 to 150 micron were used in the study of the permeabilities of isoniazid and amitriptyline hydrochloride. No changes in release rate (measured by ultraviolet spectrophotometric determination) into water were observed with either concentration or membrane thickness, but rates for the two drugs were very different and were related to the respective molecular weights of the materials. 17 refs. BRAZIL

Accession no.851099

Item 129

Biomaterials 23, No.7, April 2002, p.1649-56 **DEXAMETHASONE/PLGA MICROSPHERES FOR CONTINUOUS DELIVERY OF AN ANTI-INFLAMMATORY DRUG FOR IMPLANTABLE MEDICAL DEVICES**

Hickey T; Kreutzer D; Burgess D J; Moussy F Connecticut, University

Details are given of the development of lactic acidglycolic acid copolymer microspheres for continuous delivery of dexamethasone. The microspheres were prepared using an oil-in-water emulsion technique. Drug loading and release rates were determined by HPLC-UV analysis. 42 refs.

USA

Accession no.850089

Item 130

Weinheim, Wiley-VCH, 2000, pp.xi,255. 25cm. 6S MATERIALS FOR MEDICAL ENGINEERING: EUROMAT - VOLUME 2 Edited by: Stallforth H; Revell P (Aesculap AG; London, University College; Federation of European Materials Societies)

This book comprises part 2 of the proceedings of the EUROMAT 99 conference. 35 papers are presented on materials for medical and surgical applications. Many deal with metallic or ceramic materials, but several deal with polymeric materials. The use of composites made from caprolactone-lactic acid copolymer membrane and polylactide mesh as muscle tissue regeneration scaffolds in rabbits was investigated. The use of carbon fibrereinforced plastics as bone implants is discussed. The effect of sterilisation by gamma irradiation or hydrogen peroxide treatment on the biodegradability of carbon fibre-reinforced polylactide is reported. It is reported that the biocompatibility of a variety of thermoplastic materials can be improved by surface coating with titanium carbonitride, formed by plasma treatment with titanium (IV) diethylamide. Polystyrene and PEEK are subjected to micropatterning by plasma treatment to induce ordering in cell cultures. Novel unsaturated polyester carbonates are investigated as potential drug carriers. In the final relevant paper the antimicrobial effects of metallic silver as a filler in polyurethane catheters are investigated.

AUSTRIA; BRAZIL; CZECH REPUBLIC; DENMARK; EASTERN EUROPE; EUROPEAN COMMUNITY; EUROPEAN UNION; FINLAND; GERMANY; ITALY; JAPAN; POLAND; RUMANIA; SCANDINAVIA; SWEDEN; SWITZERLAND; UK; USA; WESTERN EUROPE

Accession no.849743

Item 131

Medical Device Technology UK 2002. Proceedings of a conference held Birmingham, UK, 13th-14th Feb. 2002.

Chester, Advanstar Communications (UK) Ltd., 2002, paper 17, pp.13, 30 cms. 012

REVIEW OF ADVANCES IN PULMONARY DELIVERY DEVICES AND FUTURE NEEDS Nichols S

Aventis Pharma

(Advanstar Communications (UK) Ltd.)

Pulmonary drug delivery devices are reviewed with respect to recent advances and future needs. The paper provides an introduction to inhaled delivery techniques, the requirements of such delivery devices, a review of the various designs available, new materials and areas of applications, followed by a gap analysis, a discussion of future needs and examples.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.849169

Item 132

Medical Device Technology UK 2002. Proceedings of a conference held Birmingham, UK, 13th-14th Feb. 2002.

Chester, Advanstar Communications (UK) Ltd., 2002, paper 16, pp.11, 30 cms. 012

BIOACTIVE BIOMATERIALS: THE INTERFACE BETWEEN MEDICAL AND DRUG DELIVERY DEVICES Woolfson D

Belfast, Queen's University (Advanstar Communications (UK) Ltd.)

Bioactive biomaterials are discussed with respect to drug delivery systems and the physicochemical principles relating to drug diffusion and delivery from biomaterials and controlled release systems. A case study is included concerning drug delivery from silicone biomaterial.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.849168

Item 133

Polymer Preprints. Volume 42. No.2. Fall 2001. Proceedings of a conference held Chicago, Il., 26th-30th August 2001. Washington, D.C., ACS, Div.of Polymer Chemistry, 2001, p.115-6 **MODIFIED SILICONES FOR THE STABILISATION OF PROTEINS AND ENZYMES**

STABILISATION OF PROTEINS AND ENZYMES IN EMULSIONS: POTENTIAL VACCINE DELIVERY SYSTEMS Zelisko P M; Brook M A McMaster University (ACS,Div.of Polymer Chemistry)

In order to establish the extent to which the native conformation of the protein is retained when in contact with functional silicones, proteins are entrapped within water-in-silicone oil emulsions and their biological activity assessed. The objective is to elucidate the nature of the interaction between the biological and synthetic polymers, the role of different polar groups on the silicones, the denaturation rate of the proteins in contact with the functionalised silicones, and the role of different polar groups on the silicone polymer. Through the use of modified silicones in conjunction with proteins at these water-oil interfaces, it may possible to increase the stability of not only the interface, but of the protein as well. The results presented, combined with the ability to entrap more than one protein in the emulsion droplets at time, offers a great potential for using these systems as delivery vehicles in oral vaccinations. 9 refs.

CANADA

Accession no.847999

Item 134

Polymer Preprints. Volume 42. Number 2. Fall 2001. Proceedings of a conference held Chicago, Il., 26th-30th August 2002.

Washington, D.C., ACS, Div. of Polymer Chemistry, 2001, p.94-5

ACRYLIC-BASED COPOLYMERS FOR ORAL INSULIN DELIVERY SYSTEMS

Foss A C; Peppas N A Purduc,University (ACS,Div.of Polymer Chemistry)

Development of an oral protein delivery device has received attention as protein therapies increase greatly in number. Acrylic-based polymers have a high degree of sensitivity to their surrounding pH and ionic strength. A network of methacrylic acid (MAA) or acrylic acid (AA) with grafted chains of PEG is synthesised to prepared a controllable system that aids in the delivery and protection of insulin. Due to the responsiveness of the mesh size of the network to pH, the material can be tailored for protein delivery. By designing a system that in the collapsed state hinders specific protein diffusion, while in the swollen state the protein is free to diffuse through the network. Emphasis is placed on insulin delivery for diabetes as it is a widespread disease. The network is tailored so that at low pH, those near the pH of the stomach, the mesh size is restrictive on insulin diffusion, trapping the insulin inside and protecting it from the harsh conditions of the stomach. While at high pH, those near the upper small intestine and further down the GI tract, the mesh size is large for be insulin to diffuse out and into the body. The materials presented not only provide a controllable oral delivery device for insulin, but also have a low cytotoxic effect on model gastrointestinal tract cells. 6 refs.

USA

Accession no.847988

Item 135

ACS Polymeric Materials Science and Engineering Fall Meeting, Volume 85.

Chicago, IL, 26th-30th August 2001, p.589-90, 012 RELEASE OF ANTIBIOTICS FROM

BIODEGRADABLE POLYMERIC BEADS

Shih-Lung Liu; Steve Wen-Neng Ueng Chang Gung,University; Chang Gung Memorial Hospital

(ACS, Div. of Polymeric Materials Science & Engng.)

Antibiotics-polymer composites were prepared by mixing the biodegradable polymer poly(D,L-lactide)co-glycolide with vancomycin powder and compressing into beads of different diameters which were sintered at 55 C. Antibiotics release was determined using an elution method and by high performance liquid chromatography. Sufficiently high release rates were obtained for 4-6 weeks, and it was possible to increase the effective release period by increasing: the compression pressure, the sintering temperature, the bead size, or by the use of multilayered beads. 4 refs.

TAIWAN Accession no.847143

Item 136

ACS POLYMERIC MATERIALS SCIENCE AND ENGINEERING. SPRING MEETING 2001. VOLUME 84. Proceedings of a conference in San Diego, Ca..

Washington, D.C., 2001, p.218, 012 NOVEL POLYMERIC SYSTEM FOR DRUG

DELIVERY de Jasus O. L. D: Ibre H. D: Freghet I.M. J: Szoka

de Jesus O L P; Ihre H R; Frechet J M J; Szoka F C California, University; Amersham Pharmacia Biotech AS (AMERICAN CHEMICAL SOCIETY)

A series of polyester dendritic systems were designed and synthesised for drug delivery applications. The polymeric carriers were highly water soluble, non-toxic and biocompatible. The retention of the dendritic carrier was improved by the formation of a polyethylene glycolpolyester hybrid system. This hybrid was used for the preparation of a new polymer-drug conjugate. This new system has potential for the development of well-defined macromolecules as drug delivery agents. 4 refs.

USA

Accession no.846695

Item 137

ACS POLYMERIC MATERIALS SCIENCE AND ENGINEERING. SPRING MEETING 2001. VOLUME 84. Proceedings of a conference in San Diego, Ca.. Washington, D.C., 2001, p.214, 012 DENDRIMERS: NOVEL CARRIERS FOR ORAL AND PARENTERAL DRUG DELIVERY

Duncan R

Cardiff,University (AMERICAN CHEMICAL SOCIETY)

Families of dendrimers were identified that might have potential for progression from the laboratory into clinical development. Parenteral or oral delivery is seen as the principal objectives. These molecules must be non-toxic, non-haemolytic, non-immunogenic and, for parenteral use, should ideally be biodegradable. A polyamidoamine (PAMAM) dendrimer-platinate showed improved tumour targeting and improved anticancer activity compared with cisplatin and therefore has potential for further investigation as a novel antitumour treatment. Anionic PAMAM dendrimers displayed serosal transfer rates that were more rapid than identified for other synthetic and natural macromolecules (including tomato lectin) studied in an everted sac system. This suggests that these nanoscale structures might have potential for further development as oral drug delivery systems. 10 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.846692

Item 138 Polymers for Advanced Technologies

13, No.2, Feb.2002, p.127-36 PHOSPHOLIPID COATED POLYLACTIC ACID MICROSPHERES FOR THE DELIVERY OF LHRH ANALOGUES

Rasiel A; Sheskin T; Bergelson L; Domb A J Jerusalem, Hebrew University

An attempt is made to develop alternative peptide-loaded microspheres using liposphere formulation - a lipid based microdispersion system. This formulation represents a new type of lipid or polymer-based encapsulation system developed for parenteral and topical drug delivery of bioactive compounds. The strategy is to utilise the liposphere formulation to improve the entrapment efficiency and release profile of triptorelin and leuprolide (luteinising hormone-releasing hormone (LHRH) analogues) in vitro. Peptides (2% w/w) are loaded into lipospheres contained of polylactic acid (PLA) or polylactic-co-glycolic acid (PLGA) with several types of phospholipids. The effects of polymer and phospholipid type and concentration, method of preparation and solvents on the liposphere characteristics, particle size, surface and bulk structure, drug diffusion rate and erosion rate of the polymeric matrix are studied. The use of L-PLA and hydrogenated soybean phosphatidylcholine (HSPC) with phospholipid-polymer ratio of 1:6 w/w, is the most efficient composition that forms lipospheres of particle size in the range of 10 mu m with most of the phospholipid embedded on the particles surface. In a typical procedure, peptides are dissolved in N-methyl-2pyrrolidone (NMP), and dispersed in a solution of polymer and phospholipids in a mixture of NMP and chloroform with the use of 0.1% polyvinyl alcohol as the emulsified aqueous medium. Uniform microspheres are prepared after solution is mixed at 2000 rpm at room temperature for 30 min. Using this formulation, the entrapment efficiency of LHRH analogues in lipospheres is up to 80%, and the peptides are released for more than 30 days. 24 refs.

ISRAEL

Accession no.844853

Item 139

Advances in Polymer Science Vol.157, 2002, p.67-112 DEGRADABLE POLYMER MICROSPHERES FOR CONTROLLED DRUG DELIVERY Edlund U; ALbertsson A-C Sweden,Royal Institute of Technology

A review is presented of the use of degradable polymers for use in controlled drug delivery. Emphasis is given to the preparation, applications, biocompatibility, and stability of microspheres from hydrolytically degradable polymers. 320 refs.

EUROPEAN UNION; SCANDINAVIA; SWEDEN; WESTERN EUROPE

Accession no.844632

Item 140

Journal of Applied Polymer Science 82, No.14, 27th Dec.2001, p.3391-5 FORMATION OF A DNA/N-DODECYLATED CHITOSAN COMPLEX AND SALT-INDUCED GENE DELIVERY

Wen Guang Liu; Kang De Yao; Qing Gang Liu Tianjin,University

A polyelectrolyte complex was formed by synthesising an N-dodecylated chitosan, from dodecyl bromide and chitosan, and assembling with DNA. Atomic force microscopy was used to examine the thermal stability of the DNA embedded in the polyelectrolyte complex. From this it was seen that the incorporation of the dodecylated chitosan enhanced the thermal stability of DNA, due to encapsulation of DNA in the chitosan. The dissociation of the complex induced by small molecular salts was investigated. The ability of Mg2+ to break the polyelectrolyte complex is greater than that of Na+ and K+. From the atomic force microscopy images it can be seen that the DNA is well protected by the dodecylated chitosan from nuclease. The polyelectrolyte complex can be used as a gene delivery carrier. 21 refs.

CHINA

Accession no.844128

Item 141

Journal of Microencapsulation 19, No.2, March/April 2002, p.191-201 RELEASE OF DIAZEPAM FROM POLY(HYDROXYBUTYRATE-HYDROXYVALERATE) MICROSPHERES Chen J; Davis S S

Guangzhou, First Medical University of PLA; Nottingham, University

Microspheres based on a hydroxybutyratehydroxyvalerate copolymer (PHBV) (Mw = 630 kD, 21% mol HV) are loaded with diazepam using different emulsion-solvent evaporation processes. Gelatin is used as a strategy to alter the release profile of the incorporated drug. The mean diameter of microspheres is from 30-40 micron. Drug release from the microspheres over a 30day period shows a characteristic triphasic release pattern with an initial burst effect, but is linear over the same period and without a burst effect when gelatin is used as a coating agent. Scanning electron microscopy reveals that the microspheres have different structures depending upon their method of preparation. 11 refs.

CHINA; EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.843897

Item 142

Journal of Microencapsulation 19, No.2, March/April 2002, p.153-64 IN VITRO ANTIBIOTIC RELEASE FROM POLY(3-HYDROXYBUTYRATE-CO-3-HYDROXYVALERATE) RODS

Gursel I; Yagmurlu F; Korksusuz F; Hasirci V US,Food & Drug Administration; Ankara,Numune Hospital; Ankara,Middle East Technical University

Provision and maintenance of adequate concentrations of antibiotics at infection sites is very important in treating highly resistant infections. For diseases like implant related osteomyelitis (IRO) it is best to provide this locally via implanted drug formulations, as systemic administration of the antibiotic may not be effective due to damaged vasculature. Poly(3-hydroxybutyrate-co-3hydroxyvalerate) (PHBV) rods containing 7, 14 and 22% (mol) 3-hydroxyvalerate are loaded with sulbactam:cefoperazone or gentamicin, and their antibiotic release behaviours are studied under in vitro conditions in physiological phosphate buffer at room temperature. The release patterns are representative of release from monolithic devices where a rapid early release phase is followed by a slower and prolonged release. With PHBV 22 rods, the latter phase continues for ~2 months. This duration is critical because a proper antibiotic therapy of IRO requires the minimal effective concentration for at least six weeks. After in vitro release, voids with sharp edges are detected on the rods, indicating that the drug crystals dissolve but the polymer does not undergo erosion within this test period. Changing the polymer:drug ratio from 2:1 to 20:1 substantially decreases the drug release rate. A change of polymer type, however, does not lead to any detectable changes in the release patterns. Gentamicin release also follows a similar pattern, except that the concentration of the drug in the release medium exhibits a decrease after long release periods, indicating degradation (or decomposition) of the antibiotic in the release medium. 34 refs.

TURKEY; USA

Accession no.843895

ltem 143

Journal of Applied Polymer Science 83, No.4, 24th Jan.2002, p.850-6 POLY-DL-LACTIDE-POLYETHYLENE GLYCOL MICROSPHERES AS ORAL AND PARENTERAL DELIVERY SYSTEMS FOR HEPATITIS B SURFACE ANTIGEN

Li X; Zhou S; Wu X; Yuan M; Liu L; Ha W; Deng X; Huang Z

Chinese Academy of Sciences; West China, University of Medical Science

An attempt is made to show the potential use of poly-DL-lactide-polyethylene glycol (PELA) microspheres as a hepatitis B surface antigen (HBsAg) delivery system following subcutaneous (s.c.) or oral immunisation over the current injection of an alum-absorbed antigen. The antigen-loading microspheres are elaborated by the solvent-extraction method based on the formation of modified multiple w/o/w emulsion. The microspheres are characterised by their particle size, HBsAg entrapment and in vitro HBsAg release behaviour. Balb/ c mice are immunised with an s.c. injection and oral administration of a single dose and two doses of a microsphere formulation. For comparison, the alumabsorbed HBsAg-immunised mice have a following intramuscular (i.m.) injection at weeks 0 and 4. At weeks 8, 10, 14 and 24 post-administration, the blood and saliva samples are collected and detected by the enzyme-linked immunosorbed assay (ELISA) method. A single injection of HBsAg PELA microspheres can induce a serum IgG antibody level comparable to the two-injection alumabsorbed HBsAg at the 14th week and higher than that at the 24th week. The saliva lgA of peroral groups is significantly higher than that of the s.c. injection of a microsphere formulation and i.m. injection of soluble antigen. These preliminary results demonstrate the potential of oral administration of antigen loading microspheres in the induction of a secretory immune response, and it is suggested that a single-dose s.c. injection of antigen-loading microspheres is an efficient immunisation schedule to elicit a protective response. 16 refs.

