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Polymers in Controlled Drug Delivery Systems

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ABSTRACT

Biodegradable materials are used in packaging, agriculture, medicine and other areas. In recent years there has been an increase in interest in biodegradable polymers. Two classes of biodegradable polymers can be distinguished: synthetic or natural polymers. There are polymers produced from feedstocks derived either from petroleum resources (non renewable resources) or from biological resources (renewable resources). In general natural polymers offer fewer advantages than synthetic polymers. The following review presents an overview of the different biodegradable polymers that are currently being used and their properties, as well as new developments in their applications.

Keywords: Biodegradable polymers; Synthetic Polymers; Natural Polymers; Novel Drug Delivery Systems

INTRODUCTION

Polymers are becoming increasingly important in pharmaceutical applications especially in the field of drug delivery. Polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions; can also be used as film coatings,

1. to disguise the unpleasant taste of a drug,
2. to enhance drug stability and
3. to modify the release characteristics.

Around sixty million patients benefit from advanced drug delivery systems today, receiving safer and more effective doses of medicines that are needed to fight a variety of human ailments, including life threatening diseases. Examples of pharmaceutical polymers and the principles of controlled drug delivery are outlined in this communiqué/report [1-2].

What is a Drug Delivery System?

A system that formulates or device that delivers therapeutic agent(s) to desired body location(s) and/or provides timely release of therapeutic agent(s), such a system by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called Drug Delivery Systems (DDS), are based on interdisciplinary approaches that combine pharmaceutics, polymer science, analytical chemistry, bioconjugate chemistry, and molecular biology [3-4]. Typical schematic examples of drug delivery systems based on polymers and nano-particulates were given in figure 1.

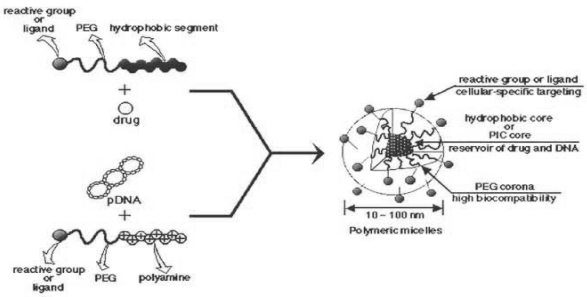

Figure 1. Polymer based drug delivery system

Novel Drug Delivery systems

To deliver drugs efficiently to specific organs, a range of organic systems (e.g., micelles (figure 2) liposomes, and polymeric nanoparticles) novel ways have been designed. In recent decades, significant advances in drug-delivery systems have enabled more effective drug administration. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under research and development. Among the several drug carriers one can name soluble polymers, microparticles (figure 3) made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, nanoparticles, Dendrimers and micelles [5-6].

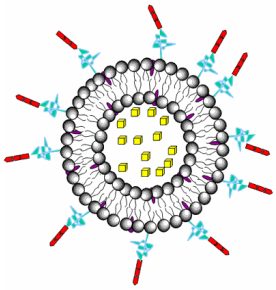

Figure 2. Drug carrier micelle

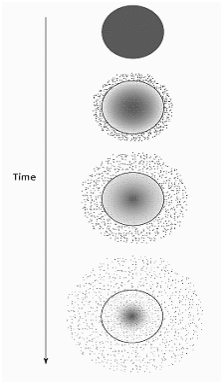

Figure 3. Drug delivery from a typical matrix drug delivery system

Drug Delivery carriers

Colloidal drug carrier systems such as types of polymers, micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. Whilst developing these formulations, the priority is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties [7].

Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions are of great interest for drug delivery applications. The drugs can be physically entrapped in the core of block copolymer micelles and transported at concentrations that can exceed their intrinsic water- solubility. Moreover, the hydrophilic blocks can form hydrogen bonds with the aqueous surroundings and form a tight shell around the micellar core. As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation. In addition, the corona may prevent recognition by the reticulo-endothelial system and therefore, preliminary elimination of the micelles from the bloodstream. A feature that makes amphiphilic block copolymers attractive for drug delivery applications is the fact that their chemical composition, total molecular weight and block length ratios can be easily changed, which allows control of the size and morphology of the micelles. Functionalization of block copolymers with crosslinkable groups the can increase the stability of the corresponding micelles and improve their temporal control. Substitution of block copolymer micelles with specific ligands is a very promising strategy to a broader range of sites of activity with a much higher selectivity.

Controlled drug delivery

Controlled drug delivery is the use of formulation components and devices to release a therapeutic agent at a predictable rate *in vivo* when administered by an injected or non-injected route. To do this, pharmacist and analyst skills are needed to develop and measure release from the formulation, *i.e.* a polymer or device construction. Controlled Drug Delivery (CDD) occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under and overdosing. An example of Controlled drug delivery was shown in figure 4.

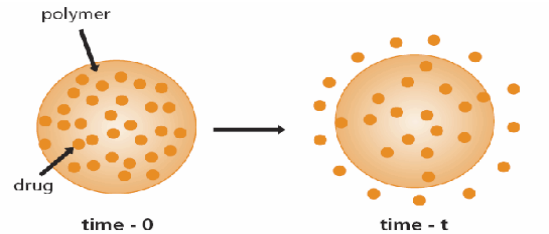

Figure 4. Example for Controlled Drug Delivery (CDD)

Controlled-release methodologies can be classified on the basis of the mechanism that controls the release of the active agent from the delivery device diffusion, osmosis, or polymer erosion. The various polymer erosion mechanisms are of 3 basic types. Type I erosion refers to water-soluble polymers that have been insolubilized by

covalent cross-links and that solubilize as the cross-links (type IA) or backbone (type IB) undergo a hydrolytic cleavage. In type II erosion, polymers that are initially water insoluble are solubilized by hydrolysis, ionization, or protonation of a pendant group. In type III erosion, hydrophobic polymers are converted to small water-soluble molecules by backbone cleavage. The choice of a particular erosion mechanism is dictated by the specific application [8].

The role of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood follows the profile shown in figure 5 in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective. In controlled drug delivery systems designed for long-term administration, remaining constant, between the desired maximum and minimum, for an extended period of time.[9] Depending on the formulation and the application, this time may be anywhere from 24 hours (Procardia XL) to 1 month (Lupron Depot) to 5 years (Norplant).

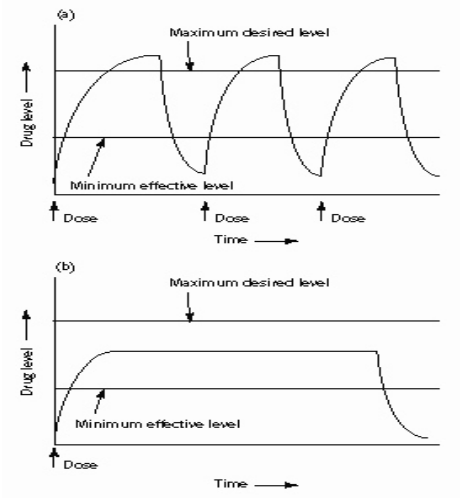

Figure 5. Drug levels in the blood with (a) traditional drug dosing and (b) controlled-delivery dosing.

Biomaterials for Delivery Systems

The polymers in the earlier stage were particularly used for non-biological uses, and were selected because of their desirable physical properties, for example:

a. Poly (urethanes) for elasticity.
b. Poly (siloxanes) or silicones for insulating ability.
c. Poly (methyl methacrylate) for physical strength and transparency.
d. Poly (vinyl alcohol) for hydrophilicity and strength.
e. Poly (ethylene) for toughness and lack of swelling.
f. Poly (vinyl pyrrolidone) for suspension capabilities.

