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A Study on Bio-Degradable Polymers for Medicine Distribution Synthesis and Their Characterization

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Abstract – Polymers are becoming increasingly important in the field of Medicine Distribution. The pharmaceutical applications of polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions. Use of polymer is now extended to control release and targeting Medicine Distribution system. Polymers are obtained from natural source as well as synthesized chemically. Polymers are classified as biodegradable and no biodegradable. Biodegradable polymers have been widely used in biomedical applications because of their known biocompatibility and biodegradability. The present review gives an overview of the different biodegradable polymers that are currently being used in the development of controlled Medicine Distribution system. There are polymers produced from feedstocks derived either from petroleum resources (nonrenewable 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 synthesis and applications.

Keywords: Biodegradable polymers; polyesters; polyamides; polyurethanes; biopolymers; biodegradable polymer blends.

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INTRODUCTION

Drug delivery is the method or process of administering pharmaceutical compound to achieve a therapeutic effect in humans or animals (Tiwari, et al., 2012. Gupta and Kumar, 2012). Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy, safety, as well as patient compliance and convenience (Shaik, et. al., 2012). Controlled drug delivery technology represents one of the most rapidly advancing areas of science in which chemists and chemical engineers are contributing to human health care. Such delivery systems offer numerous advantages compared to conventional dosage forms including improved efficacy, reduced toxicity, and improved patient compliance and convenience. Such systems often use synthetic polymers as carriers for the drugs (Martino, et. al., 2005). The objective of the present review was to compile information about various biodegradable polymers that are currently used in the development of controlled drug delivery system. Biodegradation takes place through the action of enzymes and/or chemical deterioration associated with living organisms. This event occurs in two steps. The first one is the fragmentation of the polymers into lower molecular mass species by means of either abiotic reactions, i.e. oxidation, photo degradation or hydrolysis, or biotic reactions, i.e. degradations by microorganisms. This is followed by bio assimilation of the polymer fragments by microorganisms and their mineralization. Biodegradability depends not only on the origin of the polymer but also on its chemical structure and the environmental degrading conditions. Mechanisms and estimation techniques of polymer biodegradation have been reviewed (Tiwari, et al., 2012). The mechanical behaviour of biodegradable materials depends on their chemical composition (Gupta and Kumar, 2012. Shaik, et. al., 2012) the production, the storage and processing characteristics (Nair and Laurencin, 2006. Kotwal, et. al., 2007) the ageing and the application conditions (Manthina, et. al., 2013).

REVIEW OF LITERATURE:

The same durability properties which make plastics ideal for many applications such as in packaging, building materials and commodities, as well as in hygiene products, can lead to waste disposal problems in the case of traditional petroleum-derived plastics, as these materials are not readily biodegradable and because of their resistance to microbial degradation, they accumulate in the

environment. In addition in recent times oil prices have increased markedly. These facts have helped to stimulate interest in biodegradable polymers and in particular biodegradable biopolymers. Biodegradable plastics and polymers were first introduced in 1980s. There are many sources of biodegradable plastics, from synthetic to natural polymers. Natural polymers are available in large quantities from renewable sources, while synthetic polymers are produced from non-renewable petroleum resources.

Controlled drug delivery system (CMDS): Controlled release dosage forms cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a predetermined rate and for a predetermined time. The majority of these formulations are designed for oral administration; however recently such devices have also been introduced for parenteral administration, ocular insertion and for transdermal application. The most important objective for the development of this system is to furnish an extended duration of action and thus assure greater patient compliance (Kotwal, et. al., 2007)

Advantages of controlled drug delivery: Controlled drug delivery system has various advantages over conventional drug delivery as discussed below (Kotwal, et. al., 2007):

- Decreased occurrence and intensity of adverse effects and toxicity.
- Better drug utilisation and reduced dosing frequency.
- Controlled rate and site of release.
- More uniform drug concentration in systemic circulation.
- Improved patient compliance.
- More reliable and prolonged therapeutic effect.
- A greater selectivity of pharmacological action.

Considerations for Selection of Polymers: The selection of a polymer is a challenging task for controlled drug delivery system because of the inherent diversity of structures and thus it requires a thorough understanding of the surface and bulk properties of the polymer that can give the desired chemical, interfacial, mechanical and biological functions.