CHINA

Accession no.842040

ltem 144

Journal of Microencapsulation 19, No.1, Jan./Feb. 2002, p.83-94 VANCOMYCIN RELEASE FROM POLYLACTIDE AND POLYLACTIDE-CO-GLYCOLIDE DISKS Ozalp Y; Ozdemir N; Hasirci V

Ankara, University

Polylactide and lactide-glycolide copolymer systems were developed for the controlled release of vancomysin. Degradation of the polymers was studied by SEM, NMR and GPC. The permeability of the drug through the polymer membranes and the release kinetics from disks were studied. Changes in molecular weights and heterogeneity indices were followed. 26 refs.

Accession no.841987

Item 145

Journal of Applied Polymer Science 83, No.7, 14th Feb. 2002, p.1457-64 HYDROPHILIC DRUG RELEASE FROM BIOERODIBLE POLYANHYDRIDE MICROSPHERES

Vasheghani-Farahani E; Khorram M

Biodegradable copolymers of fumaric anhydride and isophthalic anhydride were synthesised by the melt condensation polymerisation of purified prepolymer mixtures and formulated into microspheres loaded with theophylline and diltiazem hydrochloride using a solvent extraction procedure. The important parameters of the microencapsulation process were identified and in vitro release experiments carried out to obtain the release profile of both drugs. Finally, the drug release data were compared with three semi-empirical models, none of which were suitable for the complete prediction of drug release from the microspheres. 20 refs.

TARBIAT MODARRES, UNIVERSITY; IRAN, SISTAN & BALUCHISTAN UNIVERSITY IRAN

Accession no.841838

Item 146

Biomaterials 23, No.2, Jan. 2002, p.457-62 **PREPARATION OF CONTROLLED RELEASE OPHTHALMIC DROPS, FOR GLAUCOMA THERAPY USING THERMOSENSITIVE**

POLYISOPROPYLACRYLAMIDE Hsiue G-H; Hsu S-H; Yang C-C; Lee S-H; Yang I-K Taiwan,National Tsing Hua University; Tunghai,University

Controlled release ophthalmic agents for glaucoma therapy were developed based on the thermosensitivity of polyisopropyl acrylamide. The drug was entrapped in the tangled polymer chains or encapsulated within the crosslinked hydrogel and released progressively after topical application. Linear and crosslinked polymer nanoparticles containing epinephrine were prepared. The drug release rate and cytotoxicity were investigated. The intraocular-lowering effect was evaluated. 25 refs. CHINA

Accession no.840947

Item 147

Polymer Preprints. Volume 41. Number 2. Conference proceedings.

Washington, D.C., 20th-24th Aug.2000, p.1726-7 TRANSPORT OF MACROMOLECULAR DRUG CARRIERS ACROSS MICROVASCULAR BEDS El-Sayed M; Naimar M; Kiani M F; Ghandehari G Maryland, University (ACS, Div. of Polymer Chemistry)

Among macromolecular polymeric biomaterials examined as drug carriers is a family of water-soluble cascade polymers named polyamidoamine (PAMAM) dendrimers. PAMAM dendrimers are characterised by a unique treelike branching architecture that confers them a compact spherical shape in solution and a controlled incremental increase in size, molecular weight and number of surface amine groups. The potential of PAMAM dendrimers in controlled drug delivery has been extensively investigated and rises from the high number of arms and surface amine groups that can be utilised to immobilise therapeutic moieties providing a high density of biological agents in a compact system. To reach the target site, polymeric drug delivery systems including PAMAM dendrimers often must extravasate from the microvasculature across the microvessels' endothelium to the surrounding interstitial tissue. Extravasation rate of drug carriers influences the rate of drug delivery to the interstitial tissue, the site of action of most drugs. Structural features of macromolecular drug carriers, such as size, molecular weight, shape, geometry, charge and hydrophilicity influence their transvascular transport across the microvascular endothelium and hence influence the rate of drug delivery to the target site. PAMAM dendrimers are used as model probes to study the influence of a controlled incremental increase in size, molecular weight and number of amine surface groups on their extravasation across microvascular network endothelium. In an attempt to probe the influence of macromolecular geometry of polymeric drug carriers on their transvascular transport, the extravasation of linear PEG is also included and compared to its dendritic counterparts. 5 refs.

USA

Accession no.840010

Item 148

Polymer Preprints. Volume 41. Number 2. Conference proceedings.

Washington, D.C., 20th-24th Aug.2000, p.1667-8 RHEOLOGY OF PRESSURE-SENSITIVE ADHESIVE HYDROGELS DESIGNED FOR SKIN APPLICATION

Kotomin S V; Borodulina T A; Feldstein M M; Kulichikhin Russian Academy of Sciences (ACS,Div.of Polymer Chemistry)

The blends of high molecular weight poly(N-vinyl pyrrolidone) (PVP) with short-chain polyethylene glycol (PEG), containing equilibrium amount of sorbed water, may serve as an universal hydrogel matrix for enhanced transdermal delivery of various drugs. The major performance properties of transdermal patches are the pressure-sensitive adhesion toward skin and diffusivity required controlling a drug release rate. In PVP-PEG hydrogels, these properties have been shown to be due to stoichiometric hydrogen bonding of the short-chain PEG terminal hydroxyls to the carbonyls in the repeating units of longer PVP macromolecules. Required adhesive and transport properties result from specific flexible network supramolecular structure of PVP-PEG hydrogels. To be pressure-sensitive adhesive, a polymer has to couple a rubberlike elasticity, typical of crosslinked molecules, with a certain fluidity and cohesive strength. The role of enhanced molecular mobility in adhesive behaviour cannot be explained completely by known diffusion theory. According to recent views on the nature of this phenomenon, the rheological approach is much more adequate. The rheological properties of PVP-PEG hydrogels are described, and the significance of molecular mobility is elicited and rheology to adhesion is addressed. 9 refs.

RUSSIA

Item 149 Polymer Preprints. Volume 41. Number 2. Conference proceedings. Washington, D.C., 20th-24th Aug.2000, p.1643-4 THERMALLY RESPONSIVE AMPHIPHILIC BLOCK POLYPEPTIDES FOR DRUG ENCAPSULATION Zhou Y: Conticello V P

Zhou Y; Conticello V P Emory University (ACS,Div.of Polymer Chemistry)

One particularly effective method to control the biodistribution of hydrophobic drugs is encapsulation within micellar particles. Historically, these aggregates have been derived from low molecular weight surfactants (detergent micelles), however, many problems are associated with these vehicles including toxicity, environmental unfriendliness, low solubility of the drug, low loading efficiency, short circulation in blood stream, etc. To overcome these problems, amphiphilic block copolymers have been extensively developed for usage as micro-vessels for drug encapsulation. A homogeneous protein-based amphiphilic block copolymer is described with a molar mass of approximately 49 kDa that is synthesised using recombinant DNA techniques and bacterial protein expression. The lipophilic block (L) and hydrophilic block (H) are modelled on consensus pentapeptide sequences of elastin and flagelliform silk, respectively. The self-assembly behaviour of the copolymer is characterised via temperature-dependent NMR, dynamic light scattering and electronic microscopy, which reveal thermo-reversible nanoparticle formation above a lower critical solution temperature in aqueous solution. 4 refs.

USA

Accession no.836645

Item 150

Polymer Preprints. Volume 41. Number 2. Conference proceedings.

Washington, D.C., 20th-24th Aug.2000, p.1641-2 NOVEL DRUG DELIVERY SYSTEMS: NANOGEL NETWORKS

Vinogradov S; Hatrakova E; Kabanov A V Nebraska, University (ACS, Div. of Polymer Chemistry)

A novel class of drug carriers, nanogels, that significantly enhances possibilities for the control of drug binding capacity and drug release characteristics compared to common nanoparticles, is described. These carriers represent crosslinked networks of water-soluble non-ionic polymer polyethylene glycol (PEG) and positively charged polyethylenimine (PEI). They are structurally related to hydrogel materials developed for a number of technical and biomedical applications (microsphere beads, membranes, films etc.). An essential property of the nanogel particles is that their size lies in the range of ca. 20 to 220 nm, which makes them profoundly different from hydrogel nano- and microspheres with sizes ranging from 0.5 to 500 mu m proposed previously for polynucleotide delivery. Due to the smaller size, nanogel particles will be less susceptible to reticuloendothelial system clearance and will better penetrate in tissues and cells. The nanogel particles described have identical compositions to PEG-g-PEI graft copolymers recently proposed for the delivery of phosphorothioate oligonucleotides (SODNs). Similarly to PEG-g-PEI copolymers shown to form cooperative electrostatic complexes with SODNs and anionic surfactants, the PEG-PEI nanogel particles interact with negatively charged molecules (SODN, proteins, surfactants). Nanogel particles are evaluated as potential carriers for drug delivery. 5 refs.

USA

Accession no.836644

ltem 151

Polymer Preprints. Volume 41. Number 2. Conference proceedings. Washington, D.C., 20th-24th Aug.2000, p.1632 **GLUCOSE SPECIFIC POLYMERIC MOLECULAR IMPRINTS** Wizeman W; Kofinas P Maryland,University (ACS,Div.of Polymer Chemistry)

The creation of highly specific receptor sites in molecularly imprinted polymers (MIPs) has been the goal of many research groups in the past decade. Promising applications for these MIPs include tailor-made separation materials, molecular recognition materials for biosensors, highly specific catalysts and antibody mimics for quantitative assay and molecular recognition. Molecular imprinting in polymers is achieved by incorporating a template, or imprint molecule into a highly crosslinked polymer matrix. Given a polymer matrix with sufficient mechanical stability, cavities with size, shape and functionality specific to the template molecule are created upon removal of the template. The template molecule is bonded to a polymerisable functional monomer or polymer side group prior to crosslinking. Emphasis has been placed on the use of non-covalent template/polymer interactions as a means to produce molecularly imprinted polymers due to the large number of non-covalent interactions possible with biological compounds. Previous research in molecular imprinting has focused on molecular imprinting from monomer, however molecular imprinting using a readily available polymer and crosslinker would greatly simplify the synthesis of MIPs and could bring the technology closer to application. The technique presented not only employs the non-covalent approach to molecular imprinting, but also begins with a polymer having an appropriate functionality, instead of functional monomer, and is performed in aqueous solution under air. Refinement of this imprinting technique could result in a product to aid in the treatment of type 2 diabetes. The MIPs presented have potential as a glucose-binding drug capable of absorbing glucose in the stomach and duodenum and passing through the body, undigested. This drug could give people with type 2 diabetes more freedom to eat foods high in glucose with reduced need for insulin. 5 refs.

USA

Accession no.836639

ltem 152

Polymer Preprints. Volume 41. Number 2. Conference proceedings.

Washington, D.C., 20th-24th Aug.2000, p.1628-9 NEW MATRICES FOR CONTROLLED DRUG DELIVERY

Albertsson A-C; Edlund U Stockholm,Royal Institute of Technology (ACS,Div.of Polymer Chemistry)

Polylactides show excellent biocompatibility and are the most popular biodegradable excipients for drug delivery applications. They are, however, stiff with little elasticity in the body, because of having glass transition temperatures above the body temperature. Matrices with superior elasticity and tissue resorptivity may be obtained by combining polylactides with polymeric building blocks with high backbone flexibility. Research has for many years focused on the synthesis and characterisation of such new biodegradable, flexible materials based on aliphatic polyesters and an aliphatic polyether lactone, e.g. copolymers of poly(D,L-lactide), poly(L-lactide), poly(Ecaprolactone) or poly(delta-valerolactone) with poly(1,5dioxepan-2-one). These materials offer great potential as biomedical matrices. The preparation of new degradable microspheres for controlled drug delivery from copolymers and homopolymer blends based on 1,5dioxepan-2-one (DXO) and L-lactide (LLA) is described. The microsphere preparation, degradation and sustained release of incorporated drugs are presented. The matrix morphology, adjustable by means of preparation and component ratio, is shown to be a vital tool of controlling the microsphere performance in terms of degradation and drug release characteristics. 8 refs.

EUROPEAN UNION; SCANDINAVIA; SWEDEN; WESTERN EUROPE

Accession no.836637

ltem 153

Polymer Preprints. Volume 41. Number 2. Conference proceedings.

Washington, D.C., 20th-24th Aug.2000, p.1370-1 MECHANISM OF INTERACTIONS BETWEEN UNIMOLECULAR POLYMER MICELLES AND LIPID BILAYERS

Albers L N; Uhrich K E Rutgers, University (ACS, Div. of Polymer Chemistry) There has been wide interest in exploring new techniques to increase drug absorption through the skin. Liposomes as cell membrane mimics have been considered as the most efficient tools for delivering hydrophobic drugs into the cytoplasm. It has been shown that the polymeric micelle enhances subcutaneous absorption of drugs such as lidocaine. The mechanism of interactions between micelles and liposomes has been considered the most interesting topic in the field of liposome research. Previously, the physical stability of liposomes prepared from 1,2 -dipalamitoyl-glycero-sn-phosphatidylcholine in the presence of polymeric micelles was proved. Emphasis is placed here on the physical stability of liposomes in the presence of polymeric micelles, the size of the vesicles with or without the addition of polymeric micelles, and studies of calcein leakage from small unilamellar vesicles and large unilamellar vesicles in the presence of micelles. Liposomes for these studies are prepared from 1,2dilauroyl-glycero-sn-phosphatidylcholine using two different methods of sonication and extrusion. 7 refs. USA

Accession no.835402

Item 154

Polymer International 50, No.11, Nov.2001, p.1241-6 GELLAN/POLY(VINYL ALCOHOL) HYDROGELS: CHARACTERISATION AND EVALUATION AS DELIVERY SYSTEMS Cascone M G; Barbani N; Malitinti S; Lazzeri L Pisa,University

Blends of polyvinyl alcohol (PVA) with gellan were used to prepare bioartificial polymeric materials as hydrogels, using a method based on freeze/thawing cycles, and the effect of gellan on these materials was studied. The results obtained on loading the materials with human growth hormone (GH) and release of the drug indicated that the gellan favoured crystallisation of the PVA with formation of a material of more homogeneous and stable structure than that of pure PVA gels. The PVA melting enthalpy and the elastic modulus were directly related to the hydrogel gellan content, and the amount of PVA released was inversely related to it. With gellan/PVA hydrogels it was possible to release GH, and the amount of GH released was affected by the content of biological component. The amount of GH released was within the physiological range. 16 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; ITALY; WESTERN EUROPE

Accession no.835214

Item 155

Biomaterials 22, No.22, Nov. 2001, p.2999-3004 **DESIGN AND EVALUATION OF DRUG-LOADED WOUND DRESSING HAVING THERMORESPONSIVE, ADHESIVE,**

ABSORPTIVE AND EASY PEELING PROPERTIES

Lin S-Y; Chen K-S; Run-Chu L Tatung,University

A combination of self-adhesive Eudragit E film with antibacterial drug-loaded polyisopropyl acrylamide microgel beads was designed as a wound dressing. The influence of microgel beads on tack properties was determined. 24 refs.

CHINA

Accession no.832932

ltem 156

Packaging Technology and Science 14, No.4, July/Aug. 2001, p.159-70 LIQUID CRYSTALLINE POLYMER POUCHES FOR LOCAL ANAESTHETIC EMULSION Flodberg G; Axelson-Larsson L; Hedenqvist M S;

Gedde U W Swedish Institute for Packaging & Distribution;

AstraZeneca; Sweden, Royal Institute of Technology

Use of Vectra A950 liquid crystal polymer is described with reference to the production of barrier packaging for the containment of anaesthetic emulsions. The pouches were compression moulded and sealed by thermal impulse welding. Concentrations of lidocaine and prolocaine in the emulsion were studied for 14 weeks at two different temperatures, 40 degrees C and 60 degrees C, and at 100% relative humidity. Loss of substances from the emulsion was due mainly to adsorption onto the polar surface of the liquid crystalline polymer, it is reported. 21 refs. EUROPEAN UNION; SCANDINAVIA; SWEDEN; WESTERN EUROPE

Accession no.831514

Item 157

Macromolecules 34, No.11, 22nd May 2001, p.3507-9 TOWARD POLYMERIC ANTICANCER DRUG COCKTAILS FROM RING-OPENING METATHESIS POLYMERIZATION Watson K J; Anderson D R; Nguyen S T

Northwestern University

It has been demonstrated that at least three anticancer pharmaceuticals, indomethacin, 2-(4-aminophenyl)-6methylbenzothiazole and chlorambucil, can be readily modified with a norbornene group and that the resulting multifunctional molecules can be polymerised using a ruthenium carbene initiator by the technique of ringopening metathesis polymerisation. Moreover, these compounds are amenable to the synthesis of either block copolymers in combination with each other or random copolymers in combination with a triethylene glycol monomer. It is believed that the simplest route to multifunctional drug-containing block copolymers that contain a high density of drugs and a narrow polydispersity has been presented. Benefits arising from the unique ability of ROMP initiators include the polymerisation of diverse monomers under mild conditions, as well the narrow polydispersivity obtained in living ROMP chemistry which can help in the control of dosage in pharmacotherapy and pharmacokinetics. 27 refs.

