Review Article

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Biodegradable Synthetic Polymers and their Application in Advanced Drug Delivery Systems (DDS)

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ABSTRACT

Natural and synthetic polymers have been used in pharmaceutical industry for many years and have important role in the development of the conventional dosage forms or for manufacturing of various drug packaging materials. In recent years, their important application resides in the development of the most sophisticated drug delivery systems where polymers are used as a drug carrier. Biodegradable polymers are particularly attractive for application in drug delivery systems since, once introduced into the human body, they do not require removal or additional manipulation. Their degradation products are normal metabolites of the body or products that can be metabolized and easily cleared from the body. Among that, synthetic polymers offer a wide variety of compositions with adjustable properties. These materials open the possibility of developing new drug delivery systems with specific properties (chemical, interfacial, mechanical and biological) for a given application, simply by changing the building blocks or the preparation technique. Such designed complex drug delivery systems where polymers are used as functional excipients have numerous advantages such as localized delivery of drug, sustained delivery of drug, stabilization of the drug, prevention of drug's adverse side-effects, reduction of dosing frequency, minimization of drug concentration fluctuations in plasma level, improved drug utilization and patient compliance. There are range of differently designed drug delivery systems and their description and mechanism of action will be presented in this paper together with the prominent role of the polymers for each particular system. Additionally, most commonly used synthetic biodegradable polymers in drug delivery systems will be presented together with their degradation mechanism.

Keywords

Drug delivery, Biodegradable polymers, Polymer erosion, Hydrolysis.

Introduction

In order to overcome drawbacks related to small drug molecules delivered in to the human body on conventional way such as poor solubility, bioavailability, nonspecific distribution and potential toxicity, advanced drug delivery systems have been developed [1-4]. During the past two decades, new approaches and strategies have been developed to control several parameters considered essential for enhancing the treatment performance of the drug such as the release rate, time period and targeting of the delivery. The main purpose of using a drug delivery systems (DDS) is, not only to deliver an active compound in a controlled manner (time period and releasing rate) but also to maintain drug level in the body within therapeutic window as presented at Figure 1 (not below minimum effective level or above toxic level) – one of the main strategies to enable improved drug efficacy is controlled and sustained delivery of the drug [5,6].

Another important feature of DDS that enables improved drug efficacy is administration of the drug at specific site in order to avoid systemic circulation. Drug efficacy can be enhanced and toxicity minimized by localization at the organ, tissue, cellular, or organelle level. The clinical utility of a wide range of drugs, especially within oncology, is strongly curbed by dose limiting toxicities. Dosed systemically, the entire body is treated and typically, less than 0.01% of the injected dose reaches the targeted pathology (e.g. tumor). As a rule, these therapeutic regimes are not terminated because the patient is cured, but because of excessive systemic toxicity. Over the last few decades, the pharmaceutical industry has spent vast resources in trying to overcome this dilemma with various approaches for targeted drug delivery.

By enhancing delivery of drug specifically to the pathology in question the systemic exposure can be reduced (reducing toxicity) and the efficacy increased [7-10].

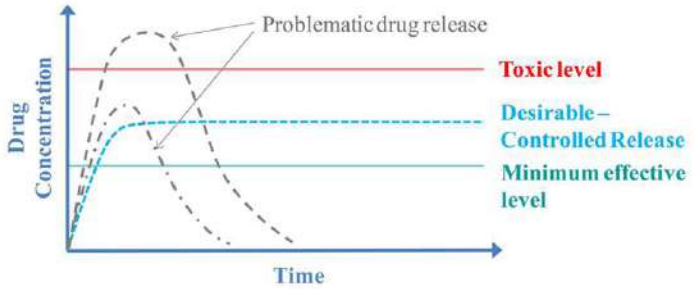


Figure 1: Plasma drug concentration as a function of time after administration of a conventional oral dosage form such as tablet or capsule (grey line) and after single administration of the same drug from the controlled release dosage form (blue line).

The main goal during design of suitable drug delivery systems is generically related to deliver suitable active compounds at a desired target without any sign of degradation during the whole process. It means that drug carrier itself, should be able to control the drug administration by means of either a physiological or chemical trigger. Mainly used drug carriers in advanced drug delivery systems are the polymers [11].

