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Synthetic Biodegradable Polymers Used in Controlled Drug Delivery System: An Overview

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Abstract

Polymers are becoming increasingly important in the field of drug delivery. 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 controlled release and targeting drug delivery system. Polymers are obtained from natural source as well as synthesized chemically. Polymers are classified as biodegradable and non-biodegradable. Biodegradable polymers have been widely used in biomedical applications because of their known bio-compatibility and biodegradability. The present review gives an overview of the different biodegradable polymers that are currently being used in the development of controlled drug delivery system.

Keywords: Synthetic polymer; Drug delivery; Biodegradable polymer

Introduction

Drug delivery is the method or process of administering pharmaceutical compound to achieve a therapeutic effect in humans or animals [1,2]. 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 [3]. 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 [4]. 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.

Controlled drug delivery system (CDDS)

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 [5].

Advantages of controlled drug delivery

Controlled drug delivery system has various advantages over conventional drug delivery as discussed below [5]:

- 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.

Classification of Polymer

Polymers are macromolecules having very large chains contain a variety of functional groups, can be blended with low and high molecular weight materials. Polymers are becoming increasingly important in the field of drug delivery. Advances in polymer science have led to the development of several novel drug delivery systems [3]. Polymers are classified into the two major types [6-10] as mentioned below.

Natural polymer

1. Protien-based polymer: Collagen, Albumin, Gelatin

2. Polysaccharides: Alginate, Cyclodextrin, Chitosan, Dextran, Agarose, Hyaluronic acid, Starch, Cellulose

Synthetic polymers

Biodegradable polymer

a) Polyester: Poly lactic acid, Poly glycolic acid

Poly hydroxyl butyrate, Polyester, Polycaprolactone

Poly lactide-co-glycolide (PLGA), Poly diaxonone

b) Polyanhydride: Poly adepic acid, Poly sebacic acid

Poly terpthalic acid,

c) Polyamides: Poly amino acid, Poly imino carbonate

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d) Phosphorous based polymer: Polyphosphates, Poly phosphonates, Poly Phosphazenes

e) Others: Poly cyanoacrylates, Poly urethanes, Poly ortho ester, Polyacetals etc.

Non-Biodegradable polymers

a) Cellulose derivative: Carboxy methyl cellulose, Ethyl cellulose

Cellulose acetate hydroxyl propyl methyl cellulose

b) Silicons: Polydimethyl siloxane, Colloidal silica, Polymethacrylate, Polymethyl methacrylate

c) Others: Poly vinyl pyrolidine, Ethyl vinyl acetate, Poloxamine etc.

Why synthetic polymers preferred over natural polymers?

Natural polymers suffer from some disadvantages as summarized below:

Microbial contamination-The moisture present in the gums and mucilages is normally 10% or more and, structurally, they are carbohydrates and, during production, they are exposed to the external environment and, so there is a chance of microbial contamination.

Batch to batch variation-Synthetic manufacturing is a controlled procedure with fixed quantities of ingredients, while the production of gums and mucilages is dependent on environmental and seasonal factors [11].

Uncontrolled rate of hydration-Due to differences in the collection of natural materials at different times as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary. There is a need to develop suitable monographs on available gums and mucilages. Reduced viscosity on storage normally, when gums and mucilages come into contact with water there is an increase in the viscosity of the formulations. Due to the complex nature of gums and mucilages (monosaccharides to polysaccharides and their derivatives), it has been found that after storage there is reduction in viscosity [12].

The use of synthetic polymer overcomes above disadvantages and hence their use in formulation is preferred.

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 [13]. The surface properties also determine the water sorption capacity of the polymers, which undergo hydrolytic degradation and swelling (hydrogels) [14]. 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 [15]. 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 [16]. Polymer should have some characteristics so that specific polymer can be select for the drug delivery system.

Following characteristics needs to be considered while selecting polymer for CDDS.

➤ It should be versatile.

➤ It should possess a wide range of mechanical, physical and chemical properties.

➤ It should be non-toxic and have good mechanical strength.

➤ It should be inexpensive and easy to construct.

➤ It should be inert to host tissue and compatible with environment.

Synthetic Biodegradable Polymers

There are various synthetic biodegradable polymers currently being investigated as drug delivery systems or as scaffolds for tissue engineering [17]. 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, haemostats, 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 [18].