In order to be used for controlled drug delivery formulations, the polymers must be chemically inert and free of leachable impurities with appropriate physical structure, minimal undesired aging, and be readily processable. Few examples are

a. Poly (2-hydroxy ethyl methacrylate)
b. Poly (N-vinyl pyrrolidone)
c. Poly (methyl methacrylate)
d. Poly (vinyl alcohol)
e. Poly (acrylic acid)
f. Polyacrylamide
g. Poly (ethylene-co-vinyl acetate)
h. Poly (ethylene glycol)
i. Poly (methacrylic acid).

However in recent years the use of polymers were extended towards medical applications and drug targeting, few examples are

a. Polylactides (PLA)
b. Polyglycolides (PGA)
c. Poly (lactide-co-glycolides) (PLGA)
d. Polyanhydrides
e. Polyorthoesters

Originally, polylactides and polyglycolides were used as absorbable suture material, and it was a natural step to work with these polymers in controlled drug delivery systems. The greatest advantage of these degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways. However, biodegradable materials do produce degradation by-products that must be tolerated with little or no adverse reactions within the biological environment. These degradation products—both desirable and potentially nondesirable—must be tested thoroughly, since there are a number of factors that will affect the biodegradation of the original materials. The most important of these factors are shown below—a list that is by no means complete, but does provide an indication of the breadth of structural, chemical, and processing properties that can affect biodegradable drug delivery systems [10-11].

Polymer Degradation

Polymer degradation is a change in the properties - tensile strength, colour, shape, etc - of a polymer or polymer based product under the influence of one or more environmental factors such as heat, light or chemicals. Deteriorative reactions occur during processing, when polymers are subjected to heat, oxygen and mechanical stress, and during the useful life of the materials when oxygen and sunlight are the most important degradative agencies. In more specialized applications, degradation may be induced by high energy radiation, ozone, atmospheric pollutants, mechanical stress, biological action, hydrolysis and many other influences. The

mechanisms of these reactions and stabilization processes must be understood if the technology and application of polymers are to continue to advance. The study of all these processes has made extensive use of modern instrumental analytical methods and the various spectrometric, chromatographic and thermal analysis techniques have been particularly prominent. Various routes for degradation of polymers is given in figure 6 and factors affecting polymer degradability (biodegradation) is shown in figure 7.

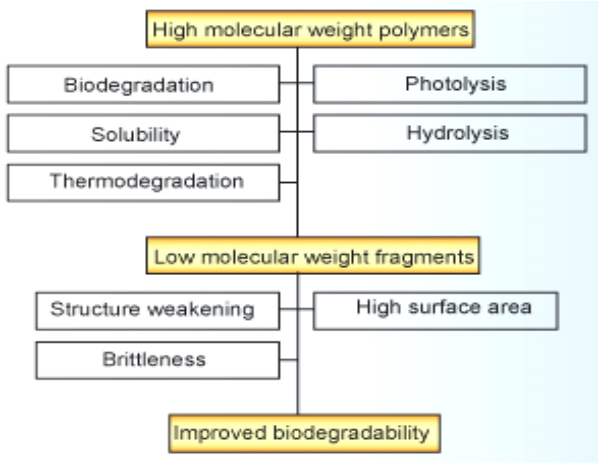

Figure 6. Various routes for degradation of polymers

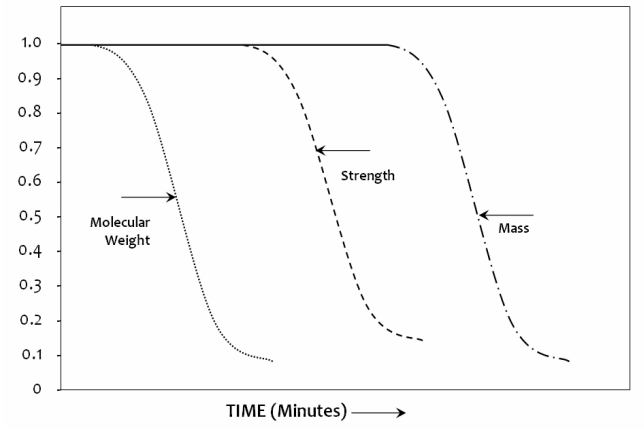

Figure 7. Factors affecting biodegradation of polymers

Some other factors which affect biodegradation of polymers are given in tables 1 and 2.