Synthetic biodegradable polymers used in drug delivery systems (DDS)

Polymers used in drug delivery systems can be classified based on their origin on natural, artificial (chemically modified natural polymers) and synthetic. Additionally, synthetic polymers can be divided based on their bio-stability on biodegradable and non-biodegradable. Non-biodegradable system requires invasive surgical interventions to remove the implant from the site of injection. For example, the use of a non-biodegradable system in the treatment of vitreoretinal diseases and subsequent invasive surgery (to remove the implant) has been linked with a number of serious side effects (e.g. cataract formation). On the contrary, biodegradable polymers have risen in popularity as the implant degrades to form non-toxic by-products e.g. carbon dioxide and water [12]. Biodegradable polymers are particularly attractive for application in DDS since, once introduced into the human body, they do not require removal or additional manipulation. Their degradation products are normal metabolites of the body or products that can be metabolized and easily cleared from the body [13]. Synthetic polymers offer a wide variety of compositions with adjustable properties. These materials open the possibility of developing new DDS with specific properties (chemical, interfacial, mechanical and biological) for a given application, simply by changing the building blocks or the preparation technique [14].

Most commonly used families of synthetic biodegradable polymers are polyesters, polycaprolactones, polyanhydrides and polyorthoesters. Their general chemical structures are presented in Table 1.

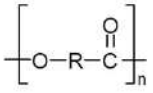
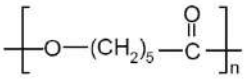
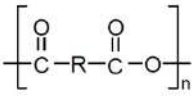
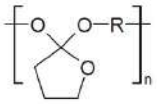
Name	Structure	Reference
Polyesters (PLA, PLGA)		[15-17]
Polycaprolactones		[18]
Polyanhidrides		[19]
Polyorthoesters	 POE I	[20]

Table 1: Chemical structure of synthetic biodegradable polymers.

Polyesters

Most popular biodegradable synthetic polymers used in drug delivery systems (DDS) are polyesters namely polyglycolide (PGA), polylactide (PLA) and their copolymers with specific architecture and chemical composition (lactide to glycolide ratio). Drug release rate can be varying based on the differences in lactide to glycolide ratio. Polymer rich in lactide results in a highly hydrophobic polymer which degrades slowly and absorbs less water.

Additionally, polylactide polymers can be amorphous or semi-crystalline, depending on the stereo regularity and differences in arrangement of the methyl side group (R) along macro radical chain which can be isotatic, atatic and syndiotatic. Depends on this differences homopolymers and copolymers of PLA can be obtained with different physical and application properties. DDS containing PLGA, have been used to deliver a wide range of molecules ranging from small hydrophilic and/or hydrophobic to large protein/peptide molecules such as bupivacaine, diltiazem, leuprolide acetate, human growth hormone, buserelin acetate, aspirin, naltrexone, fenretinide and risperidone. There is a long list of pharmaceutical product and also medical devices approved by FDA and already on the market. Based on their degradation mechanism they can be classified as bulk-eroding systems, more detailed explanation will be given in the text below [15-17].

Polycaprolactones

Polycaprolactone is another widely studied biodegradable polymer used in DDS. It is semi-crystalline polymer with high mechanical strength crucial for some application. Its degradation rate is markedly slower in comparison to polylactide-based polymers, taking up to 2 to 3 years to degrade. It is therefore ideal as drug carrier for extremely prolonged release DDS. For extended release DDS it is often combined with with amorphous PLA or with biocompatible PEG in some multiblocks [18].

Polyanhidrydes

Polyanhydrides have been considered as an important biomaterial used as drug carrier to various organs of the human body such

as brain, bone, blood vessels, and eyes. Biomedical device GLIADEL® - a chemotherapy wafel, already in clinical use for treating brain cancer uses degradable polyanhydride copolymer. Due to their rapid degradation the main application for this class of polymers is in short-term controlled delivery of bioactive agents. The main advantage of this class of polymers is that they have a well-defined structure with controlled molecular weight and degrade by surface erosion hydrolytically at a predictable rate. Besides the benefits of polyanhydrides, there are some limitations to this class of polymers, namely, hydrolytic instability which requires storage under moisture free frozen conditions and low mechanical strength [19].