Drug release mechanisms for Controlled drug delivery

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

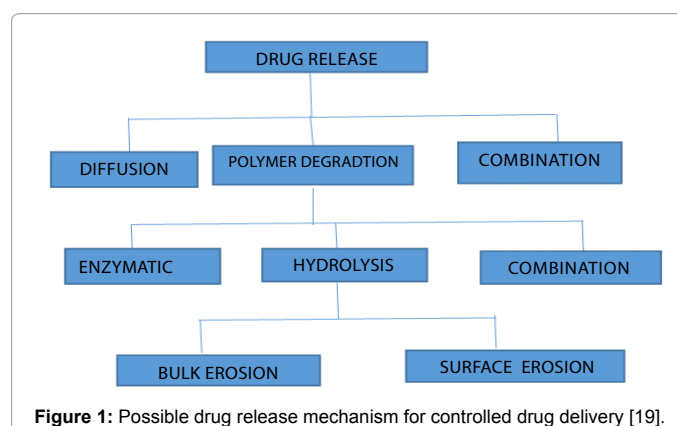Controlled-release approaches can be classified on the basis of the

Figure 1: Possible drug release mechanism for controlled drug delivery [19].

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 [19,20].

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.

Chemical erosion: There are three general chemical mechanisms that cause bio erosion.

Type I erosion: This type of erosion is evident with water soluble polymers cross-linked to form three-dimensional network. As long as crosslinks remain intact, the network is intact and is insoluble. When it is placed in aqueous environment, it swells only to the extent permitted by its cross-link density [20]. Generally, degradation of type IA polymers provide high molecular weight, water-soluble fragments, while degradation of type IB polymers provide low molecular weight, water soluble oligomers and monomers.

Type II erosion: This type of erosion occurs with polymer that were earlier water insoluble but converted to water soluble forms by ionization, protonation or hydrolysis of the pendant group [20]. With this mechanism, the polymer does not degrade and its molecular weight remains essentially unchanged. Materials like cellulose acetate derivatives and partially esterified copolymers of maleic anhydride are displaying type II erosion. These polymers showing type II erosion and become soluble by ionization of carboxylic group [18].

Type III erosion: Degradation of insoluble polymers with labile bonds Hydrolysis of labile bonds causes scission of the polymer backbone, thereby forming low molecular weight, water-soluble molecules. Polymers like poly (lactic acid), poly (glycolic acid) and their copolymers, poly (ortho esters), undergoes type III erosion. The three mechanisms described are not mutually exclusive; combinations of them can occur [18].

Figure 2: General mechanism of Controlled drug delivery.
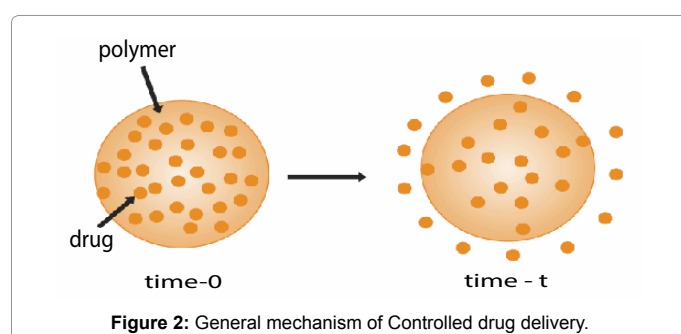
Physical erosion: The physical erosion mechanisms can be characterized as heterogeneous or homogeneous type. In heterogeneous erosion, also called as surface erosion, the polymer erodes only at the surface, and sustains its physical integrity as it degrades. Crystalline regions eliminate water. Therefore, highly crystalline polymers tend to undergo heterogeneous erosion. Most polymers undergo homogeneous erosion, means the hydrolysis occurs at uniform rate throughout the polymeric matrix. Generally these polymers tend to be more hydrophilic than those showing surface erosion. As a result, water penetrates the polymeric matrix and increases the rate of diffusion. In homogeneous erosion, there is loss of integrity of the polymer matrix [18]. Hydrophilic excipients can accelerate the release of drugs, though they may also increase the initial burst effect [21].