The choice of polymer, in addition to its physico-chemical properties, is dependent on the need for extensive biochemical characterization and specific preclinical tests to prove its safety. Surface properties such as hydrophilicity, lubricity, smoothness and surface energy govern the biocompatibility with tissues and blood, in addition to influencing physical properties such as durability, permeability and degradability (Khodaverdi, et. al., 2012). The surface properties also determine the water sorption capacity of the polymers, which undergo hydrolytic degradation and swelling (hydrogels) (Bottino, et. al., 2014). Bulk properties that need to be considered for controlled delivery systems include molecular weight, adhesion, solubility based on the release mechanism (diffusion or dissolution controlled), and its site of action (Kolawole, et. al., 2012).

Structural properties of the matrix, its micromorphology and pore size are important with respect to mass transport (of water) into and (of drug) out of the polymer. For non-biodegradable matrices, drug release in most cases is diffusion-controlled and peptide drugs with low permeability can only be released through the pores and channels created by the dissolved drug phase (Teasdale and Brüggemann, 2013). Polymer should have some characteristics so that specific polymer can be select for the drug delivery system.

Synthetic Biodegradable Polymers: There are various synthetic biodegradable polymers currently being investigated as drug delivery systems or as scaffolds for tissue engineering (Li, et. al. 2013). Biodegradable polymers are mainly used where the transient existence of materials is required and they find applications as sutures, scaffolds for tissue regeneration, tissue adhesives, hemostats, and transient barriers for tissue adhesion, as well as drug delivery systems. Each of these applications demands materials with unique physical, chemical, biological, and biomechanical properties to provide efficient therapy. Consequently, a wide range of degradable polymers, both natural and synthetic, have been investigated for these applications. However, natural polymer composition varying from source to source:

Advantages of Biodegradable Polymers as Drug Carriers: The five most important advantages of Biodegradable polymers as drug carriers include: localized delivery of drug, sustained delivery of drug, stabilization of the drug, release rate which is less dependent on the drug properties and steady release rate with time.

Drug release mechanisms for Controlled drug delivery: The possible drug release mechanisms for polymeric drug delivery are depicted in Figure 1.

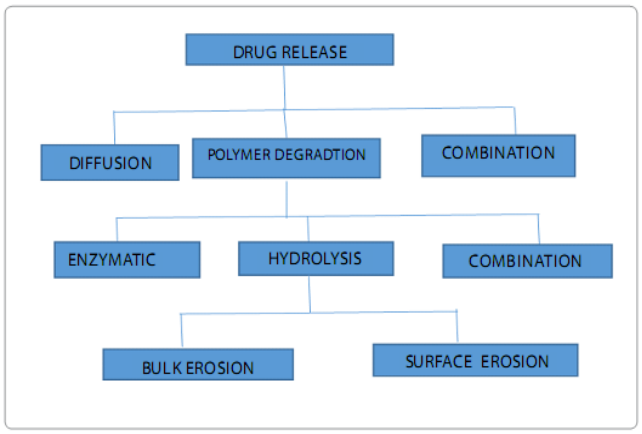

Figure 1: Possible drug release mechanism for controlled drug delivery

Controlled-release approaches can be classified on the basis of the mechanism that controls the release of the pharmaceutically active agent from the delivery system by diffusion, osmosis, or polymer erosion. In some cases, the term 'biodegradation' is limited to the explanation of chemical processes, while 'bio erosion' may be limited to refer to physical processes that result in weight loss of a polymer device. General mechanism for controlled drug delivery system is shown in Figure 2. The degradation is primarily the process of chain cleavage leading to a reduction in molecular weight. On the other hand, erosion is some all of the processes leading to the loss of mass from matrix of polymer. Degradation by erosion normally takes place in devices that are prepared from soluble polymers. In such cases, the device erodes as water is absorbed into the systems causing the polymer chains to hydrate, swell, disentangle, and finally dissolved away from the dosage form. Alternatively, degradation can also result from chemical changes to the polymer including cleavage of covalent bonds, ionization and protonation of polymer backbone or side chains. The erosion mechanism of polymers can be described both physically and chemically.

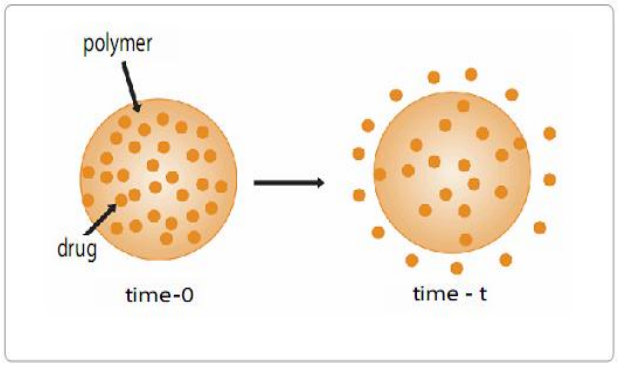

Figure 2: General mechanism of Controlled drug delivery

Factor affecting Biodegradation: Following are the factors which affect the biodegradation process of Polymer.