Polyorthoesters

Polyorthoesters are another successful biodegradable family of biodegradable polymers. Main characteristics of this polymer family is that they contains orthoester linkage which are acid labile and like polyanhydrides undergo surface erosion. Several DDS that contains POE's are already on the market and approved by FDA. This is mainly related to the POE IV generation. Previous generations have difficulties in achieving a reproducible synthesis. Only IV generation accomplished successful commercialization. The key feature of the 4th generation of POE IV is that contains diol together with short segments of so-called latent monomer mainly based on glycolic or lactic acid esters that can catalyze hydrolysis of the polymer chains. This allows accurate control of the erosion rate of the polymer matrix and consequently controlled release rate of the drug molecule over several days or weeks depends on the polymer composition [20]

Polymeric-Based Drug Delivery Systems

There are three main categories of polymeric drug delivery systems; colloidal carriers (micro, nanoparticles, micelles, micro/nanogels), implantable networks or hydrogels, and polymer drug conjugates (Figure 2) [21].

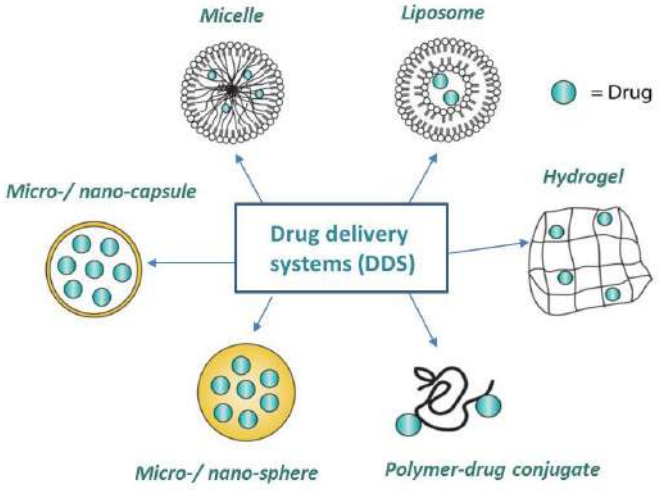


Figure 2: Overview of polymeric-based drug delivery systems (DDS) [23].

Unfortunately, there is no "silver bullet" for effective delivery of broad classes of therapeutics. Selection of a drug delivery system must be driven by the nature of the drug and the inherent properties of the DDS. In addition, the choice of drug delivery system determines the drug loading capacity, longevity of release, and the route best suited for administration. It should be noted that drug release from any type of polymer carrier is determined by a complex interaction between the drug properties, polymer characteristics, and environmental/*in vivo* conditions [22].

Based on the mechanism of action, polymeric based DDS can be classified as diffusion controlled systems, solvent-activated systems, chemically controlled systems and externally activated or modulated systems. In advanced DDS several different mechanisms are involved although one can be dominant in comparison to the others [24].

Diffusion controlled systems can be divided to reservoir and matrix systems. Reservoir system is based in a polymeric membrane that surrounds a core containing the drug. Drug release is controlled by biodegradable membrane. Mainly non-biodegradable polymers are used in this type of systems. Matrix systems are based on a polymer matrix in which the drug is distributed homogeneously. Drug release is controlled by polymer erosion, drug diffusion and/or by combination of both [24]. Schematic representation of reservoir and matrix system is presented at Figure 3.

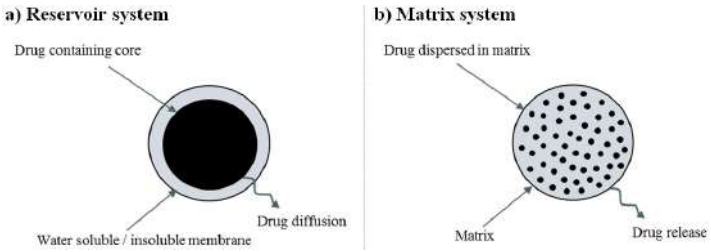


Figure 3: Schematic representation of reservoir (a) and matrix (b) systems.

Solvent-activated systems can be controlled either by swelling or by osmosis. Osmotically controlled systems relies on a device containing a semipermeable membrane through which a solvent without or with small amount of drug flows toward a chamber in which the drug is contained. The solvent flow increases pressure inside the chamber containing the drug and forces the exit of the drug though an orifice present in the device. Swelling controlled systems are based on a hydrophilic polymeric crosslinked chain that is able to absorb large amounts of water without dissolving. This water uptake allows the drug inside the system to diffuse outwards at a velocity that depends on the amount of water that enters the polymeric matrix [25]. Schematic representation of osmotically and swelling controlled system is presented at Figure 4.