Factor affecting Biodegradation

Following are the factors which affect the biodegradation process of Polymer [22,23].

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 CDDS

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 [24]. Slow release drug delivery system with Polylactic acid hydrogels was developed for Mitomycin C and Dexamethasone sodium phosphate for prevention of tracheal wall fibroplasias [25].

some examples of the drugs with which PLA used for controlled drug delivery system are shown in Table 1 [20].

Polyglycolic acid (PGA)

PGA (Figure 4) is commonly obtained by ring-opening polymerization of the cyclic diester of glycolic acid, glycolide [26,27]. PGA is a hard, tough, crystalline polymer with a melting temperature of 225°C and a glass transition temperature, T_G, of 36°C [26]. Unlike closely related polyesters such as PLA, PGA is insoluble in most common polymer solvents. PGA has excellent fiber-forming properties and was
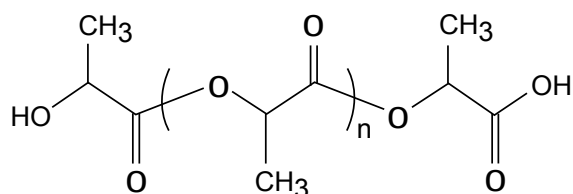
Figure 3: General structure of polylactic acid.

Drug	Drug Delivery Device
Haemoglobin	Nanocapsules
Lidocaine	Nanopartical
Vapreotide	Implants

Table 1: Controlled drug delivery system containing PLA Polymer.
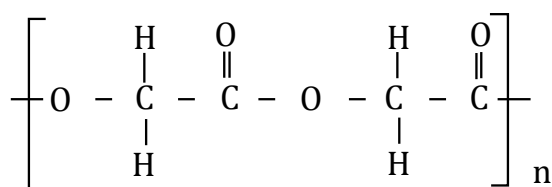

Figure 4: General structure of polyglycolic acid.

commercially introduced in 1970 as the first synthetic absorbable suture under the trade name Dexon™ [26]. 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 [24].

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 [28]. 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 [29,30]. PLGA (Figure 5) is used in various drug delivery applications. Studies have been performed on PLGA for delivering anticancer agent having low water solubility [31].

Non-steroidal anti-inflammatory drugs, e.g., diflunisal [32] and diclofenac sodium [33,34], 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 [24].

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 [35]. PHB matrix was used for development of controlled delivery system of Nanogels of lithium neutralized polyacrylic acid for bone regeneration [36].

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 [34]. Recently, enzymatic catalyzed polymerization of e-CL has been reported [37,38]. PCL crystallizes readily due to the regular structure and has a melting temperature of 61°C. It is tough and flexible [34]. 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 [39].

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,
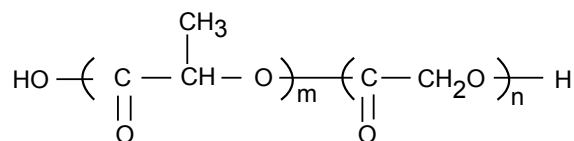

Figure 5: General structure of Poly (lactide-co-glycolide), PLGA.

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

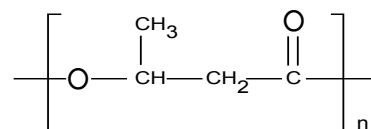**Table 2:** Biodegradation of lactide/glycolide polymers (PLGA).

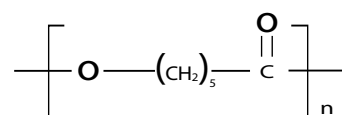**Figure 6:** General structure of polyhydroxybutyrate.

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

however, proceeds by homogeneous erosion at a much slower rate than PLA and PLGA [40]. Hydrolysis of PCL is faster at basic pH and higher temperatures [34]. 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 [24]. 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 (Table 3) [41].

Polydioxanone (PDS)

Polydioxanone (Figure 8) is prepared by a ring-opening polymerization of the pdioxanone monomer. It is characterized by a degree of crystallinity of about 55%. Constituents prepared with PDS show improved flexibility due to the presence of ether oxygen within the backbone of the polymer chain. When used in vivo, it degrades into monomers with low toxicity and also has a lower modulus than PLA or PGA. Poly-dioxanone on implantation does not display any severe or toxic effects [42]. Recently PDS has been used for nanofibrous drug delivery system of metronidazole and ciprofloxacin [43].