USA

Accession no.830257

Item 158

Macromolecular Symposia Vol.172, June 2001, p.149-56 Patent Number: . SULPHONAMIDE-CONTAINING POLYMERS: NEW CLASS OF PH-SENSITIVE POLYMERS AND GELS Kang S I; Na K; Bae Y H Kwangju,Institute of Science & Technology

New pH-responsive polymers and hydrogel nanoparticles are synthesised, which bear either sulphapyridine or sulphamethoxypyridazine. The linear copolymers in water show soluble/insoluble transition, while the hydrogel nanoparticles in aqueous solutions experience association/ dissociation transition in a narrow pH range. Their pH sensitivity is confirmed by the change in turbidity or particle size as a function of pH. The ionisation of SO2NH group in sulphonamides is responsible for aggregation of the polymers or hydrogel nanoparticles. The transition pH is determined by the amount of SO2NH groups in the copolymers or on the hydrogel nanoparticle surface; at an optimum composition, the transitions occur near physiological pH. These systems may present a potential for various biomedical and bioengineering fields, such as pulsatile drug delivery, targeting, embolisation, sensors and bioseparation. 9 refs.

KOREA

Accession no.829069

Item 159

Macromolecular Symposia Vol.172, June 2001, p.127-38 POLYMERIC ORGANOIRON COMPOUNDS AS PRODRUGS IN CANCER RESEARCH Neuse E W Witwatersrand,University

Ferrocene has for almost half a century been a focal point of research activities in the realm of organotransitionmetal chemistry and physics, with ramifications into numerous technologies. More recent years have witnessed the emergence of a new research trend, probing the behaviour of ferrocene in the biological realms, notably in the transformed, i.e. cancerous, cell system. Following initial reports attesting to the pronounced antiproliferative properties of certain water-soluble derivatives of ferrocene and its one-electron oxidation product, the ferricenium radical cation, earlier programmes were set up with the objective of developing water-soluble polymeric conjugates in which the bioactive ferrocene unit is bioreversibly tied to macromolecular carriers in order to enhance its therapeutic effectiveness. These earlier investigations of polymer-ferrocene conjugation are briefly reviewed, and the current, considerably broadened synthetic programme is introduced. The carriers are predominantly of the highly versatile polyaspartamide type, but other structures resulting from ester-amine polycondensation reactions are included. Carrier anchoring of the ferrocenylation agent, 4ferrocenylbutanoic acid, is brought about both by acylation of carrier-attached amino groups, leading to amide links in the spacer, and by acylation of polymerbound hydroxy groups, resulting in ester linking of the ferrocene unit. Selected conjugates are screened in cell culture tests for antiproliferative activity against the HeLa and LNCaP human cancer lines, and preliminary results are highly promising. In view of the relatively low level of toxic side effects expected for these organoiron compounds, the results presented offer challenging opportunities for the development of iron-containing, polymer-anchored drug systems as chemotherapeutic agents in cancer research. 23 refs.

SOUTH AFRICA

Accession no.829068

Item 160

Macromolecular Symposia Vol.172, June 2001, p.73-86 TREATMENT OF INTRAOCULAR DISEASES WITH POLYORTHOESTER)BASED DELIVERY SYSTEMS

Einmahl S; Behar-Cohen F; Tabatabay C; Gurny R Geneva, University; Paris, Hopital Hotel Dieu

A polyorthoester (POE) is investigated as a carrier for controlled delivery in intraocular therapy. The intraocular biocompatibility of POE is assessed in a rabbit after intravitreal as well as suprachoroidal injections. In both cases, the injection is feasible and reproducible, and the tolerance of POE is good, with no clinical or cellular signs of inflammation. The polymer degrades slowly within two to three weeks, with total bioresorption. POE allows to sustain release of an antifibroblastic agent in a model of glaucoma filtering surgery in the rabbit. A formulation based on POE and 5-fluorouracil is administered to prevent failure of the surgery. This POE formulation is effective in inhibiting the fibrotic response, allowing a local and controlled release of a small amount of the antiproliferative drug, while reducing its toxicity. Based on these results, POE appears to be a promising carrier for sustained drug delivery in treatment of intraocular affections. 16 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; FRANCE; SWITZERLAND; WESTERN EUROPE

Accession no.829064

Item 161

Macromolecular Symposia Vol.172, June 2001, p.35-47 MECHANISMS OF ANTICANCER ACTION OF HPMA COPOLYMER-BOUND DOXORUBICIN Minko T; Kopeckova P; Kopecek J Utah, University

The peculiarities of HPMA copolymer-bound doxorubicin as an anticancer drug are described. It is found that polymer-bound doxorubicin demonstrates higher anticancer activity compared with free doxorubicin. This phenomenon is explained by the following mechanisms of its anticancer action: preferential accumulation in tumours, internalisation in membrane-limited organelles, ability to overcome existing multi-drug resistance and not to induce it de novo, high intracellular toxicity and inhibition of detoxification enzymes, cell death induction by the activation of specific signalling pathways and triggering of caspase activation cascades. 22 refs. USA

Accession no.829060

1000001110.022

Item 162

Chemistry and Industry No.24, 18th Dec. 2000, p.800 ARTIFICIAL MEMBRANE HOLDS PROTEINS

Scientists at the Institut fuer Physikalische Chemie are reported to have developed an artificial membrane that mimics the biological behaviour of a cell's outer membrane which will allow the incorporation of fully functional membrane proteins in it. Brief details are given of the research, in which the artificial membrane is produced using a fluid plastic matrix which has stability and fluidity similar to that of a normal cell membrane. One of the most promising pharmacological and biotechnological applications for this technology is reported to be a biosensor to screen potential drugs for their activity on certain cellular proteins.

INSTITUT FUER PHYSIKALISCHE CHEMIE SWITZERLAND; WESTERN EUROPE

Accession no.828616

Item 163

Journal of Biomedical Materials Research 57, No.2, Nov.2001, p.248-57 POLY(L-LACTIDE)ACID/ALGINATE COMPOSITE MEMBRANES FOR GUIDED TISSUE REGENERATION Milella E; Barra G; Ramires P A; Leo G; Aversa P; Romito A

PASTIS-CNRSM; CNR

A system composed of a poly(L-lactide)acid(PLLA) asymmetric membrane combined with an alginate film was prepared. The PLLA membrane functioned to both support the alginate film and separate the soft tissue, while the alginate film was intended to act as a potential vehicle

for the growth factors to promote osteogenesis. The structural, morphological and mechanical properties of the bilamellar membrane and its stability in culture medium were evaluated. The feasibility of using the alginate membranes as controlled release delivery vehicles for the growth factor TGF-beta was monitored. The early bacterial adhesion and permeability of Streptococcus mutans were also evaluated. 26 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; ITALY; WESTERN EUROPE

Accession no.827322

Item 164

Journal of Biomedical Materials Research 57, No.2, Nov.2001, p.151-64 SELF-ASSEMBLED MOLECULAR STRUCTURES AS ULTRASONICALLY-RESPONSIVE BARRIER MEMBRANES FOR PULSATILE DRUG DELIVERY

Kwok C S; Mourad P D; Crum L A; Ratner B D Washington, University

The concept of using moderately impermeable, selfassembled, ordered methylene chains as an 'on-off' switch in ultrasound-modulated drug delivery was investigated. Ciprofloxacin antibiotic was used in preliminary studies as a model drug to demonstrate the concept and insulin was then investigated. Delivery vehicles for ciprofloxacin and insulin were developed and used as substrates on which ordered methylene chains were immobilised. These uncrosslinked methylene chains, built on a drugcontaining polyhydroxyethyl methacrylate matrix, acted as self-sealing barriers in an ultrasound-modulated delivery device. The pulsatile release was examined with ultrasound irradiation and related to the surface molecular structures. An in-vitro functional assay based on (C14)deoxyglucose uptake in adipocyte cells assessed the biological activity of the insulin releasate. 45 refs.

USA

Accession no.827319

Item 165

Biomaterials 22, No.17, Sept.2001, p.2319-24 POLYMERIC SYSTEM FOR THE INTRA-ORAL DELIVERY OF AN ANTI-FUNGAL AGENT

Patel M P; Cruchley A T; Coleman D C; Swai H; Braden M; Williams D M

London, University, Queen Mary & Westfield College; St.Bartholomews & Royal London School of Medicine & Dentistry

A self-curing system based on polyethyl methacrylate(PEM) and tetrahydrofurfuryl methacrylate(THFM) was used with chlorhexidine diacetate(CX) added at levels between 0 and 12% w/w. Water uptake by the device was assessed gravimetrically and CX release measured by UV spectroscopy. Anti-

candidal activity was established by culturing azole sensitive and resistant strains of Candida albicans in the presence of the polymeric delivery device with and without CX. Candidal growth was measured by turbidimetry or surviving colony-forming unit(CFU) formation. There was an initial high release of CX over 24 h followed by a slow diffusion up to 7 days. CX inhibited candidal growth and survival markedly in vitro, with the test samples showing less than 0.00000005 CFU/ ml compared with 0.0000003 to 0.0000004 CFU/mol for the controls. These results indicated the potential of a chlorhexidine-containing PEM/THFM polymeric system in the treatment of persistent candidal infections. 38 refs. EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.827288

Item 166

Polymer News

25, No.12, Dec. 2000, p.424-6 SOME NEW INVESTIGATIONS ON WATER TRANSPORT AND DRUG RELEASE FROM CROSSLINKED GUAR GUM GRAFTED POLYACRYLAMIDE HYDROGEL MICROSPHERES

Soppimeth K S; Kulkarni A R; Aminabhavi T M Karnatak University

Details are given of the ongoing research in the development of novel crosslinked hydrogel microspheres. Natural guar gum was grafted with polyacrylamide to give a copolymer matrix. Water uptake into these microspheres was studied to understand its effect on drug release. Verapamil hydrochloride was chosen as a model candidate. 10 refs.

INDIA

Accession no.825738

Item 167

Journal of Applied Polymer Science 81, No.5, 1st August 2001, p.1238-47 RELEASE AND DIFFUSION OF SULFAMETHOXAZOLE THROUGH ACRYLAMIDE-BASED HYDROGEL Bajpal A K; Rajpoot M

Jabalpur, Government Autonomous Science College

The swelling and drug-release dynamics of two polymeric hydrogels (xerogels) containing polyvinyl pyrrolidone-crosslinked polyacrylamide and polyvinyl alcohol-crosslinked polyacrylamide loaded with sulphamethoxazole drug were studied at a fixed pH and 27 deg.C. The effects of xerogel composition, crosslinking density, and drug loading on the xerogel swelling and drug release pattern were studied, and the kinetic parameters, i.e. the diffusion exponent n, diffusion constant k, and diffusion coefficient D were evaluated and analysed. The percentage of drug released by the xerogels was compared with the amount released by crosslinked gelatin gels. 29 refs. INDIA

Accession no.825466

ltem 168

Journal of Microencapsulation 18, No.5, Sept./Oct. 2001, p.559-65 IN VITRO MODIFIED RELEASE OF ACYCLOVIR FROM ETHYL CELLULOSE MICROSPHERES

Cheu S-J; Chen R R-L; Chen P-F; Lin W-J Taiwan, National University

Ethyl cellulose microspheres were prepared by an oil-inwater solvent evaporation technique and the effects of polymer viscosity, polymer/drug ratio and polymer concentration on acyclovir encapsulation efficiency and dissolution characteristics were investigated using a 23 full factorial experimental procedure. The percentages of drug released from the microspheres in simulated gastric and intestinal fluid were determined and the stability of acyclovir before and after encapsulation evaluated at various temperatures over a period of 12 weeks. Sustained drug release was found to be more prominent in the simulated intestinal fluid than in the simulated gastric fluid. 9 refs.

TAIWAN Accession no.822923

Item 169

Advanced Materials 13, No.11, 5th June 2001, p.837-9 CONTROLLED DRUG DELIVERY FROM POLYMERS BY MECHANICAL SIGNALS Kuen Yong Lee; Peters M C; Mooney D J Michigan, University

The use of mechanical signals to control the release of drugs from polymers is described. Two types of model systems, one in which the drug molecules do not interact with the polymer matrix and the other where both free and bound drug molecules Are present, are considered and the results obtained with three different model drugs (trypan blue, methylene blue, vascular endothelial growth factor) incorporated into alginate hydrogels are reported. 21 refs.

USA

Accession no.820601

Item 170

Polymer Bulletin 46, No.4, May 2001, p.241-8 **SYNTHESES AND ANTITUMOR ACTIVITIES OF POLYMERS CONTAINING ACRYLAMIDOMETHYLPROPANESULFONIC ACID OR 5-FLUOROURACIL** Lee S M; Ju S S; Chung H Y; Ha C S; Cho W J Pusan, National University

Polymers containing acrylamidomethylpropanesulphonic acid were prepared by radical polymerisations. The polymers were identified by FTIR, proton and carbon 13 NMR spectroscopies. Number average molecular weights were determined by GPC. In vivo antitumour activities were examined. 22 refs.

KOREA

Accession no.820236

Item 171 Biomaterials 22, No.13, July 2001, p.1763-9 POLYHYDROXYETHYL METHACRYLATE FILM AS A DRUG DELIVERY SYSTEM FOR PILOCARPINE Hsiue G-H; Guu J-A; Cheng C-C

National Chiao Tung University

Details are given of pilocarpine trapped in a matrix diffusion-controlled drug delivery system using hydrophilic inserts of polyhydroxyethyl methacrylate. The physical and chemical properties of pilocarpine were investigated to determine the mechanism of drug-polymer interaction and the effect of drug release behaviour of controlled release polymeric devices. 22 refs. CHINA

Accession no.819930

Item 172

Journal of Biomaterials Science: Polymer Edition 12, No.1, 2001, p.55-62

POLYETHYLENE TEREPHTHALATE YARN WITH ANTIBACTERIAL PROPERTIES

Buchenska J; Slomkowski S; Tazbir J W; Sobolewska E Lodz, Technical University; Polish Academy of Sciences

PETP yarn was loaded with a cephalosporin-type antibiotic. The release of the antibiotic from the fibres was monitored and its bioactivity was examined. 15 refs. EASTERN EUROPE; POLAND

Accession no.815542

Item 173 Chemical Engineering 108, No.1, Jan.2001, p.51/4 **SEPARATION RESINS: JUST WHAT THE DOCTOR ORDERED** Crabb C

This detailed article focuses on ion exchange resins (separation resins), which have long been used in traditional pharmaceutical processes. It examines the key role that these chemicals play in the production of novel bioengineered therapeutic drugs. It also discusses the market for these resins, and recent restructuring and consolidation amongst manufacturers.

PUROLITE INTERNATIONAL; DOW CHEMICAL CO.; AP BIOTECH; TOSOH BIOSEP LLC; MITSUBISHI CHEMICAL AMERICA INC.; AMERSHAM PHARMACIA BIOTECH AS; BAYER AG; SYBRON CHEMICALS INC.; ROHM & HAAS CO.; TOSOHAAS; TOSOH CORP.; US,FOOD & DRUG ADMINISTRATION; RESINTECH EUROPEAN COMMUNITY; EUROPEAN UNION; GERMANY; JAPAN; SCANDINAVIA; SWEDEN; UK; USA; WESTERN EUROPE

Accession no.813373

ltem 174

Journal of Applied Polymer Science 80, No.4, 25th April 2001, p.639-49 STUDIES ON SEMI-INTERPENETRATING POLYMER NETWORK BEADS OF CHITOSAN-POLYETHYLENE GLYCOL FOR THE CONTROLLED RELEASE OF DRUGS Gupta K C; Ravi Kumar M N V

Roorkee, University

Blends of chitosan and PEG were prepared and characterised for controlled release of drugs. Structural studies of beads were performed using FTIR and SEM. The swelling behaviour, solubility, hydrolytic degradation and loading capacity of the beads for isoniazid were investigated. 25 refs.

INDIA Accession no.811372

ltem 175

Macromolecules 34, No.6, 13th March 2001, p.1548-50 NOVEL CHOLESTEROL LOWERING POLYMERIC DRUGS OBTAINED BY MOLECULAR IMPRINTING

Huval C C; Bailey M J; Braunlin W H; Ho,mes-Farley S R; Mandeville W H; Petersen J S; Polomoscanik S C; Sacchiro R J; Xi Chen; Dhal P K GelTex Pharmaceuticals Inc.

The molecular imprinting technique was outlined. This technique was applied to prepare novel bile acid sequestrants. Imprinted polymer networks were obtained by crosslinking partially neutralised poly(allylammonium chloride) with epichlorohydrin in the presence of a sodium cholate template. The sodium cholate template was removed from the polymer network after completion of the crosslinking reaction, leaving the imprinted polyammonium salt network. These were shown to be effective as bile acid sequestrants in both in-vitro and in-vivo studies. 15 refs.