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

Synthetic Biodegradable Polymers for CMDS:

Polylactic acid (PLA): PLA is thermoplastic biodegradable polymer produced synthetically by polymerization of lactic acid monomers or cyclic lactide dimmers (Figure 3). Lactic acid is produced by fermentation of natural carbohydrates for example, maize or wheat or waste products from the agricultural or food industry. PLA has number of biomedical applications, such as sutures, stents, dialysis media and drug delivery devices. Aliphatic polyester undergoes bio-degradation by bulk erosion. The lactide/glycolide chains are cleaved by hydrolysis to the acids and are eliminated from the body through Krebs cycle, primarily as carbon dioxide and in urine. Slow release drug delivery system with Polylactic acid hydrogels was developed for Mitomycin C and Dexamethasone sodium phosphate for prevention of tracheal wall fibroplasias. Some examples of the drugs with which PLA used for controlled drug delivery system are shown in Table 1.

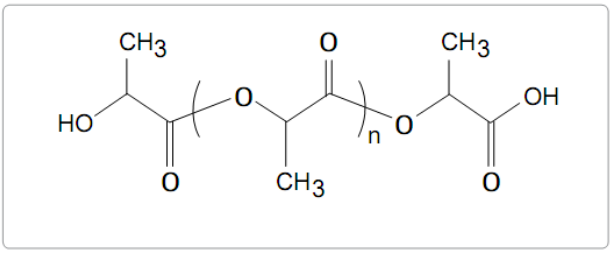

Figure 3: General structure of polylactic acid

Table 1: Controlled drug delivery system containing PLA Polymer

Drug	Drug Delivery Device
Haemoglobin	Nanocapsules
Lidocaine	Nanopartical
Vapreotide	Implants

Polyglycolic acid (PGA): PGA (Figure 4) is commonly obtained by ring-opening polymerization of the cyclic diester of glycolic acid, glycolide. PGA is a hard, tough, crystalline polymer with a melting temperature of 225°C and a glass transition temperature, TG, of 36°C.

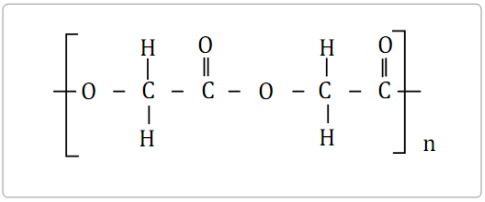

Figure 4: General structure of Polyglycolic acid

Unlike closely related polyesters such as PLA, PGA is insoluble in most common polymer solvents. PGA has excellent fiber-forming properties and was commercially introduced in 1970 as the first synthetic absorbable suture under the trade name Dexon™. The low solubility and high melting point of PGA limits its use for drug delivery applications, since it cannot be made into films, rods, capsules, or microspheres using solvent or melt techniques. Lactide/glycolide polymers, show wide range of hydrophilicity which makes them versatile in designing controlled release system.

Poly (lactide-co-glycolide), PLGA: Both L- and DL-lactides have been used for co polymerization. The ratio of glycolide to lactide at different compositions permits control of the degree of crystallinity of the polymers. When the crystalline PGA is co-polymerized with PLA, the degree of crystallinity is decreased and as a result this leads to increases in rates of hydration and hydrolysis. It can therefore be concluded that the degradation time of the copolymer is related to the ratio of monomers used in production. In general, the higher the content of glycolide the quicker the rate of degradation. However, an exception to this rule is the 50:50 ratio of PGA: PLA, which shows the fastest degradation. PLGA (Figure 5) is used in various drug delivery applications. Studies have been performed on PLGA for delivering anticancer agent having low water solubility. Non-steroidal anti-inflammatory drugs, e.g., diflunisal and diclofenac sodium, have been incorporated into PLGA microspheres and investigated for the treatment of rheumatoid arthritis, osteoarthritis, and related diseases. Also in the Implants of Trypsin inhibitor, PLG 50:50 is used as polymer. Some examples of PLGA with their biodegradation time are shown in following Table 2.