Polyanhydrides

Poly anhydride (Figure 9) is class of biodegradable polymer characterized by anhydride bonds that connect repeat unit of polymers backbone chain. The majority of polies (anhydrides) are prepared by melt-condensation polymerization. To obtain a device that erodes heterogeneously, the polymer should be hydrophobic yet contain water sensitive linkages. One type of polymer system that meets this requirement is the poly (anhydrides). Poly- (anhydrides) undergoes hydrolytic bond cleavage to form water-soluble degradation products

Drug	Polymer/CO-polymer	Drug delivery system
Cyclosporine	PCL	Nanopartical (100nm)
Ciprofloxacin	PCL	Dental implants of ciprofloxacin β-cyclodextrin inclusion complex
17-β-estradiolprogresterone	dl-lactide-co-PCL (83:17)	Microspheres
Colchicine	PLA-PCL	PEG-coated microsphere(3-6mm)

Table 3: Examples of drug delivery system containing PCL and its CO-polymer [20].
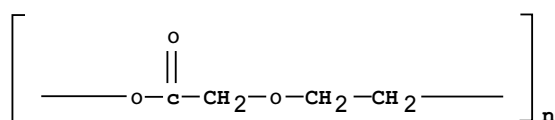

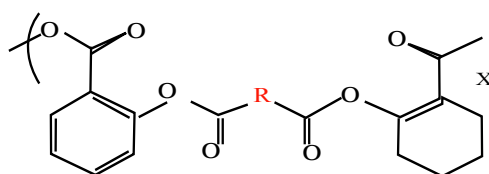**Figure 8:** General structures of Polydioxanone (PDS).

Figure 9: General structure of polyanhydride.

that can dissolve in an aqueous environment, thus resulting in polymer erosion. Polies (anhydrides) are believed to undergo predominantly surface erosion due to the high water liability of the anhydride bonds on the surface and the hydrophobicity which prevents water penetration into the bulk [44].

Polyamide

The synthetic aliphatic polyamides are polymeric compounds frequently referred to as Nylons which form an important group of poly condensation polymers. They are linear molecules (i.e. aliphatic) that are semi-crystalline and thermoplastic in nature. A typical polyamide chain consists of amide groups separated by alkane segments and the number of carbon atoms separating the nitrogen atoms which defines the particular polyamide type (Figure 10). The aliphatic polyamides are very useful and versatile material that are Polyglutamic acid [20]. In 2012 US patent has been published on '*Polyamide rate-modulated monolithic drug delivery system*' [45].

Phosphorous based derivatives

Polyphosphazenes

It consists of phosphorous atoms attached to either carbon or oxygen. Polyphosphazenes (Figure 11), another new class of polymer are being investigated for delivery of proteins. The uniqueness of this class of polymer lies in the chemical reactivity of phosphorous which enables a wide range of side chains to be attached for manipulating the biodegradation rates and the molecular weight of polymer [16]. Phosphazenes undergo facile hydrolysis to Phosphate and ammonia which are easily undergo metabolised and excreted respectively [20]. Studies were reported in literature on drug and gene delivery using polyphosphazenes and its chemically modified form [46].

Poly (phosphoester) s (PPE)

General structure of Poly (phosphoester) s (PPE) is shown in Figure 12. These polymers are generally referred to as Phophonates (P-O-C), polyphosphonates (P-C) orpolyphosphites depending upon the nature of the side chain attached to the phosphorus. This undergoes hydrolysis to alcohol and phosphates which easily undergo excretion and metabolism respectively.

Co-polymer of PPE:-

1) Poly (ethylene Terephthalate) based PPEs [BHET-EOP]

2) PPEs based on cyclohexane-1, 4-dimethyl (CHDM) phosphate backbone

A controlled gene delivery system with PPE has been developed in 2008 and has been patented (Table 4) [47].

Polyorthoesters

Poly (orthoester) s (POE) (Figure 13) is another family of polymers identified as degradable polymers suitable for orthopaedic applications. With the addition of lactide segments as part of the polymer structure, tuneable degradation times ranging from 15 to hundreds of days can be achieved. The degradation of the lactide segments produces carboxylic acids, which catalyze the degradation of the orthoester.