USA

Accession no.811023

ltem 176

International Polymer Science and Technology 28, No.1, 2001, p.T/40-4 BIODEGRADABLE POLYMERS AND THEIR USE IN MODERN MEDICINE. 4. MICROSYSTEMS FOR CONTROLLED RELEASE OF MEDICINES Polishchuk A Y; Kazakova M V; Zaikov G E

Russian Academy of Sciences

A descriptive work is presented together with a discussion of empirical results, which reviews recent research into the creation of specific microsystems for the controlled release of medicines. Microsystems both in sphere and capsule forms are examined with reference to choice of optimum materials. At present, polyester and polyanhydride microsystems and systems based on biopolymers have been most widely used. 19 refs. (Translated from Plasticheskie Massy, No.4, 2000, p.31) RUSSIA

Accession no.808337

ltem 177

Polymers for Advanced Technologies 12, Nos.1-2, Jan./Feb.2001, p.85-95 CONTROLLED RELEASE FROM AMPHIPHILIC POLYMER AGGREGATES Kimura S; Kidchob T; Imanishi Y Kyoto,University; Nara,Institute of Science & Technology

The literature on controlled release from amphiphilic polymer aggregates is reviewed. Two terms, biodegradation and organisation of polymers, are discussed as characteristic points for the authors' approach to polymer aggregates. Microcapsules are considered, with particular reference to sustained release from polypeptide microcapsules, pH-responsive release from polypeptide microcapsules, thermoresponsive microcapsules, and degradation. Microspheres are then discussed and polypeptide vesicles are examined. 81 refs. JAPAN

Accession no.807251

Item 178

IUPAC Polymer Symposium: Functional and High Performance Polymers. Conference proceedings. Taipei, 14th-16th Nov.1994, p.481-2 **TEMPERATURE EFFECT ON THE CHARACTERISTICS OF THERMALLY ON-OFF SWITCHING MEMBRANE** Lin Y-Y; Chen K-S; Lin S-Y

Tatung,Institute of Technology; Taipei,Veterans General Hospital (IUPAC; Taiwan,Polymer Society)

The effects of manufacturing temperature and store conditions on drug permeability across cholesteryl oleyl carbonate (COC)-embedded membranes are investigated.

The membranes are prepared by vacuum filtration and stored at different temperatures. Salbutamol sulphate is used as a model drug across the COC-embedded membrane. It is evident that both manufacturing and store temperature significantly affect the characteristic of membranes. The thermally on-off switching membrane can be obtained by preparing the membranes above the liquid crystal transition temperature. 4 refs.

TAIWAN

Accession no.803980

ltem 179

ACS Polymeric Materials: Science and Engineering. Fall Meeting 2000. Volume 83. Washington, D.C., 20th-24th Aug.2000, p.495-7 **EXPLOITATION OF A NOVEL ARTIFICIAL MUSCLE FOR CONTROLLED DRUG DELIVERY**

Madou M J; He K Ohio,State University (ACS,Div.of Polymeric Materials Science & Engng.)

Non-porous barrier layer valves and polymer valves for novel responsive drug delivery systems are fabricated. The non-porous barrier layer valves are irreversible and application of a small current between the metal valve electrode and the counter electrode leads to rupture of the thin metallic barrier layer. The super porous hydrogel shows fast swelling and shrinking from -10% to 60% when the pH is varied from 2 to 13. The glucose oxidase doped super porous hydrogel also exhibits a linear swelling response to glucose in a concentration range from 0.005 M to 0.06 M. The reversible polymer valves (artificial muscle), consisting of a redox polymer and a hydrogel, combine the good qualities of a highly swelling hydrogel and a fast voltage controllable redox polymer. The artificial muscle is also voluminous, smooth and uniform. Its growth can be located on conductor substrates such as gold, platinum, carbon and be integrated in various microfabricated structures. The artificial muscle material and structure designs introduced can effectively be used to fabricate microactuators or microvalves in a controlled drug delivery system. 20 refs.

USA

Accession no.802356

ltem 180

Journal of Microencapsulation 18, No.1, Jan./Feb. 2001, p.111-21 SPRAY-DRIED MICROSPHERES CONTAINING KETOPROFEN FORMULATED INTO CAPSULES AND TABLETS Moretti M D L; Gavini E; Juliano C; Pirisino G; Giunchedi P Sassari,University

Microspheres were produced by spray drying of solutions of ketoprofen and mixtures of cellulose acetate butyrate and hydroxypropylmethylcellulose phthalate in different weight ratios. The morphological properties, particle size and drug content of the spray dried particles were determined using various techniques, including SEM, light scattering and UV spectrophotometry. In-vitro release tests were performed on microsphere-filled capsules and tablets obtained by compression of with microparticles mixed maltose or hydropropylmethylcellulose. The microspheres were found to be suitable for use as delivery systems for the oral administration of non-steroidal anti-inflammatory drugs. 16 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; ITALY; WESTERN EUROPE

Accession no.800218

ltem 181

Polymer Preprints. Volume 40. Number 2. August 1999. Conference proceedings. New Orleans, La., August 1999, p.888-9 SYNTHESIS AND CHARACTERISATION OF POLYANHYDRIDE COPOLYMERS FOR CONTROLLED DRUG DELIVERY Sanders A J; Li B; Bieniarz C; Harris F W Akron,University

(ACS, Div. of Polymer Chemistry)

Since 1980, researchers have taken advantage of the hydrolytic instability of polyanhydrides in controlled release applications. Polyanhydrides and their degradation products have proven to be highly biocompatible. In addition, certain hydrophobic polyanhydrides undergo surface erosion. Thus, polyanhydride matrices can be designed to release drugs at nearly constant rates. Drugs can also be delivered in vivo at the site of action to maximise the therapeutic effect with no need for surgical removal of the implant. The major approach to the desired polyanhydrides has involved the copolymerisation of aliphatic and aromatic diacids. By varying the ratio of diacid monomers in the copolymer, hydrolytic degradation rates can be tailored to specific patient requirements. For example, as the number of methylene units in the aromatic monomer is increased, the polymer becomes more hydrophobic, and the erosion rate is markedly decreased. The objective is to increase the melt processability of polyanhydrides, while maintaining their desirable release rate characteristics. The approach involves the synthesis of new hydrophobic, aromatic diacid monomers containing branched aliphatic spacers. These monomers are then copolymerised with sebacic acid. 8 refs.

USA

Accession no.798797

ltem 182

Polymer Preprints. Volume 40. Number 2. August 1999. Conference proceedings. New Orleans, La., August 1999, p.236-7

SYNTHESIS OF NOVEL SHELL CROSS-LINKED MICELLES WITH HYDROPHILIC CORES

Butun V; Billingham N C; Armes S P Sussex, University (ACS, Div. of Polymer Chemistry)

The synthesis of shell crosslinked 'knedel' (SCK) micelles has been reported. Various applications, in areas as diverse as solubilisation, catalysis, fillers, coatings and delivery, have been proposed for these nanoparticles. However, in all studies the micelle cores are based on PS or polyisoprene and are therefore permanently hydrophobic. The synthesis of two new classes of SCK micelles with hydrophilic micelle cores are reported. Successful shell crosslinking relies on selective quaternisation of the A block, which comprises 2-(dimethylamino)ethyl methacrylate (DMAEMA) residues. The B block comprises 2-(N-morpholino)ethyl methacrylate (MEMA) and forms the micelle core. The second class is zwitterionic SCK micelles, prepared from precursor DMAEMA-2-tetrahydropyranyl methacrylate diblock copolymers. Depending on the synthetic route employed, two types of zwitterionic SCK micelles can be obtained: Type I micelles, with anionic cores and cationic coronas, and Type II micelles, with cationic cores and anionic coronas. These zwitterionic SCK micelles exhibit isoelectric points in aqueous solution. 14 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.797396

ltem 183

Biorelated Polymers and Gels. London, Academic Press Ltd., p.135-92 BIOADHESION IN MUCOSAL DRUG DELIVERY

Yang X; Robinson J R Wisconsin,University Edited by: Okano T

The robust field of bioadhesives for drug delivery is reviewed. Clearly the youth of this field implies that firstgeneration bioadhesive polymers would be 'off-the-shelf' polymers that do not present a problem for regulatory agencies. The next generation of polymers will need to have the following properties: greater specificity for targeting to certain tissue domains or cell types, multifunctional abilities beyond simply retaining a product at a site, such as penetration enhancement and enzyme inhibition, non-toxic and non-irritating characteristics, and ability to modulate the release of both water-soluble and water-insoluble drugs. 181 refs.

USA

Accession no.789859

Item 184 Journal of Microencapsulation 17, No.6, Nov./Dec.2000, p.677-90

INTERPENETRATING POLYMER NETWORKS OF ALGINATE AND POLYETHYLENE GLYCOL FOR ENCAPSULATION OF ISLETS OF LANGERHANS

Desai N P; Sojomihardjo A; Yao Z; Ron N; Soon-Shiong P

American BioScience Inc.

A mixture of alginate and PEO was investigated as a system for the encapsulation of islets of Langerhans. The physical aspects of gelation of these systems were investigated. Diffusion of dextrans of known molecular weight through these gels was studied in order to shed light on the hydrogel porosity and permeability. Biocompatibility is discussed. 29 refs.

USA

Accession no.789534

Item 185

Journal of Microencapsulation 17, No.5, Sept.-Oct.2000, p.625-38 5-FLUOROURACIL-LOADED CHITOSAN COATED POLYLACTIC ACID MICROSPHERES AS BIODEGRADABLE DRUG CARRIERS FOR CEREBRAL TUMOURS

Chandy T; Das G S; Rao G H R Minnesota, University

The preparation of monodisperse biodegradable microspheres of polylactic acid coated with chitosan to increase capsule shelf stability and biocompatibility and evaluation of these microspheres for the delivery of anticancer drugs (5-fluorouracil) into the brain are reported. The effects of various parameters on microsphere preparation were examined by determination of total microsphere yield, microsphere size, surface morphology, drug loading efficiency and drug delivery and in vitro drug release from the microspheres suspended in phosphate buffered saline was assessed using UV spectrophotometry. 33 refs.

USA

Accession no.789494

ltem 186

Chemistry and Industry No.17, 4th Sept.2000, p.559 **PLASTIC ASPIRIN REDUCES SIDE EFFECTS** Murphy M

This short item brings a new development to our attention: polyaspirin - a plastic aspirin, which is made up of molecules of aspirin strung together to form an elastic compound. Brief details of the new drug are provided.

AMERICAN CHEMICAL SOCIETY; RUTGERS,UNIVERSITY USA Accession no.787825

Item 187 **Polymer Testing** 19, No.8, 2000, p.889-97 **TRANSDERMAL DRUG TRANSFER FROM A POLYMER DEVICE. STUDY OF THE POLYMER AND THE PROCESS**

Ouriemchi E M; Ghosh T P; Vergnaud J M Saint Etienne, University; Lavipharm Laboratories Inc.

Details are given of the nature of the acrylate polymer and the process of drug delivery in a transdermal drug delivery system. The process of drug delivery was studied through in vitro and in vivo tests. Parameters of diffusion through the skin were calculated. 18 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; FRANCE; USA; WESTERN EUROPE

Accession no.786668

Item 188

Biomaterials 21, No.20, Oct.2000, p.2073-9 **MORPHOLOGY OF AND RELEASE BEHAVIOUR FROM POROUS POLYURETHANE MICROSPHERES**

Jabbari E; Khakpour M Amir Kabir, University

Details are given of the effect of chain extending agent on the porosity and release behaviour of PU microspheres prepared using a two-step suspension polycondensation method. The influence of chain extender on microsphere morphology was studied using SEM. The release behaviour of microspheres was investigated with diazinon as the active agent. 49 refs.

IRAN

Accession no. 783443

Item 189

Journal of Applied Polymer Science 77, No.11, 12th Sept.2000, p.2411-7 POLY-ALPHA,BETA-(3-HYDROXYPROPYL)-DL-ASPARTAMIDE: A NEW DRUG CARRIER Gu-Ping Tang; Zhu K J; Chen Q Q Zhejiang,University

The above polymer(PHPA) was synthesised by the ringopening reaction of polysuccinimide and 3hydroxypropylamine. The polymer was characterised by proton NMR, carbon-13 NMR, FTIR and GPC methods. Mark-Houwink coefficients were obtained by viscometry and GPC measurements. The acute toxicity of PHPA was examined and no death was observed in ICR mice up to a dose of 15.3 kg/kg and haematological parameters showed no significant difference between treated and control animals. The potential use of PHPA as a drug carrier was also investigated. In a typical case, a contraceptive drug, norethindron, was bonded to PHPA, and the drug exhibited sustained release for as long as 120 days in an in-vitro test. 7 refs.

CHINA

Accession no.783179

ltem 190

Computational and Theoretical Polymer Science 10, No.5, 2000, p.391-401 PROCESSES OF DRUG TRANSFER WITH THREE DIFFERENT POLYMERIC SYSTEMS WITH TRANSDERMAL DRUG DELIVERY Ouriemchi E M; Vergnaud J M Saint Etienne, University

Three transdermal therapeutic systems were examined, a monolithic device made of a polymer containing the drug (metroprolol), the same monolithic device in contact with a drug reservoir and a porous polymer containing the drug. It was found that the monolithic device could maintain a constant drug delivery only when the diffusivity of the drug through this polymer was very high. This device was more efficient when used in association with a reservoir. The system made of a porous polymer with convective transfer of the drug appeared to be more effective, providing a constant drug concentration on the skin surface, which was responsible for a constant rate of drug transfer through the skin and a constant plasma drug level over a long period of time. 29 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; FRANCE; WESTERN EUROPE

Accession no.781079

Item 191

ACS, Polymeric Materials Science & Engineering Fall Meeting 1999. Volume 81. Conference proceedings. New Orleans, La., 22nd-26th Aug.1999, p.108-9 **DYNAMICS OF SELF-RELEASE POLYMERIC**

DYNAMICS OF SELF-RELEASE POLYMERIC DERIVATIVES

Rizos A K; Tsatsakis A M,; Shtilman M I; Doetschman D C

Crete, University; Mendeleev University of Chemical Technology; New York, State University at Binghamton (ACS, Div.of Polymeric Materials Science & Engng.)

The last few decades have witnessed concerted efforts to enhance the effectiveness of drugs used in therapeutic, diagnostic and preventive medicine. Many of the problems associated with conventional drug therapy may be circumvented by the use of delivery systems which in a variety of ways will optimise drug action. The concept of targeted drug delivery was first aired early this century and entails the use of carrier systems to deliver drugs to where they are needed or facilitate their release there. Among the systems being investigated, formulations with the polymeric drug carrier covalently bonded to the drug hold considerable promise. The latter release the active ingredient during hydrolysis. Static and dynamic light scattering measurements are performed in a series of water-soluble polymeric derivatives containing the same polymeric backbone but with different side-groups of varying hydrophobic character. The light scattering data display changes and trends in the dynamics and scattering intensifies that are discussed in terms of the concentration of the side groups present in the parent polymer and also as a function of time. In the electron paramagnetic resonance spin probe experiments the partitioning of the probe between the solution, the polymer clusters and a minor third environment are examined. 13 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; GREECE; RUSSIA; USA; WESTERN EUROPE

Accession no.780742

Item 192

Macromolecular Symposia Vol.152, March 2000, p.151-62 HYDROPHILIC POLYMERS FOR DRUG DELIVERY

Ulbrich K; Subr V; Pechar M; Strohalm J; Jelinkova M; Rihova B

Czech Republic, Academy of Sciences

The synthesis and biological properties of two types of water-soluble polymer drug carrier systems, designed for site-specific therapy, are reported. The polymer drug carrier systems are a non-degradable poly(N-(2-hydroxypropyl)methacrylamide with biodegradable oligopeptide side chains and a degradable polyethylene glycol with biodegradable N2,N6-bis(glutamyl)lysine oligopeptide links having the anti-cancer drug, doxorubicin, or model proteins and antibodies attached thereto. 10 refs.

CZECH REPUBLIC

Accession no.778693

Item 193

Journal of Biomedical Materials Research 51, No.1, July 2000, p.96-106 LOCALISED DRUG DELIVERY USING CROSSLINKED GELATIN GELS CONTAINING LIPOSOMES; FACTORS INFLUENCING LIPOSOME STABILITY AND DRUG RELEASE Ditzio V; Karlgard C; Lilge L; Khoury A E; Mittelman M E; DiCosmo F

Toronto, University; Toronto General Hospital

A drug delivery vehicle is described that combines the sustained release properties of liposomes with the structural advantages of crosslinked gelatin gels that can be implanted directly or coated onto medical devices. Liposome inclusion in gelatin gels does not compromise thermal stability nor does it interfere with the resiliency of gels to tensile force. However, electron spin resonance analysis of sequestered DPPC liposomes reveals a slight depression (ca. 1 deg.C) of the gel-to-fluid phase transition relative to liposomes in suspension. The level of liposome release from gels is determined by liposome concentration, liposome size and the presence of polyethylene oxide chains in the gel matrix or in the liposome membrane. Both neutral and charged liposomes display relatively high affinities for polyethylene glycol gelatin gels, with only 10-15% release of initially sequestered liposomes while liposomes in which polyethylene glycol is included within the membrane are

not as well retained (approximately 65% release). The in vitro efflux of ciprofloxacin from liposomal gels immersed in scrum is nearly complete after 24 h compared to 38% release of liposomal chloyhexidine after 6 days. The serum-induced destabilisation of liposomal ciprofloxacin depends on the accessibility of serum components to gels as partly immersed gels retain approximately 50% of their load of drug after 24 h. In vivo experiments using a catheterised rabbit model of urinary tract infection reveal the absence of viable Escherichia coli on coated catheter surfaces in seven out of nine cases while all untreated catheter surfaces examined (n = 7) are contaminated. 33 refs.