Biodegradable polymers are a fairly broad region of investigation. At present the application of the various types of biodegradable polymers in therapy, surgery, and pharmacology is considered. In practice resorbable polymers are used, as biocompatible materials as a rule, in the healing period of wounds or in the growth of injured tissues and organs and temporarily fulfill the function of the latter. A resorbable polymer may also play the role of a drug depot providing a more or less long-term supply of drug to the blood at a constant rate [10].

Table 1. Other factors affecting biodegradation of polymers

FACTORS AFFECTING BIODEGRADATION OF POLYMERS		
» *Chemical structure.* » *Chemical composition.* » *Distribution of repeat units in multimers.* » *Presents of ionic groups.* » *Presence of unexpected units or chain defects.* » *Configuration structure.* » *Molecular weight.* » *Molecular-weight distribution.* » *Annealing.*	» *Morphology (amorphous/semi-crystalline, microstructures, residual stresses).* » *Presence of low-molecular-weight compounds.* » *Processing conditions.* » *Sterilization process.* » *Storage history.* » *Shape.* » *Site of implantation.* » *Adsorbed and absorbed compounds (water, lipids, ions, etc.).*	» *Physicochemical factors (ion exchange, ionic strength, and pH).* » *Physical factors (shape and size changes, variations of diffusion coefficients, mechanical stresses, stress- and solvent-induced cracking, etc.).* » *Mechanism of hydrolysis (enzymes versus water).*

Table 2. Biodegradable polymers for medical applications

Polymers	Structure	Tg[1] (°C)	Tm[2] (°C)	Tens. mod.[3] (GPa)	Tensile str.[4] (MPa)	Elonga-tion (%)	Mass degrad. (m)	Strength retention (m)
Polyglycolide (PGA)	-O-CH_2-CO-	35	225	7.0	75	~ 0	3	1
Poly-L-lactide (PLLA)	-O-$CHCH_3$-CO-	55	175	2.7	45	3	18-24	6-12
Poly-D,L-lactide (PDLLA)	-O-$CHCH_3$-CO-	50	none	1.9	n.a.	n.a.	12-16	3-10
Poly-ε-caprolactone (PCL)	-O-$(CH_2)_5$-CO-	- 60	60	0.4	32	750	>24	>24
Poly-1,4-dioxane-2-one (PDO)	-O-CH_2CH_2-O-CH_2-CO-	- 14	110	1.5	36		4-6	1.5
Polytrimethylene-carbonate (PTMC)	-O-$CH_2CH_2CH_2$-O-CO-	- 15	52	0.006	1.2	830	4-8	n.a.
Poly-β-hydroxy-butyrate (PHB) (?)	-O-$CHCH_3CH_2$-CO-	5	175	2.3	26	3	n.a.	n.a.

[1] Glass transition temperature, [2] Melting point, [3] Tensile modulus, [4] Tensile strength

* Copolymers of PGA, PLA, PCL, PTMC

CONCLUSION

Polymers possessing a unique strength in their application towards drug delivery application which enables the new advancement in the formulating new drug delivery systems which improves the therapy and treatment. Although drug delivery technologies, if appropriately applied, should be able to improve therapeutic outcomes, these technologies are required in some instances to simply enable therapy, as is the case with gene therapy and drug targeting. Drug delivery is also intuitively the logical and sensible thing to do. Depositing billions of drug molecules in the blood or gut and allowing the hapless molecules to locate their target, by uncontrolled diffusion, is surely a therapeutic strategy of yesterday and not of tomorrow. Guiding sufficient numbers of molecules in sufficient time directly to their targets is the future. Polymers have helped this endeavor and will continue to enable this effort in the foreseeable future.

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