POE-based norethindrone implants were prepared along with water soluble excipients. These water soluble osmogens attract water into the otherwise hydrophobic polymer and there is subsequent swelling and release of incorporated drug.
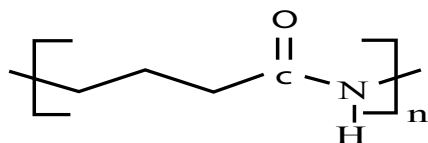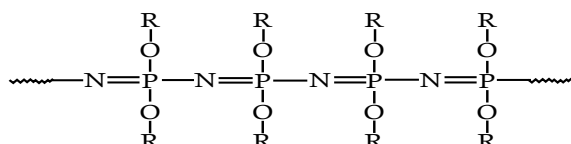
Figure 10: General structure of polyamide.

An ether substituted polyphosphazene. (R is a wild card, standing for any hydrocrabon group)
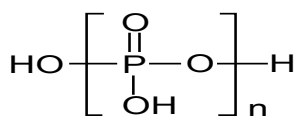
Figure 11: General structures of polyphosphazenes.

Figure 12: General structure of Poly (phosphoester) s (PPE).

Drug	Polymer/Co-polymer	Drug delivery system
Lidocaine	P(BHDPT-EOP, 50/50)	Microspheres
Doxorubicin	P(tranc-CHDM-HOP)	Viscous gel
Lidocaine	P(tranc-CHDM-HOP)	Viscous gel

Table 4: Examples of drug delivery system including C-polymer of PPE [20].
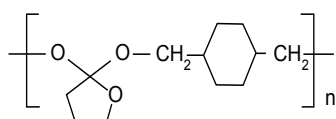

Figure 13: General structure of polyorthoester.

Even low Water-soluble acidic salt calcium lactate induces both bulk erosion and surface erosion.

Long term erosion controlled of levonorgestrel was achieved by stabilising the device interior with Mg (OH) 2 [20]

Poly (amino acids)

Polyglutamic acid: General structure of Poly-L-glutamic acid is shown in Figure 14. Poly-L-glutamic acids due to its biodegradability, high water solubility, presence of multiple carboxyl groups are amenable for chemical modification, low immunogenicity and low toxicity. Its dielectric charge is also favourable for controlling in vivo disposition characteristic of anti-tumour agent Poly-L-glutamic acid has been glycosylated to facilitate liver-specific targeting [20]. Nanoscaled Poly (l-glutamic acid)/Doxorubicin-Amphiphile Complex as pH-responsive Controlled drug delivery has been reported in literature for effective treatment of Nonsmall Cell Lung Cancer in Non-small cell lung cancer (NSCLC) [48].

Poly (iminocarbonates): Poly (amino acids) are highly insoluble,
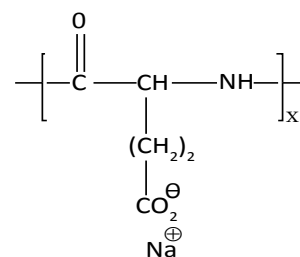

Figure 14: General structure of Poly-L-glutamic acid.

nonprocessible, and antigenic when the polymers contain three or more amino acids [49]. To circumvent these problems, "pseudo"-poly (amino acids) synthesized from tyrosine dipeptide were investigated [50]. These degradable polymers are derived from the polymerization of desaminotyrosyl tyrosine alkyl esters. Tyrosine-derived polies (carbonates) are readily processible polymers that support the growth and attachment of cells and have also shown a high degree of tissue compatibility [51]. Tyrosine-derived poly (carbonates) is characterized by their relatively high strength and stiffness exceeding poly (esters) such as poly (ortho esters) but not poly (lactic acid) or poly- (glycolic acid) [52,53]. The postulated mechanism of in vitro degradation involves hydrolysis of the pendent ester bonds and the imino-carbonate bonds of the backbone [54]. Degradation rates are comparable to the degradation rate of poly (L-lactic acid), occurring over a period of months. Polies (iminocarbonates) are currently being investigated for use in small bone fixation devices as bone screws and pins [54].

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.

Conflict of Interest

The author(s) declare(s) that there is no conflict of interests regarding the publication of this article.

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