CANADA

Accession no.778014

Item 194

Biomaterials 21, No.12, June 2000, p.1235-46 SYNTHESIS AND CHARACTERISATION OF A NOVEL BIODEGRADABLE ANTIMICROBIAL POLYMER

Woo G L Y; Mittelman M W; Santerre J P Toronto, University; Altran Corp.

A polyurethane was synthesised from 1,6-hexane diisocyanate, polycaprolactone diol and a fluoroquinolone antibiotic, ciprofloxacin and characterised by size exclusion chromatography and elemental analysis. The PU was incubated in a solution of an inflammatory cell-derived enzyme, cholesterol esterase or phosphate buffer for 30 days at 37C and its biodegradability determined by HPLC, mass spectroscopy and Carbon 14 radiolabel release. Analysis of the solution revealed that ciprofloxacin was released and able to inhibit the growth of Pseudomonas aeruginosa. 53 refs.

CANADA; USA Accession no.774164

Item 195 Biomaterials 21, No.12, June 2000, p.1191-6 TRANSMUCOSAL DELIVERY SYSTEMS FOR CALCITONIN: REVIEW Torres-Lugo M; Peppas N A Purdue University

Purdue, University

A review is presented on the controlled release of calcitonins from polymeric matrices and oil-based formulations covering the period 1992-8. Polymers covered include biodegradable polymers, such as polyglycolic acid, polylactic acid and copolymers thereof, and non-biodegradable polymers, such as styreneisopropyl acrylamide copolymers and poly(methacrylic acid-g-ethylene glycol) copolymers, for oral calcitonin delivery systems. 28 refs.

USA Accession no.774161

ltem 196

Journal of Biomedical Materials Research 50, No.3, 5th June 2000, p.397-404 IN VIVO BIOCOMPATIBILITY OF DEXTRAN-BASED HYDROGELS

Cadee J A; van Luyn M J A; Brouwer L A; Plantinga J A; van Wachem P B; de Groot C J; den Otter W; Hennink W E

Utrecht,Institute for Pharmaceutical Sciences; Groningen,University; Utrecht,University

Dextran-based hydrogels were produced by the polymerisation of aqueous solutions of methacrylated dextran or lactate-hydroxyethyl methacrylate-derivatised dextran and implanted subcutaneously in rats for up to 6 weeks. The effects of initial water content and degree of substitution of these hydrogels on tissue response were examined and the relationship between in vitro and in vivo degradation behaviour was investigated. The results obtained indicated that these hydrogels were biocompatible and could be potential candidates for drug delivery systems. 20 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; NETHERLANDS; WESTERN EUROPE

Accession no.768204

Item 197

Medical Device Technology 11, No.2, March 2000, p.12/7 SOPHISTICATED MEDICAL DEVICES AS LOCAL DRUG-DELIVERY SYSTEMS Schierholz J M; Beuth J Cologne,University

It is explained that invasive medical device procedures predispose patients to infection in several ways. This article reviews developments to reduce these adverse reaction in catheters, coronary stents and total hip endoprosthesis. New methods of reducing wound infection and improving wound healing are also described. The methods all involve the sustained release of relevant drugs. 13 refs.

MERCK

EUROPE-GENERAL; EUROPEAN COMMUNITY; EUROPEAN UNION; GERMANY; USA; WESTERN EUROPE

Accession no.767621

ltem 198

Journal of Microencapsulation 17, No.1, Jan.-Feb.2000, p.81-93 USE OF ADDITIVES TO MODULATE THE RELEASE OF A SPARINGLY WATER SOLUBLE DRUG ENTRAPPED IN PLA50 MICROPARTICLES

Mallard C; Coudane J; Rault I; Vert M Montpellier I,Universite; Ardix

One of the major problems raised by the microencapsulation of drugs which are sparingly soluble

in water is the difficulty to achieve a controlled and total release of the drug. It has previously been shown that the microencapsulation of a model water insoluble drug, namely 1-(2-(4-fluorobenzoyl)aminoethyl)-4-(7methoxynaphthyl) piperazine hydrochloride (FAMP) with a hydrophilic additive like low molar mass polyethylene glycols (PEG) can fulfil these requirements, provided all the drug and additive matter is in contact with the surrounding liquid medium via open pores and percolating channels. PEG is replaced here by other additives, selected due to their potential ability to increase the solubility of FAMP in pH = 7.4 isosomolar phosphate buffer (PBS). The idea is that increasing the solubility locally in microparticles allows the drug to be released, despite its poor solubility in aqueous media like body fluids, and be absorbed before recrystallisation. The solubility in PBS of FAMP mixed with additive, in the form of solid dispersions, is determined for various additives, namely citric acid, dimyristoyl DL-alpha-phosphatidyl choline (DMPC), poloxamer, copolymers of different compositions and poly(dodecyl L-lysine citramidate) (PLCAC12 100), an aggregate-forming hydrophilic polyelectrolyte containing 100% hydrophobising ester groups which can accommodate lipophilic compounds in hydrophobic pockets present in the aggregates. 23 refs. EUROPEAN COMMUNITY; EUROPEAN UNION; FRANCE; WESTERN EUROPE

Accession no.765184

ltem 199

Journal of Biomaterials Science: Polymer Edition 11, No.1, 2000, p.27-43 CONTROLLED RELEASE OF ANTIHYPERTENSIVE DRUG FROM THE INTERPENETRATING NETWORK POLYVINYL ALCOHOL-GUAR GUM HYDROGEL MICROSPHERES Soppimath K: Kulkarni A. B: A minabhavi T. M

Soppimath K; Kulkarni A R; Aminabhavi T M Karnatak University

Polyvinyl alcohol-guar gum interpenetrating network microspheres are prepared by crosslinking with glutaraldehyde. Nifedipine, an antihypertensive drug, is loaded into these matrices before and after crosslinking to study its release patterns. The extent of crosslinking is analysed by Fourier transform infrared spectroscopy and differential scanning calorimetry. Furthermore the microspheres are characterised for drug entrapment efficiency, particle size, transport of water into the matrix and drug release kinetics. Scanning electron microscopic photographs confirm the spherical nature and surface morphology. The mean particle size of the microspheres is found to be around 300 mu. The molecular transport phenomenon, as studied by the dynamic swelling experiments, indicate that an increase in crosslinking affects the transport mechanism from Fickian to non-Fickian. The in vitro release study indicates that the release from these microspheres is not only dependent upon the

extent of crosslinking but also on the amount of the drug loaded as well as the method of drug loading. 25 refs. INDIA

Accession no.765042

Item 200

Journal of Microencapsulation 16, No.6, Nov.-Dec.1999, p.777-92 IN VITRO AND IN VIVO RELEASE PROPERTIES OF BRILLIANT BLUE AND TUMOUR NECROSIS FACTOR-ALPHA (TNF-ALPHA) FROM POLY(D,L-LACTIC-CO-GLYCOLIC ACID) MULTIPHASE MICROSPHERES

Iwata M; Nakamura Y; McGinity J W Dainippon Pharmaceutical Co.Ltd.; Texas, University at Austin

The dissolution properties of two model compounds, brilliant blue and tumour necrosis factor (TNF-alpha), from poly(D,L-lactic-co-glycolic acid) (PLGA) multiphase microspheres are investigated. In addition, the in vivo release of TNF-alpha from the microspheres, in mice, is studied. The microspheres are prepared by an anhydrous multiple emulsion solvent evaporation method. Multiphase microspheres containing brilliant blue exhibit a three phase release profile in vitro, and display a significantly lower level of dye released during the initial phase compared to conventional matrix-type microspheres. Slow release of the dye is observed during the second phase, which is followed by a disintegration of the polymer wall during the third phase of the release process. In vitro dissolution profiles of TNF-alpha are calculated by compensation for the simultaneous degradation of the protein in the dissolution medium. The initial burst release of TNF-alpha is significantly reduced with the multiphase microspheres. The three phase release profile, as seen with the dye, is not observed for the microspheres containing the TNF-alpha. The rate of release of the protein from the microspheres is determined in vivo by analysing the residual level of TNFalpha remaining in the particles following intraperitoneal administration of the microspheres to mice. The release of the protein from the microspheres in vivo is significantly faster than predicted from the results of the in vitro studies. The absence of an initial burst release of TNF-alpha from the multiphase microspheres is reflected in a significant reduction in the plasma level of TNF-alpha when compared to the matrix-type microspheres and a solution of the protein. The controlled release property of the multiphase microspheres is expected to overcome the adverse reactions due to dose dumping that occurs following the local administration of TNF-alpha. 22 refs.

USA

Accession no.759001

Item 201 Journal of Microencapsulation 16, No.6, Nov.-Dec.1999, p.731-40

NIOSOMAL DELIVERY OF 5-FLUOROURACIL

Namdeo A; Jain N K Dr.HariSingh Gour,University

Non-ionic surfactant vesicles (niosomes) have shown promise as cheap, chemically stable alternatives to liposomes. Niosomes of spans (Sorbitan monoesters) have shown promise of commercial exploitation. Niosomes are prepared of 5-fluorouracil (FU) using different spans. They are prepared by the hand shaking method (HSM), reverse phase evaporation (REV) and ether injection method (EIM) using a series of spans, i.e. Span 20, 40, 60 and 80. HSM giving least permeable vesicles are used to study the effect of variables like type of span, composition of lipid and total lipid concentration on entrapment efficiency (EE) and release rate. Increase in the amount of lipid used translates into an almost linear increase in EE. Biodistribution of drug in rats is modified on encapsulation. The concentration of niosomal drug in liver, lung and kidney is increased while it decreases in intestine compared to free drug solution following intravenous administration. The niosomal formulation displays higher and sustained plasma drug level profile compared to free drug solution. Pharmacokinetic calculations reveal an increase in half-life, area under the curve and decrease in volume of distribution of the drug on encapsulation. It is suggested that niosomes can act as promising carriers for 5-fluorouracil. 27 refs.

INDIA

Accession no.758999

Item 202

Journal of Microencapsulation 16, No.6, Nov.-Dec.1999, p.715-29 DEVELOPMENT OF ORAL DRUG DELIVERY SYSTEM USING FLOATING MICROSPHERES Lee J-H; Park T G; Choi H-K Chosun,University; Korea,Advanced Institute of Science & Technology

Floating acrylic resin microspheres with an internal hollow structure are prepared by a solvent diffusion and evaporation method. The yield of microspheres depends on the diffusion rate of ethanol and/or isopropanol in the organic phase. They are successfully produced when a mixture of ethanol and isopropanol is used instead of ethanol alone. The mixing ratio of components in the organic phase affects the size and the yield of microspheres and the best results are obtained at the volume ratio of ethanol:isopropanol:dichloromethane (8:2:5). Direct introduction of the organic phase into the aqueous phase through a glass tube also significantly improves the yield by avoiding the contact of organic phase with the surface of water. The optimum rotation speed and temperature are 250 rpm and 25 deg.C, respectively. Several different drugs with various physicochemical properties are used as model drugs for encapsulation and release tests. When a drug has low solubility in dichloromethane and high solubility in both

water and a mixture of ethanol/isopropanol, the loading efficiency is the lowest. The release profiles are significantly different depending on the solubility of a drug in the release medium and the physicochemical properties of an encapsulated drug. 16 refs.

KOREA

Accession no.758998

Item 203

Journal of Applied Polymer Science 74, No.7, 14th Nov.1999, p.1752-61 DRUG RELEASE BEHAVIOR OF ELECTRICAL RESPONSIVE POLY(VINYL ALCOHOL)/ POLY(ACRYLIC ACID) IPN HYDROGELS UNDER AN ELECTRIC STIMULUS So Yeon Kim; Young Moo Lee

Hanyang,University

The dependence of the release behaviour of drugs (theophylline and cefazoline) from PVAl/polyacrylic acid IPN hydrogels on electric stimulus was studied in relation to the use of such systems as electrically-modulated drug delivery systems. The release behaviour of drugs was examined by varying influencing factors such as applied voltage, content of charge group within PVAl/polyacrylic acid IPN, ionic properties of drugs and ionic strength of release medium. 31 refs.

KOREA

Accession no.754159

Item 204

Journal of Biomedical Materials Research (Applied Biomaterials)

48, No.5, 1999, p.613-20

IN VITRO ELUTION OF VANCOMYCIN FROM BIODEGRADABLE BEADS

Shih-Jung Liu; Steve Wen-Neng Ueng; Err-Cheng Chan; Song-Shu Lin; Chia-Hsun Tsai; Fu-Chan Wei; Chun-Hsiung Shih

Chang Gung, University; Chang Gung Memorial Hospital

The possibility of using biodegradable polymers as antibiotic beads for long-term drug release was examined. Polylactide-glycolide copolymers were mixed with vancomycin. The mixture was compressed and sintered at 55C to form beads of different sizes. An elution method was used to characterise the release rate of antibiotic over a 35-day period at 37C. Biodegradable beads released high concentrations of antibiotic in-vitro for the period of time needed to treat bone infection, i.e. 4 to 6 weeks. A bacterial inhibition test was carried out to determine the relative activity of the released antibiotics. The diameter of the sample inhibition zone ranged from 6.5 to 10 mm, which was equivalent to 12.5 to 100% of relative activity. By changing the processing parameters, the release rate of the beads could be controlled. This offered the advantage of meeting the specific antibiotic requirement for patients with various surgical infections. 36 refs. TAIWAN Accession no.754133

Item 205

Journal of Biomaterials Science: Polymer Edition 10, No.8, 1999, p.805-25 INTRANASAL IMMUNIZATION AGAINST INFLUENZA VIRUS USING POLYMERIC PARTICLES

Lemoine D; Deschuyteneer M; Hogge F; Preat V Louvain,Universite Catholique; SmithKline Beecham Biologicals SA

The potential of poly(D,L-lactide-co-glycolide) nano- and microspheres, with a mean diameter of 220 nm and 8 micro m, respectively, for enhancing the nasal and systemic immune responses against influenza virus antigen was evaluated. High encapsulation levels of antigen were achieved in all cases. Neither the molec.wt. nor the antigenicity of the entrapped antigen were affected by the encapsulation procedure. Following nasal immunisation, the nasal washes IgA and the serum 1gC responses were evaluated. With the soluble antigen, relatively high immune responses were observed. With nanospheres, nasal washes IgA levels were significantly lower and serum lgC levels were not significantly different from those obtained with the soluble antigen. With microspheres, both nasal washes IgA and serum IgC levels were significantly lower that the levels found for the soluble antigen. In addition, fluorescent microspheres administered intranasally failed to reach the nasalassociated lymphoid tissue(NALT). The lack of particle uptake by NALT and the high immunogenicity of the antigen used in this study could explain the absence of enhancement of the immune responses by the polymeric particles. 49 refs.

BELGIUM; EUROPEAN COMMUNITY; EUROPEAN UNION; WESTERN EUROPE

Accession no.748387

Item 206

Polymer International 48, No.8, Aug.1999, p.627-9 NOVEL POLYMERIC CONJUGATE CARRYING TWO DIFFERENT ANTICANCER DRUGS Soo-Chang Song; Chong Ok Lee; Youn Soo Sohn Korea,Institute of Science & Technology; Korea,Research Institute of Chemical Technology

Anti-tumour chemotherapeutic agents, doxorubicin and (dach)platinum(II) complex (where dach is trans-1,2diaminocyclohexane) were introduced into poly(organophosphazene) using L-glutamic acid as a spacer. The in vivo anti-tumour activity increased with increasing (dach)platinum(II) content, the conjugate containing 12.3 mol% of doxorubicin and 47.6 mol% of (dach)platinum(II) having the highest activity. 10 refs. KOREA

Accession no.747695

Item 207

Journal of Microencapsulation 16, No.5, Sept.-Oct.1999, p.639-46 MODIFICATION OF THE INITIAL RELEASE OF A HIGHLY WATER-SOLUBLE DRUG FROM ETHYL CELLULOSE Lin W-J: Wu T L

Taipei, National Taiwan University

An attempt is made to develop a microspherical dosage form for a highly water-soluble drug, fenoterol HBr, by using the water insoluble, non-biodegradable polymer, ethyl cellulose. Fenoterol HBr is used as a model drug, based on its pharmacokinetic properties, i.e. the short halflife, incomplete absorption from the gastro intestinal tract due to the first pass effect. Three factors, the initial amount of drug, the volume of non-solvent (petroleum benzin) and the stirring speed of homogeniser, are varied during microsphere preparation. The release of fenoterol HBr from these microparticulate delivery systems is compared, and a possible release mechanism proposed. The encapsulation efficiency of the drug, the morphology and the particle size of the microspheres are also investigated. The oil-in-oil solvent evaporation method efficiently encapsulates fenoterol HBr in these ethyl cellulose microspheres. A significant increase in the encapsulation efficiency of fenoterol is observed when the drug/polymer ratio decreases from 15 to 5%. The particle size of microparticles is in the range of 10-250 mu, and most microspheres have a particle size less than 100 mu. Only the volume of petroleum benzin shows a significant effect on the particle size of prepared microspheres. Both the initial drug loading and the addition of non-solvent significantly affects the initial release of fenoterol from the ethyl cellulose microspheres. The diffusion-controlled release followed by a constant release is exhibited in these microspheres. 13 refs.