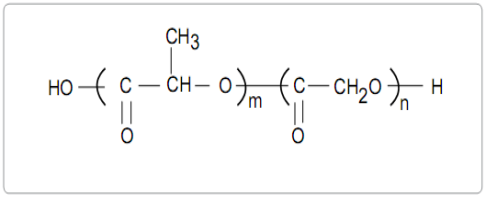

Figure 5: General structure of Poly (lactide-co-glycolide), PLGA

Table 2: Biodegradation of lactide/glycolide polymers (PLGA)

Polymer	Approximate time for biodegradation (month)
Poly(l-lactide)	18-14
Poly(dl-lactide)	12-16
Poly(glycolide)	2-4
50:50 (dl-lactide-co-glycolide)	2
85:15 (dl-lactide-co-glycolide)	5
90:10 (dl-lactide-co-glycolide)	2

Polyhydroxybutyrate (PHB): PHB (Figure 6) is a biopolymer, which is present in all living organisms. Many bacteria produce PHB in large quantities as storage material. It is not toxic and is totally biodegradable. The polymer is primarily a product of carbon assimilation (from glucose or starch) and is employed by microorganisms as a form of energy storage molecule to be metabolized when other common energy sources are not available. PHB and its copolymers have attracted much attention because they are produced biosynthetically from renewable resources. Microcapsules from PHB has been prepared by various techniques and investigated for the release of bovine serum albumin. PHB matrix was used for development of controlled delivery system of Nano gels of lithium neutralized polyacrylic acid for bone regeneration.

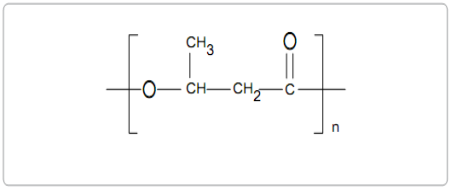

Figure 6: General structure of polyhydroxybutyrate

Poly (e-caprolactone), PCL: PCL (Figure 7) is obtained by ring-opening polymerization of the 6-membered lactone, e-caprolactone (e-CL). Anionic, cationic, coordination, or radical polymerization routes are all applicable. Recently, enzymatic catalyzed polymerization of e-CL has been reported. PCL crystallizes readily due to the regular structure and has a melting temperature of 61°C. It is tough and flexible. The Tg of PCL is low (–60°C). Thus, PCL is in the rubbery state and exhibits high permeability to low molecular species at body temperature. These properties, combined with documented biocompatibility, make PCL a promising candidate for controlled release applications.

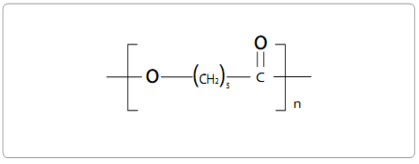

Figure 7: General structure of Poly (e-caprolactone), PCL

PCL degradation proceeds through hydrolysis of backbone ester bonds as well as by enzymatic attack. Hence Hydrolysis of PCL yields 6-hydroxycaproic acid, an intermediate of the w-oxidation, which enters the citric acid cycle and is completely metabolized. Hydrolysis, however, proceeds by homogeneous erosion at a much slower rate than PLA and PLGA. Hydrolysis of PCL is faster at basic pH and higher temperatures. PCL hydrolyzes slowly compared to PLA and PLGA; it is most suitable for long term drug delivery. PCL is show long term delivery system for a period of more than one year. PCL and its derivative have been assessed to be well suited for controlled drug delivery due to high permeability to many drugs freedom from toxicity. Biodegradable In Situ gel-forming Controlled drug delivery system based on thermosensitive Poly (e-caprolactone)- Poly(ethylene glycol)-Poly(e-caprolactone) hydrogel has been reported in literature.

CONCLUSION:

Polymers possess a unique strength in their application towards drug delivery systems which enables the new advancement in the formulation of new drug delivery systems which improves the therapy and treatment. Biodegradable polymers have proven their potential for the development of new, advanced and efficient drug delivery system. They are capable of delivering a wide range of bioactive materials. From a polymer chemistry perspective, it is important to appreciate that the mechanisms of controlled-release require polymers with a variety of physico-chemical properties. Several types of polymers have been investigated as potential drug delivery systems, including Nano and micro-particles, dendrimers, Nano and micro-spheres, capsosomes and micelles. In these systems, drugs can be encapsulated or conjugated into polymer matrices to control the drug release.

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