TAIWAN

Accession no.745635

Item 208

Journal of Microencapsulation 16, No.5, Sept.-Oct.1999, p.551-63 CARBOPLATIN-LOADED PLGA MICROSPHERES FOR INTRACEREBRAL INJECTION: FORMULATION AND CHARACTERISATION Chen W; Lu D R Georgia,University

An attempt is made to prepare and characterise injectable carboplatin-loaded poly(D,L-lactic-co-glycolic) acid copolymer (PLGA) microspheres for the intracerebral

treatment of malignant glioma. The microspheres are prepared by an acetone/mineral oil emulsion and solvent evaporation method. Preparation variables are optimised and the following processing conditions result in the highest drug loading and best yields of the microspheres compared with those prepared with the other variables: the PLGA concentration is 8% (w/w) in the internal phase; the emulsifier (Span 80) concentration is 8% (w/w) in the external phase; the ratio of the internal phase:external phase is 1:8; the stirring speed 1500 rpm; the emulsion time is 15 min; the solvent evaporation time is 3.75 hr. Microspheres so prepared are analysed for size distribution, drug loading, in vitro release and morphological characteristics. The drug release in phosphate buffer solution starts with a 10-day slow release period, followed by a fast near zero order release period from 12 to 22 days. The carboplatin release in brain homogenate is slower than in phosphate buffer solution. The morphological changes of the microspheres during the in vitro degradation correlate with the drug release profile. In conclusion, the carboplatin-loaded PLGA microspheres are specifically prepared to meet the specification as an injectable and biodegradable brain implant. 26 refs.

USA

Accession no.745628

Item 209

Revista de Plasticos Modernos 77, No.511, Jan.1999, p.60-70 Spanish BIODEGRADABLE POLYMERS IN MEDICINE:

BIOMEDICAL APPLICATIONS AND CONTRIBUTION TO ADVANCED TISSUE REGENERATION PROCESSES

Gallardo A; Elvira C; San Roman J; Lopez A Instituto de Ciencia y Tecnologia de Polimeros; Avila,Hospital Provincial

Developments in the use of biodegradable polymers in biomedical and surgical applications are reviewed. Applications discussed include tissue engineering, bone fracture fixation devices, resorbable sutures, vascular grafts, temporary barriers for the prevention of postoperative adhesion, artificial skin and systems for controlled drug release. 92 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; WESTERN EUROPE

Accession no.742558

Item 210

Journal of Microencapsulation 16, No.4, July/Aug.1999, p.475-87 EFFECT OF FORMULATION VARIABLES ON IN VITRO DRUG RELEASE AND MICROMERITIC PROPERTIES OF MODIFIED RELEASE IBUPROFEN MICROSPHERES

Perumal D; Dangor C M; Alcock R S; Hurbans N; Moopanar K R

Durban-Westville, University

The influence of formulation variables on the in vitro drug release and micromeritic properties (drug content, particle size diameter and particle size distribution, of microspheres prepared using the emulsion solvent diffusion technique was investigated. The methacrylic polymers, Eudragit RL 100 and Eudragit RS 100, were used to embed the anti-inflammatory drug, ibuprofen, in modified-release microspheres. These polymers were found to modify the drug release properties as a function of polymer type and concentration. The effect of coating of the microspheres with additional Eudragit RS 100 using a fluid bed on the drug release properties of the coated microspheres is also reported. 16 refs.

SOUTH AFRICA

Accession no.741275

ltem 211

ACS, Polymeric Materials Science and Engineering. Vol.76. Conference proceedings. San Francisco, Ca., Spring 1997, p.558-9. 012 ON THE IMPORTANCE OF THE BURST EFFECT DURING DRUG RELEASE FROM POLYMER FILMS Nerrosimban P: Langer P.

Narasimhan B; Langer R Massachusetts,Institute of Technology (ACS,Div.of Polymeric Materials Science & Engng.)

Numerous drug formulations are prepared by loading a drug in a dissolved or dispersed phase within a polymer matrix. When the polymer is placed in contact with a thermodynamically compatible liquid, the polymer begins to release its contents to the surrounding fluid and the drug diffuses through the polymer matrix. The release of the drug could be controlled by the diffusion of the drug, the penetration of the release medium or by relaxation of the polymer chains. Such drug delivery systems have been widely used as controlled drug delivery devices. Since the transport in these devices is usually in one dimension, these designs have resulted in rectangular slabs. In such systems, the rate of release of the drug is inversely proportional to the square root of release time. Drug release models normally do not predict the burst effect, normally observed during release. An analysis to account for the burst effect is presented. 3 refs.

USA

Accession no.738839

Item 212

ACS, Polymeric Materials Science and Engineering. Vol.76. Conference proceedings.

San Francisco, Ca., Spring 1997, p.499-500. 012 INTRACELLULAR DRUG DELIVERY USING PH- AND LIGHT-ACTIVATED DIPLASMENYLCHOLINE LIPOSOMES

Gerasimov O; Qualls M; Rui Y; Thompson D H Purdue University

(ACS, Div. of Polymeric Materials Science & Engng.)

Liposome-encapsulated drugs, currently used for the treatment of cancers and fungal infections, are undergoing accelerated development for applications in gene therapy. These applications utilise actively and passively targeted liposomes as the drug carrier due to their site selectivity, biocompatibility, high drug:lipid ratios and blood clearance characteristics. Unfortunately, existing methods for transporting the liposomal contents to the target cell cytoplasm are either inefficient or lack sufficient plasma stability for in vivo applications. This obstacle is especially problematic for the cytoplasmic delivery of peptides, antisense oligonucleotides, and gene constructs A hybrid liposome system, incorporating both folate receptor-mediated cell targeting and a pH-sensitive trigger using the naturally-occurring vinyl ether-linked phospholipid diplasmenylcholine is reported. This carrier is designed to efficiently deliver the liposomal contents to the cytoplasm of KB cells, a human nasopharyngeal epidermal carcinoma cell line, upon exposure to their acidic endosomal compartments. Acid-catalysed hydrolytic triggering in this system is analogous to the photoinduced triggering previously reported for plasmenylcholine liposomes, as both triggering approaches utilise chemical activation mechanisms to produce lipid phase transitions by degrading lamellar phase-forming phospholipids to a pair of single-chain surfactant products. 8 refs.

USA

Accession no.738810

Item 213

ACS, Polymeric Materials Science and Engineering. Vol.76. Conference proceedings. San Francisco, Ca., Spring 1997, p.495-6. 012 LIPOSOMES: DELIVERY SYSTEMS FOR NOVEL THERAPEUTIC AGENTS Taylor P W

Ciba Pharmaceuticals

(ACS,Div.of Polymeric Materials Science & Engng.)

The unique properties of liposomes make them particularly promising vehicles for the in vivo delivery of a wide variety of drugs. Liposomes are closed vesicles that enclose an internal aqueous space; this internal compartment is separated from the external environment by one or a number of lipid bilayer membranes composed of discrete lipid molecules. These stable particulate structures can be prepared from a wide variety of lipids over a wide range of sizes. The presence of an aqueous compartment, which distinguishes them from other particulate carrier systems such as oil-in-water emulsions, can be used to accommodate hydrophilic drugs, whereas hydrophobic drug molecules can be incorporated into the lipid bilayer in therapeutically meaningful quantities. Thus, liposomes have been used to entrap a wide variety of drugs that include anticancer, antifungal, antibacterial and anti-inflammatory agents. Traditionally, the

membrane components of liposomes have been phospholipids, particularly phosphatidyl cholines, partly because they are the building blocks that nature itself uses to form membranes and partly because the common phospholipids are lamella-forming lipids under all conditions and form stable structures without the need of other components. However, incorporation of cholesterol into phospholipid bilayers has facilitated the design of vehicles with altered rates of drug leakage and residence time in the circulatory system. Bilayer membrane vesicles have been constructed rising single-chain aniphiphiles or non-ionic surfactants which have properties similar or complimentary to conventional liposomes. 10 refs. EUROPEAN COMMUNITY; EUROPEAN UNION; UK;

WESTERN EUROPE

Accession no.738808

Item 214

ACS, Polymeric Materials Science and Engineering. Vol.76. Conference proceedings. San Francisco, Ca., Spring 1997, p.234-5. 012 **GEL-COATED CATHETERS AS DRUG DELIVERY SYSTEMS** Gehrke S H; McBride J F; O'Connor S M; Zhu H;

Fisher J P

Cincinnati, University

(ACS, Div. of Polymeric Materials Science & Engng.)

Medical catheters are often coated with hydrogels to increase lubricity to aid insertion. This coating can also absorb therapeutic agents which can be released as needed during catheter use. Basic information about the nature of a hydrogel coating is needed to optimise the coating's ability to deliver therapeutic drug directly to the desired location. Catheters can be coated with anionic, cationic or non-ionic gel coatings. In the initial phase of this work, it was necessary to prove that the gel coatings on commercially available catheters behaved as bulk gels by examining the swelling of the gel as a function of pH and ionic strength and its interactions with cationic and anionic solutes and proteins. Based on this information, work has been initiated to develop novel gel coatings and drug loading techniques which are optimised for drug delivery applications rather than lubricity.

USA

Accession no.737993

Item 215

ACS, Polymeric Materials Science and Engineering. Vol.76. Conference proceedings.

San Francisco, Ca., Spring 1997, p.367-8. 012 WATER-SOLUBLE IONIC COPOLYMERS WITH POLYPHOSPHAZENE BACKBONE AS MATERIALS FOR CONTROLLED RELEASE TECHNOLOGIES

Andrianov A K; Sargent J R; Sule S S; LeGolvan M P; Payne L G

Virus Research Institute Inc.

(ACS, Div. of Polymeric Materials Science & Engng.)

Interest in polyphosphazenes as materials for biomedical uses, especially for use in drug delivery and controlled release technology, has increased dramatically recently. Poly(di(carboxylatophenoxy)phosphazene) (PCPP) appears to be of particular interest as a biomaterial because of its ability to form hydrogel microcapsules under mild physiological conditions and also because of its powerful immunoadjuvant properties. However, hydrophobicity of the side groups, being apparently one of the important parameters in this phosphazene polyelectrolyte, also leads to a decreased polymer solubility and swellability under neutral, acidic and higher ionic strength conditions that can limit some of this polymer's potential applications. In order to expand the solubility range of carboxylatophenoxy groups containing polyphosphazene and to investigate the effect of the increased hydrophilicity on the functional properties of polymer, such as adjuvant activity and microcapsule formation, the mixed substituent copolymers of PCPP and polyphosphazenes with hydrophyllic alkyl ether alkoxy groups are synthesised. Their preparation, characterisation and physicochemical studies are reported, together with their potential for controlled release and vaccine delivery applications. 8 refs.

USΛ

Accession no.737090

Item 216

Journal of Materials Science:Materials in Medicine 10, No.5, May 1999, p.301-7 HYDROGELS BASED ON CHITOSAN AND DEXTRAN AS POTENTIAL DRUG DELIVERY SYSTEMS Cascone M G; Maltinti S

Pisa,University

PVAI was blended in different ratios with dextran and chitosan, respectively, and the blends were used to prepare hydrogels, using a freeze-thawing method. The hydrogels were loaded with human growth hormone(GH) and their potential use as delivery systems was investigated. The release with time of PVAl, in aqueous medium, was also monitored and evaluated. SEM was used to investigate the structure of the hydrogels. The results obtained indicated that GH could be released from both dextran/PVAl and chitosan/PVAl hydrogels. The initial GH concentration used for sample loading affected the total amount of GH released but not the pattern of release. The amount of GH released was affected by the content of the biological component. The percentage of PVAl released was low but it was, however, related to the content of chitosan and dextran in the blends. 24 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; ITALY; WESTERN EUROPE Accession no. 734625

Item 217

Polymer Preprints. Volume 40. Number 1. March 1999. Conference proceedings. Boston, Ma., March 1999, p.501-2. 012 **BIODEGRADABLE HYDROGELS FOR CONTROLLED CELL AND DRUG DELIVERY** Bouhadir K H; Rowley J A; Kruger G M; Lee K Y; Mooney D J Michigan,University (ACS,Div.of Polymer Chemistry)

Sodium alginate has found a wide use in tissue engineering applications as a cell and drug delivery vehicle. Alginate is a natural polymer extracted from seaweed, and is comprised of block polymers of beta-mannuronic acid, alpha-Lguluronic acid, and an alternating sequence of both sugars. An attractive feature of alginate is its gentle gelling behaviour in the presence of divalent cations such as calcium to form hydrogels. However, cells cannot directly adhere to alginate, and alginate is not truly biodegradable. It dissolves in an uncontrolled manner following the loss of calcium ions. Furthermore, alginate hydrogels have limited mechanical properties. Cell adhesion ligands have been successfully coupled to the alginate backbone. These ligands promote cell adhesion and proliferation. New polymers have also been developed derived from alginate that are biodegradable, have controllable mechanical properties and allow the coupling of cell adhesion peptides. These polymers show promise in both cell and drug delivery applications. 6 refs.

USA

Accession no.730435

ltem 218

Polymer Preprints. Volume 40. Number 1. March 1999. Conference proceedings. Boston, Ma., March 1999, p.359-60. 012 **POLYSACCHARIDE AS A DRUG COATING POLYMER** Lee K; Na K; Kim Y Chonnam,National University

(ACS,Div.of Polymer Chemistry)

There has been recent interest in using biopolymers, such as polysaccharide or proteins, as a biodegradable hydrogel in drug delivery systems. The use of polysaccharides as matrices for controlled release has received considerable attention and the use of hydrophilic polysaccharides has been proposed since their ingestion never produces adverse dietary, physiological or toxic effects in animals or humans. A large number of polysaccharides are able to form physical gels by using simple modification. A pullulan, lactan, guar gum and dextran are acetylated. Pullulan acetate and lactan acetate are known to have a pH sensitivity and dextran is known to be degradable by dextranase in the colon. The synthesis of polysaccharide microspheres for pH-sensitive drug delivery and enzyme sensitive drug release is described. 7 refs.

KOREA

Accession no.730085

ltem 219

Polymer Preprints. Volume 40. Number 1. March 1999. Conference proceedings. Boston, Ma., March 1999, p.355-6. 012 **IONICALLY CROSSLINKED POLYPHOSPHAZENE MICROSPHERES** Andrianov A K; Chen L; Sule S S Avant Immunotherapeutics Inc. (ACS,Div.of Polymer Chemistry)

Polymeric hydrogel microspheres have been used extensively in the development of advanced drug delivery systems and controlled release technologies. In particular, polyphosphazene hydrogel microspheres are of interest as carriers for a variety of prophylactic and therapeutic agents due to good biocompatibility and the fact that they can be designed to generate any combination of properties needed for specific biomedical application. Microspheres based on phosphazene polyelectrolytes, such as poly(di(carboxylatophenoxy)phosphazene) (PCPP) also display powerful immunostimulatory properties, making them ideal candidates for vaccine delivery vehicles. A novel method of preparing ionotropic polyphosphazene hydrogel microspheres with controlled microsphere size distribution has recently been examined. The potential of the coacervation method in the preparation of polyphosphazene hydrogel microspheres with controlled erosion properties is examined. In particular, the effect of the ionic crosslinker on the erosion characteristics of microspheres under physiological conditions is studied. The preparation, characterisation and study of the hydrolytic stability of polyphosphazene microspheres crosslinked with aluminium ions are described. 8 refs. USA

Accession no.730083

Item 220

Polymer Preprints. Volume 40. Number 1. March 1999. Conference proceedings. Boston, Ma., March 1999, p.314-5. 012 **ORAL DELIVERY OF MACROMOLECULAR DRUGS** Leone-Bay A Emisphere Technologies Inc.

(ACS,Div.of Polymer Chemistry)

During the past decade, dramatic progress in the field of biotechnology has resulted in a large increase in the number of commercially available macromolecular drugs that require, for a multitude of reasons, parenteral dosing. These new drugs have enormous therapeutic potential, but their use is often limited by their invasive route of administration and with it the complications of patient discomfort and noncompliance. Non-parenteral macromolecular drug delivery has obvious benefits but represents a major clinical challenge because these drugs are plagued by poor absorption, rapid metabolism, and biological and chemical instability. A variety of non-invasive routes of administration for these new therapeutics are under investigation including pulmonary, nasal, transdermal, buccal and oral. Of these methodologies, the most desirable route is the oral route, but it is also the most difficult because the gastrointestinal tract is designed to degrade large molecules and to prevent their absorption. A new approach to oral drug delivery is described as the design and synthesis of novel, peptide-like delivery agents that promote the gastrointestinal absorption of macromolecular drugs like Interferon, recombinant human growth hormone and heparin. These delivery agents can be administered in combination with macromolecular drugs to effect their oral absorption. 5 refs.

USA

Accession no.730076

Item 221

Polymer Preprints. Volume 40. Number 1. March 1999. Conference proceedings.

Boston, Ma., March 1999, p.288-9. 012

PENTANYL-LOADED PLGA MICROSPHERES FOR LOCAL ANAESTHESIA

Lee H B; Khang G; Cho J C; Rhee J M; Lee J S KRICT; Chonbuk, National University; Samchundang Pharmaceutical Co.

(ACS, Div. of Polymer Chemistry)

The development of long-acting local anaesthetics is needed for post-operative analgesia and control of chronic pain for cancer patients. Several attempts have been made to prolong the action of local anaesthetic. One example is a transdermal therapeutic system fentanyl known as Durageic. It is intended for the treatment for chronic pain requiring strong opioids, but not for the treatment of acute pain such as post-operative pain, as it is not possible to individualise and titrate the dose to an effective and safe level in painful conditions requiring short-term treatment; i.e., the precise control of fentanyl release rate through skin is difficult. Fentanyl citrate (FC) is developed for highly water soluble small drug loaded poly(lactide-coglycolide) microspheres (MSs) for local anaesthesia with precise and effective control of FC administration over 15 days. An attempt is made to develop and characterise biodegradable drug delivery systems, prepare FC/PLGA MSs by a novel W' (acetic acid)/O (acetonitrile, MeCN)/ O (mineral oil) method to achieve the higher initial loading efficiency and the more homogeneous distribution of FC in MSs and compare with O (MeCN)/O (mineral oil) method and to investigate the effect of the experimental condition on morphology of MSs. Finally, the in vitro release pattern of FC and the biodegradation of FC/PLGA MSs is observed by high performance liquid chromatography and scanning electron microscopy. 7 refs. KOREA

Accession no.730068

Item 222

Polymer Preprints. Volume 40. Number 1. March 1999. Conference proceedings.

Boston, Ma., March 1999, p.256. 012 **STRATEGIES OF ORAL DRUG DELIVERY** Lee V H L Southern California, University (ACS, Div. of Polymer Chemistry)

The development of innovative oral drug delivery systems is imminent. This is due to a better understanding of gastrointestinal physiology and cell biology, a better appreciation of the interplay of polymer chemistry and cell biology, and the avalanche of drug candidates made possible by high throughput drug discovery paradigm. Targeted drug delivery to the colon is used to illustrate the impact of the first two factors. The colon is an attractive site for oral peptide drug delivery for three reasons: availability of systems targeting drug release in the colon; low protease activity compared to the small intestine; and relative low drug efflux activity due to the P-glycoprotein 170, which has been shown to deter the passive diffusion of lipophilic peptides such as cyclosporine A. 22 refs.

USA

Accession no.730059

Item 223

Polymer Preprints. Volume 40. Number 1. March 1999. Conference proceedings. Boston, Ma., March 1999, p.254-5. 012 **BARRIERS AND POTENTIAL SOLUTIONS TO CONTROLLED DRUG DELIVERY ACROSS MUCOSAL TISSUES** Robinson J R Wisconsin,University (ACS,Div.of Polymer Chemistry)

Optimum delivery of drugs across mucosal tissue barriers entails an understanding of the important biological barriers limiting drug delivery and successful strategies to deal with these issues. While drug related issues such as water solubility and hydrolytic/oxidative stability can be limiting concerns for specific drugs, it is the biological barriers that are common concerns. The two most important biological barriers are clearance of drug and drug delivery system from the extended site of absorption and lack of adequate permeability across the absorbing tissue. 4 refs.

USA

Accession no.730058

Item 224

ACS Polymeric Materials Science & Engineering. Volume 74. Conference proceedings. New Orleans, La., Spring 1996, p.372-3. 012 **RELEASE OF INSULIN FROM GLUCOSE-SENSITIVE HYDROGELS** Podual K; Doyle F J; Peppas N A

Purdue University (ACS,Div.of Polymeric Materials Science & Engng.) One of the promising methods for the treatment of diabetes mellitus is by insulin release from a hydrogel device that incorporates glucose and pH sensitivity. Environmentally-sensitive gel devices are preferred as they can be designed to respond to glucose concentration in a way that would simulate biological conditions. Environment-sensitive hydrogels with pH sensitivity have been used often for the controlled release of drugs. For example, anionic gels, such as, poly(methacrylic acid-gethylene glycol) swell at high pH and deswell at low pH values. The drug inside the gel may be 'squeezed out' due to the collapse. Cationic gels exhibit an opposite equilibrium swelling behaviour. In general, a decrease in the pH induces the gel to swell and the drug to be released from the network. Cationic hydrogels of poly(diethyl aminoethyl methacrylate-g-ethylene glycol) are used to study the release of insulin at desirable time intervals. These hydrogels are pH sensitive, and can swell at low pH values. Incorporation of glucose oxidase in these gels renders them glucose-sensitive. Thus, these gels react with glucose from the surrounding medium in the presence of glucose oxidase to produce gluconic acid and hydrogen peroxide. The formation of acid in the micro environment induces the gel to swell releasing the insulin incorporated in it. In general, the oxidation reaction of the glucose is limited by the amount of oxygen in the medium. This limitation can partially be overcome by the addition of catalase which is capable of reducing hydrogen peroxide to oxygen and water. 7 refs.

USA

Accession no.724752

Item 225

ACS Polymeric Materials Science & Engineering, Spring Meeting 1998. Volume 78. Conference proceedings.

Dallas, Tx., Spring 1998, p.194.012 SYNTHESIS AND CHARACTERISATION OF A POLYMERIC PRODRUG

Erdmann L; Uhrich K Rutgers, University (ACS, Div.of Polymeric Materials Science & Engng.)

An attempt is made to synthesise a polymer that will act as a controlled delivery device in targeting specific areas, such as the colon, over an extended period of time. The polymers being synthesised, polyanhydride esters, are composed of alkyl chains linked by ester bonds to aromatic moieties, specifically salicylic acid - the active component of aspirin. With the medicinal properties attributed to salicyclic acid and the ease of metabolism, the incorporation of this compound into a polymer backbone yields a polymeric prodrug that may have potential in a variety of applications, in particular, inflammatory bowel disease. For these reasons, a synthetic scheme that yields the desired polyanhydride esters is designed. Characterisation of the polymers is performed and presented along with preliminary in vitro and possible in vivo degradation studies. Interest in these polymers arises from the fact that the polymer degradation products may reduce inflammation associated with inflammatory bowel disease. This abstract includes all the information contained in the original article.

USA

Accession no.719111

Item 226

Journal of Applied Polymer Science 71, No.11, 14th March 1999, p.1819-21 APPLICATION OF MOLECULARLY IMPRINTED POLYHEMA AS A TEMPLATE RESPONSIVE RELEASE SYSTEM Sreenivasan K

Sree Chitra Tirunal Inst.for Med.Sci.& Technology

Polyhydroxyethyl methacrylate imprinted for hydrocortisone was used to absorb testosterone. Potential applications for developing drug release systems capable of modulating release with respect to the presence of specific molecules are discussed. 12 refs. INDIA

Accession no.716990

Item 227

ACS Polymeric Materials Science and Engineering. Fall Meeting 1998. Volume 79. Conference proceedings. Boston, Mas., 23rd-27th Aug.1998, p.278-9. 012 **POLYMERIC MICELLE SYSTEM FOR DRUG TARGETING** Kataoka K

Tokyo, University

There has been a strong impetus for developing efficient systems for site-specific delivery of drugs by the use of appropriate vehicle systems. Nanoscopic vehicles having a microcontainer separated from the outer environment are promising for this purpose. Block copolymers composed of hydrophobic and hydrophilic segments have the potential to form self-associates (micelles) in aqueous milieu. The hydrophobic segment forms the hydrophobic core of the micelle, while the hydrophilic segment surrounds the core as a hydrated outer shell. Since most drugs have a hydrophobic character, these drugs are easily incorporated in the inner core segment either by covalent bonding or by non-covalent bonding through hydrophobic interaction with core-forming segments. 17 refs.

Accession no.713387

Item 228

ACS Polymeric Materials Science and Engineering. Fall Meeting 1998. Volume 79. Conference proceedings. Boston, Mas., 23rd-27th Aug.1998, p.269-70. 012

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WATER-SOLUBLE DENDRIMERS AS POTENTIAL DRUG CARRIERS Liu M; Kono K; Frechet J M J California,University

Polymers used in drug delivery systems have been widely studied as the therapeutic efficacy of many low molecular weight drugs can be improved by combining them with polymers. Furthermore, controlled and/or targeted delivery of drugs can be obtained by using polymeric delivery systems. Drugs can either be physically mixed with a polymer matrix, or chemically bound to an appropriate polymer carrier, generally through a biodegradable linkage. Dendrimers are highly branched, three-dimensional macromolecules that have attracted much attention in recent years due to their unique structure and properties. The well-defined structure, size, and controllable surface functionalities of dendrimers make them excellent potential candidates for use as drug carriers. Therefore, drugs can be either entrapped within dendritic structure or attached to their surface to form conjugates. Although dendrimers; have been proposed as novel drug/gene delivery systems, only a few studies have been reported. A simple design of a dendrimer-based drug carrier that may be used to advantage in drug delivery schemes is reported. As most drugs are hydrophobic, polyethylene glycol chains are attached to the dendrimer to render the dendrimer-drug conjugates water soluble. In order to incorporate both PEG and drug molecules into dendrimers, a polyether dendrimer with two different types of surface functionalities is prepared, and PEG and model drug molecules are attached, respectively. 7 refs. USΛ

Accession no.713384

Item 229

ACS Polymeric Materials Science and Engineering. Fall Meeting 1998. Volume 79. Conference proceedings.

Boston, Mas., 23rd-27th Aug.1998, p.493-4. 012 CONTROLLED RELEASE WITH DOSAGE FORMS MADE OF CORE AND SHELL WITH DIFFERENT DRUG CONCENTRATION Ouriemchi E M; Vergnaud J M

Saint Etienne, University

With conventional oral therapeutic systems with drug immediate release, the drug passes quickly into the blood compartment, leading to high peaks of concentration followed by low troughs resulting from the following stage of elimination. Thus the plasma level alternates between high peaks and low troughs, either above or below the therapeutic concentrations, and bad side effects may result. Controlled release dosage forms orally taken are able to deliver the drug at a more controlled rate, and they are associated with a more constant plasma drug level. Generally these dosage forms with controlled release consist of the drug dispersed into a polymer playing the role of matrix. When the amount of liquid entering the stable polymer is low, the diffusivity is constant, while a high amount of liquid is associated with a swelling and a concentration-dependent diffusivity. A main drawback appears when the drug release is controlled by diffusion, with the rate of dissolution which is very high at the beginning and decreases exponentially with time, without telling that all the drug is released after infinite time. In order to reduce this inconvenience, dosage forms made of a core and shell have been studied, with a lower drug concentration in the shell. Thus the rate of drug delivery is lower at the beginning and more constant than that obtained without shell. 12 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; FRANCE; WESTERN EUROPE

Accession no.713369

Item 230 Chemical and Engineering News 77, No.3, 18th Jan.1999, p.63 **HYPERBRANCHED POLYMERS DELIVER DRUGS STEADILY** Rouhi M

Rutgers University has developed a new series of highly branched water-soluble polymers for use as controlledrelease drug delivery materials. A series of polymers has been prepared that behave like unimolecular micelles. The polymers maintain the good characteristics of conventional micelles, but they are not sensitive to concentration changes in the body which can affect micelle integrity. The polymers are assembled from mucic acid, fatty acids and polyethylene glycol.

RUTGERS,UNIVERSITY USA

Accession no.711195

Item 231

Macromolecular Chemistry and Physics 199, No.11, Nov.1998, p.2601-8 LECTIN-N-(2-HYDROXYPROPYL)METHACRYLAMIDE COPOLYMER CONJUGATES. POTENTIAL ORAL DRUG CARRIERS FOR TARGETTING DISEASED TISSUES

Wroblewski S; Kopeckova P; Rihova B; Kopecek J Utah, University; Czech Republic, Academy of Sciences

Conjugates of N-(2-hydroxypropyl)methacrylamide copolymer with two lectins, i.e.peanut agglutin and wheat germ agglutin were synthesised. Biorecognition of these two conjugates by healthy rat intestinal tissue resulted in different binding by the two materials. The one containing wheat germ agglutin showed strong binding whereas the one containing peanut butter showed minimal, but specific binding. This differential binding suggests that sitespecific drug delivery via specific lectin recognition may be feasible for treatment of colon inflammation or cancer since drugs could target inflamed areas. 33 refs.

CZECH REPUBLIC; USA

Item 232

Polymers for Advanced Technologies 9, Nos.10-11, Oct.-Nov.1998, p.786-93 **CARRIER-BOUND PLATINUM AND IRON COMPOUNDS WITH CARCINOSTATIC PROPERTIES**

Neuse E W

Witwatersrand, University

Polymer bound diaminedichloroplatinum complexes for cancer treatment are briefly discussed. Organoiron compounds of the ferrocene type are also mentioned. A series of water-soluble ferrocene conjugates are presented in which ferrocenylbutanoic acid is reversibly polymerbound by coupling with pendant amino groups. 43 refs. SOUTH AFRICA

Accession no.702994

Item 233

Journal of Microencapsulation 15, No.6, Nov./Dec.1998, p.789-801 IODO-2'-DEOXYURIDINE(IUDR) AND 125IUDR LOADED BIODEGRADABLE MICROSPHERES FOR CONTROLLED DELIVERY TO THE BRAIN Reza M S; Whateley T L

Strathclyde, University

A sustained local release system for radiolabelled I-125 IUdR from biodegradable polymeric microspheres was developed to facilitate the controlled delivery of 125IUdR to brain tumours. Poly(lactic-co-glycolic acid)(PLGA) microspheres containing the Auger-electron emitter 125I as 125IUdR and cold IUdR were prepared using various emulsion-solvent evaporation methods and the in vitro release profiles of IUdR and 125IUdR from these microspheres of PLGA were studied. 25 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.700288

Item 234

Journal of Biomedical Materials Research (Applied Biomaterials)

43, No.3, Fall 1998, p.313-7 ORAL MUCOSAL ADHESIVE FILM CONTAINING LOCAL ANAESTHETICS: IN-VITRO AND CLINICAL EVALUATION

Yamamura K; Ohta S; Yano K; Yotsuyanagi T; Okamura T; Nabeshima T

Nagoya, University; Nagoya, City University

In-vitro and in-vivo studies were conducted to gauge the effectiveness of a novel oral mucosal adhesive, moderately water-soluble, pliant polymer artificial dentifrice film containing dibucaine for relief of pain due to oral erosion. The film was prepared from a hydroxypropyl cellulose-M ethanol solution containing varying amounts of dibucaine, as well as polyethylene glycol. 9 refs.

JAPAN

Accession no.697199

Item 235

Pure and Applied Chemistry 70, No.6, June 1998, p.1283-7 NEW CONCEPTS IN CONTROLLED DRUG DELIVERY Rao K P India,Central Leather Research Institute

Details are given of the preparation of collagen polyhydroxyethyl methacrylate hydrogels as implants for the delivery of anticancer drugs. The controlled release of contraceptive steroids was examined using hybrid copolymers of collagen with PEG and polyvinylpyrrolidone. 4 refs.

NDIA

Accession no.696014

Item 236

European Polymer Journal 34, No.9, Sept.1998, p.1283-93 **KINETICS OF A DRUG RELEASE FROM A DELAYED RELEASE DEVICE** Bichara A; Montheard J P; Taverdet J L

Saint Etienne, University

The reaction of the sodium salt of benzoic acid with methacryloyl chloride was shown to result in an anhydride which could be polymerised by a radical process or copolymerised with various percentages of ethylene glycol dimethacrylate to obtain crosslinked products. Hydrolysis reactions of the resulting polymers were carried out in various aqueous solutions and the rate of release of benzoic acid (used to simulate a drug) appeared to depend on both the percentages of crosslinking comonomer and the pH of the solution. A model is proposed for the delayed release of benzoic acid. 14 refs. EUROPEAN COMMUNITY; EUROPEAN UNION; FRANCE; WESTERN EUROPE

Accession no.695449

Item 237

Polymer 39, No.25, 1998, p.6251-9 **THERMOGELATION OF METHYLCELLULOSES: NEW EVIDENCE FOR UNDERSTANDING THE GELATION MECHANISM**

Hirrien M; Chevillard C; Desbrieres J; Axelos M A V; Rinaudo M CERMAV-CNRS; INRA

The thermal gelation of commercial samples of methyl celluloses with a heterogeneous distribution of substituents, and laboratory made samples with more homogeneous distributions, was investigated by cloud point and rheological measurements, differential scanning calorimetry, fluorescence spectroscopy, light scattering, exclusion chromatography and nuclear magnetic resonance spectroscopy. It was concluded that hydrophobic interactions were the origin of the gelation, irrespective of the composition of the material, and that trisubstituted units were required for the proposed mechanism. 34 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; FRANCE; WESTERN EUROPE

Accession no.694447

Item 238

Biomaterials 19, No.13, July 1998, p.1119-36 SKIN ADHESIVES AND SKIN ADHESION. I. TRANSDERMAL DRUG DELIVERY SYSTEMS Venkatraman S; Gale R ALZA Corp.

The use of pressure-sensitive adhesives(PSAs) for skincontact applications is discussed and the requirements of these adhesives in various applications are examined. Commercially-available classes of PSAs used for skincontact applications include acrylics, polyisobutylenes and silicone polymers. Particular attention is paid in this review to transdermal drug delivery. The role of the PSAs in two types of transdermal designs is described and correlations between in-vivo and ex-vivo measurements of adhesion are discussed. Reports in the literature on human studies of various commercially-available transdermal systems are examined critically, with the aim of assessing the relative performance capabilities of each type of transdermal design. A list of currently commercialised transdermals is presented. 32 refs. USA

Accession no.691448

Item 239

Advanced Materials and Processes 153, No.6, June 1998, p.16 MESHLIKE MATERIAL IMPROVES DRUG DELIVERY, MEMBRANES

A class of materials has been developed that has potential applications from a coating that would repel liquids to a membrane for waste water treatment and drug delivery, report researchers at Purdue University, West Lafayette, Indiana. The copolymer networks are built from intersecting chains of small molecules linked together to form a larger mesh-like structure. The monomers are acrylic acid and a derivative of oligoethylene glycol. The materials are particularly suited for separation applications, such as filtering mechanisms for waste water treatment, where only certain substances are allowed to pass through the mesh formed by the interlacing polymers. As the acrylic acid content is increased, the oligoethylene glycol chains move further apart, increasing the mesh size, and determining the substances that can pass through. The acrylic acid makes the materials sensitive to the acidity of the environment. Thus a capsule incorporating the copolymer network and containing a particular drug,

could remain closed in the mouth, but open in the stomach to release the drug. The properties can also be modified to absorb various amounts of liquid. This abstract includes all the information contained in the original article.

PURDUE UNIVERSITY USA

Accession no.687894

Item 240

Journal of Applied Polymer Science 69, No.2, 11th July 1998, p.263-9 WATER-SOLUBLE QUATERNARY AMINE POLYMERS AS CONTROLLED RELEASE CARRIERS Konar N; Kim C

Philadelphia, Temple University

New bioerodible, water-soluble materials were prepared by copolymerisation of a monomer containing a quaternary ammonium group (trimethylaminoethyl methacrylate chloride, trimethylaminoethyl acrylate chloride or methacrylamidopropyltrimethylammonium chloride) with an alkyl acrylate or methacrylate monomer (methyl methacrylate, butyl methacrylate, ethyl methacrylate or methyl acrylate). The copolymers were bound with anionic drugs (sodium sulphathiazole and diclofenac sodium) to form water-insoluble complexes. Sodium sulphathiazole was bound to the copolymers more strongly than diclofenac sodium. As the quaternary amine content of the copolymer was increased, the degree of binding of diclofenac sodium to the polymer increased (from 79,9 to 96.2%). Compressed tablets were prepared from the drug-polymer complexes, and their release profiles were well described by the dissociation/erosion mechanism. The release rate constant increased with increasing quaternary amine content of the polymer and decreased as longer alkyl methacrylates were used in the copolymer. The release kinetics were also dependent on the structures of the quaternary amines used. Drug release was independent of the pH and ionic strength of the release medium. 11 refs.

USΛ

Accession no.684700

Item 241

Polymers for Advanced Technologies 9, No.4, April 1998, p.266-70 **POLYURETHANES AS CARRIERS OF ANTITUMOROUS DRUGS**

lskakov R; Batyrbekov E; Zhubanov B; Teleuova T; Volkova M

Kazakhstan, Academy of Sciences

Details are given of the preparation of various drug delivery systems based on PU with antitumour drugs. An in vitro technique was used to determine the release characteristics of drugs into biological media. Thermodynamic parameters of drug release were determined. 12 refs.

KAZAKHSTAN Accession no.679409

Item 242

Macromolecular Rapid Communications 19, No.4, April 1998, p.167-72 THERMALLY INDUCED CORE-SHELL TYPE HYDROGEL BEADS HAVING IPN STRUCTURE Park T G; Choi H K

Korea, Advanced Institute of Science & Technology; Chosun, University

Hydrogel beads composed of calcium alginate and crosslinked polyisopropylacrylamide were prepared based on a simultaneous IPN process. The thermally reversible formation of the core-shell structure in the hydrogel was applied to temperature modulated drug release using indomethacin. 12 refs.

KOREA

Accession no.678599

Item 243

Journal of Microencapsulation 15, No.3, May-June 1998, p.299-318 NEW STRATEGIES FOR THE MICROENCAPSULATION OF TETANUS VACCINE

Schwendeman S P; Tobio M; Joworowicz M; Alonso M J; Langer R

Massachusetts Institute of Technology; Santiago,University

An attempt was made to enhance the stability of tetanus toxoid(TT) in poly(lactide-co-glycolide)(PLGA) by designing a system composed of hydrophilic microcores containing TT surrounded by a hydrophobic PLGA coating. The microcapsules thus prepared actually optimised the stability of the antigen during encapsulation, although release of TT was by a swelling-controlled mechanism. 44 refs. EUROPEAN COMMUNITY; EUROPEAN UNION; SPAIN; USA; WESTERN EUROPE

Accession no.677786

Item 244

Macromolecular Symposia No.127, Feb.1998, p.37-41 STARCH-PVAL-ACETAL: A WATER-SOLUBLE FILM Keilbach A; Tomka I Swiss Federal Institute of Technology

Details are given of the preparation of starch-PVAL copolymer films to package dosage units of active ingredients. Thorough mixing was achieved using a corotating twin screw extruder. Data for mechanical properties and biodegradation are listed. 3 refs.

SWITZERLAND; WESTERN EUROPE

Accession no.672880

Item 245 Medical Device Technology

9, No.2, March 1998, p.10/6 RIGHT TIME AND RIGHT PLACE: CONCEPTS AND CONCERNS OF DRUG DELIVERY SYSTEMS Williams D

Royal Liverpool University Hospital

The distinction between active drugs and active biomaterials is being gradually eroded. One of the areas where the interface between drugs and devices needs greater clarity is controlled delivery of drugs by materials; the basic mechanisms that are involved are described. EUROPEAN COMMUNITY; EUROPEAN UNION; UK; WESTERN EUROPE

Accession no.668798

Item 246

Journal of Biomaterials Applications 12, No.3, Jan. 1998, p.258-71 BIOMEDICAL SILICONE ELASTOMERS AS CARRIERS FOR CONTROLLED RELEASE Andreopoulos A G; Plytaria M Athens, National Technical University

The potential of biomedical siloxane elastomers as carriers for controlled release of drugs was assessed. A twocomponent silicone gel system was used and various crosslinking agent ratio was applied in order to produce networks with varying crosslink density. Swelling experiments in toluene were conducted in order to evaluate the network characteristics. The silicone elastomer was loaded with salicylic acid and propanolol hydrochloride and their delivery in distilled water was followed. The results showed that release was almost of zero order for high loading of salicylic acid, while delivery seemed to be diffusion-controlled up to a certain limit. The drug concentrations administered were relatively low if silicone discs were used, due to the hydrophobic nature of this material. When membranes with a thickness of 0.1-0.2 mm were used, on the other hand, the delivery rate was much higher depending, of course, on the hydrophilic character of the drug. 18 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; GREECE; WESTERN EUROPE

Accession no.668285

Item 247

Journal of Microencapsulation 15, No.1, Jan.-Feb.1998, p.1-19 POLYMER-COATED LONG-CIRCULATING MICROPARTICULATE PHARMACEUTICALS Torchilin V P

Massachusetts General Hospital; Harvard Medical School

A review is presented of the literature on the above, covering the basics of steric protection with polymers, polyethylene glycol(PEG) and other polymers for steric protection of liposomes and particles, polymer-protected
long-circulating liposomes, sterically protected nanoparticles and PEG-containing micelles. 102 refs. USA

Accession no.668262

Item 248 Chimica e l'industria 78, No.2, March 1996, Supplt., p.3-6 Italian SYNTHETIC POLYMERS FOR BIOMEDICINE: DEVELOPMENTS AND APPLICATIONS Sbarbati Del Guerra R

CNR, Institute of Clinical Physiology

A survey is made of developments in the use of polymers in biomedical applications, including vascular prostheses, orthopaedic implants, membranes for haemodialysis and haemofiltration, intraocular and contact lenses, controlled drug release, artificial skin and artificial pancreases. 19 refs.

EUROPEAN COMMUNITY; EUROPEAN UNION; ITALY; WESTERN EUROPE

Accession no.663521

Item 249 Trends in Polymer Science 5, No.12, Dec.1997, p.388-93 HYPERBRANCHED POLYMERS FOR DRUG DELIVERY Uhrich K Rutgers,University

A review is presented of the literature on hyperbranched and dendritic polymers that have already been evaluated as drug carriers or, because of their desirable properties, have potential as drug delivery systems. The characteristics of polymeric drug delivery systems considered include prolonged circulation in the blood, interactions with cell membranes, biodistribution, targeting with antibodies, encapsulation, delivery of drugs and genes, biodegradation, and biocompatibility. Particular attention is paid to polyamidoamine dendrimers. 35 refs.

USA

Accession no.662994

Item 250

Macromolecular Symposia Vol.123, Sept.1997, p.225-34 POLYMER-DRUG CONJUGATES: MANIPULATION OF DRUG DELIVERY KINETICS

Pitt C G; Wertheim J; Wang C T; Shah S S Amgen Inc.

Three methods for manipulating the kinetics of hydrolysis of polymer conjugates were evaluated. It was demonstrated that either first-order, zero-order or S-shaped kinetic profiles could be achieved by systematic changes in the chemical composition of several series of model side-chain substituted polyacrylates. The changes in kinetics were shown to arise from an increase in the rate constant during solvolysis, resulting from predictable changes in either the water content, secondary structure or lower critical solution temp. of the polymer conjugate. 22 refs. (IUPAC 37th Microsymposium on (Bio)degradable Polymers: Chemical, Biological and Environmental Aspects, Prague, Czech Republic, July 1996)

USA

Accession no.658698

Item 251

Journal of Biomaterials Science : Polymer Edition 8, No.11, 1997, p.817-24 PHASE TRANSITION PARAMETERS OF POTENTIAL THERMOSENSITIVE DRUG RELEASE SYSTEMS BASED ON POLYMERS OF N-ALKYLMETHACRYLAMIDES

Chytry V; Netopilik M; Bohdanecky M; Ulbrich K Czech Republic, Academy of Sciences

The phase separation and its thermohysteresis in dilute aqueous solutions of polymeric components of potential drug release systems (polymers and copolymers of Nisopropyl(meth)acrylamide, N-propylmethacrylamide, Nsec-butylmethacrylamide and N-(2-hydroxypropyl) methacrylamide) were studied, both on heating and on cooling. Plots of light transmission versus temp. were constructed and the parameters characterising them were correlated with polymer structures. Qualitative information was obtained on the rate of formation of the concentrated phase on heating and its disappearance on cooling. Attention was paid to the improper identification of the cloud point temp., measured at an arbitrary concentration, with the lower critical solution temp. 28 refs.

CZECH REPUBLIC Accession no.655565

Item 252

Biomaterials 18, No.12, June 1997, p.839-44 **CONTROLLED RELEASE OF ANTIBIOTICS FROM BIOMEDICAL POLYURETHANES: MORPHOLOGICAL AND STRUCTURAL FEATURES**

Schierholz J M; Steinhauser H; Rump A F E; Berkels R; Pulverer G Cologne,University

Antistaphylococcal antimicrobial substances (ciprofloxacin, gentamycin, fosfomycin, flucloxacillin) were incorporated into PUs by the solvent casting technique. Drug release rates, bacterial colonisation and morphological features were evaluated to predict and understand the antimicrobial activity of these delivery systems. PU-antibiotic combinations were most homogeneous for gentamycin-base and flucloxacillin as shown by SEM. In polymers loaded with the other compounds, a granular structure of the crystallised drug embedded in the PU matrix could be demonstrated. 25 refs. EUROPEAN COMMUNITY; EUROPEAN UNION; GERMANY; WESTERN EUROPE

Accession no.637778

Item 253

Journal of Biomaterials Science : Polymer Edition 8, No.5, 1997, p.391-409 **INJECTABLE MICROCAPSULES PREPARED**

WITH BIODEGRADABLE POLY(ALPHA-HYDROXY) ACIDS FOR PROLONGED RELEASE OF DRUGS

Ogawa Y

Takeda Chemical Industries Ltd.

Microencapsulation techniques for the preparation of drug-containing monolithic microcapsules for prolonged release using biodegradable poly(alpha-hydroxy) acids, such as polylactic acid, poly(lactide-co-glycolide) and copoly(lactic/glycolic) acid are reviewed in detail. Phase separation, solvent evaporation, and spray drying procedures are discussed. To achieve controlled-release formulations of highly water-soluble drugs that are entrapped efficiently, various manufacturing techniques and procedures have been developed. 85 refs.

JAPAN

Accession no.632452

Item 254

Angewandte Makromolekulare Chemie Vol.245, March 1997, p.1-8 POLYMERIC PRODRUGS: SYNTHESIS, RELEASE STUDY AND ANTIMICROBIAL PROPERTIES OF POLYMER-BOUND ACRIFLAVINE

Patel H; Raval D A; Madamwar D; Sinha T J M VP & RPTP Science College; Sardar Patel University; Hindustan Inks & Resins Ltd.

Methyl methacrylate-maleic anhydride copolymer matrices with different percentages of surface anhydride functional groups were prepared by solution copolymerisation. Acriflavine was bound on the matrix surfaces by chemical bonding in organic medium. The amount of acriflavine bound to the matrix was spectroscopically characterised, and the in-vitro release rate of acriflavine in weakly basic medium was established along with the determination of its antimicrobial activity. 9 refs.

INDIA

Accession no.632377

Item 255 Advances in Polymer Science No.107, 1993, p.199-265

CELLULOSE DERIVATIVES

Doelker E

Geneva, University

Fundamental and derived properties of cellulose derivatives are presented concomitantly with applications in various life sciences (pharmaceuticals, cosmetics, food, packaging). Emphasis is placed on drug delivery systems. Because most applications are related to solubility of the materials, the subject is reviewed with regard to this parameter: derivatives soluble in water; derivatives soluble in organic solvents; derivatives soluble in organic media and organic solvents; derivatives soluble in water and organic solvents. The data are presented on a comparative basis to emphasise the difference between similar derivatives. 167 refs.

SWITZERLAND; WESTERN EUROPE *Accession no.476704*

Item 256

Journal of Biomaterials Science : Polymer Edition 4, No.3, 1993, p.275-89 RELEASE BEHAVIOUR OF BIOACTIVE AGENTS FROM PH-SENSITIVE HYDROGELS Khare A R; Peppas N A Purdue University

The diffusion behaviour of low molec.wt. drugs (theophylline, proxyphylline and oxprenolol.HCl) from pH-sensitive, anionic, initially glassy copolymer networks of 2-hydroxyethyl methacrylatc with acrylic acid and/or methacrylic acid was studied as a function of pH, ionic strength and the nature of the dissolution medium. The dissolution media used were simulated physiological fluids such as simulated gastric fluid, a phosphate buffer of pH 7.4 and a glutarate buffer solution of pH 7. 19 refs. USA

Accession no.474733

Item 257

Makromolekulare Chemie, Rapid Communications 8, No.10, Oct. 1987, p.481-5 THERMO-SENSITIVE POLYMERS AS ON-OFF SWITCHES FOR DRUG RELEASE Bae Y H; Okano T; Hsu R; Kim S W Utah University

Details are given of the synthesis of a crosslinked isopropylacrylamide-butyl methacrylate copolymer which has thermo-sensitive swelling behaviour. The copolymer was studied for applications as a thermal on-off switch for a pulsatile drug release system. 2 refs.

Accession no.345789

Item 258 Journal of Polymer Science : Polymer Chemistry Edition 20,No.2,Feb.1982,p.319-26

ALIPHATIC POLYESTERS. III. MOLECULAR WEIGHT AND MOLECULAR WEIGHT DISTRIBUTION IN ALCOHOL-INITIATED POLYMERISATIONS OF EPSILON-CAPROLACTONE

Schindler A; Hibionada Y M; Pitt C G

The effect of initiation of epsilon-caprolactone polymerisation with mono- and polyfunctional alcohols was investigated. The resulting linear and star-shaped polymers were characterised by measurement of the molec.wt. and MWD. The polymerisations were characterised by rapid initiation, by invariance of the number of growing chains corresponding to the amount of initiator, and by the dominant role played by ester interchange reactions. 19 refs.

Accession no.208401

Item 259

Journal of Applied Polymer Science 26,No.11,Nov.1981,p.3779-87 ALIPHATIC POLYESTERS. I. DEGRADATION OF POLY-EPSILON-CAPROLACTONE IN VIVO Pitt C G; Chasalow F I; Hibionada Y M; Klimas D M; Schindler A

Results are presented of studies of the degradation of polyepsilon-caprolactone in rabbits, rats and water by measurement of changes in intrinsic viscosity, molec.wt., crystallinity, Young's modulus and weight. 19 refs. *Accession no.203137*

Item 260 Biomaterials 2,No.4,Oct.1981,p.215-20 ALIPHATIC POLYESTERS. II. THE DEGRADATION OF POLY(DL-LACTIDE),POLY(EPSILON-CAPROLACTONE), AND THEIR COPOLYMERS IN VIVO Pitt C G; Gratzl M M; Kimmel G L; Surles J; Schinder

A

The mechanisms of biodegradation of polylactide, polycaprolactone and caprolactone copolymers with dilactide copolymer, valerolactone copolymer, and decalactone copolymer in the rabbit were shown to be qualitatively similar. The rate of the first stage of the degradation process, non enzymatic random hydrolytic chain scission, was found to vary by an order of magnitude and was dependent on morphological as well as chemical effects. 17 refs.

Accession no.179457

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