Chemically activated system can be divided to biodegradable polymer system and pendant chain systems. In both system types, erosion or/and degradation of polymer matrix or membrane occurs. Pendant chain systems it's a type of system in which the drug molecule is chemically linked to the backbone of the polymer. In the body in the presence of enzymes and biological fluids, chemical hydrolysis and/or enzymatic cleavage, occurs with concomitant release of the drug at a controlled rate. The drug can be linked

directly to the polymer or via a "spacer group". Different types of biodegradable or hydrolysable chemical linkages are used to attach the drug to the polymer backbone.

These polymer-drug conjugates usually possess a transport system which is responsible for directing of the polymer to target organs or tissues. In the biodegradable polymer system, the controlled release of the drug involves biodegradable polymers than gradually erodes. The drug is dispersed uniformly throughout polymer matrix and it slowly released as the polymer disintegrates. At time t = 0, before the release, drug is dispersed in the matrix and at time t = t, partial release by drug diffusion and/or polymer matrix erosion occurs. Most of the biodegradable polymeric based DDS works on that way [26]. Schematic representation of pendant chain and biodegradable polymer systems is presented at Figure 5.

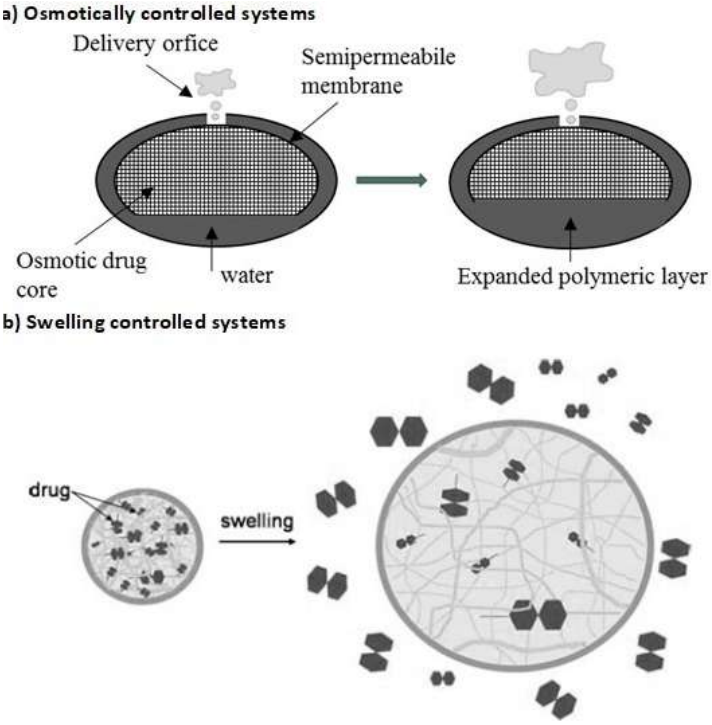


Figure 4: Schematic representation of osmotically (a) and swelling (b) controlled systems.

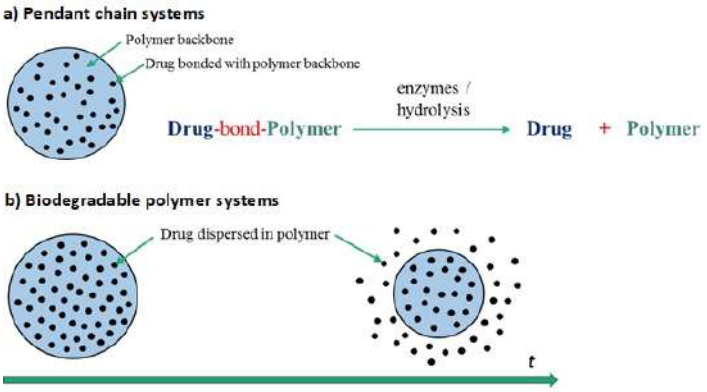


Figure 5: Schematic representation of pendant chain (a) and biodegradable polymer systems (b).

Polymer Bio-degradation and Erosion

The process of polymer erosion can be described as combination of chemical erosion or biodegradation and physical erosion / dissolution and diffusion of small fragments (monomers and oligomers) formed as a consequence of chemical degradation (Figure 6).

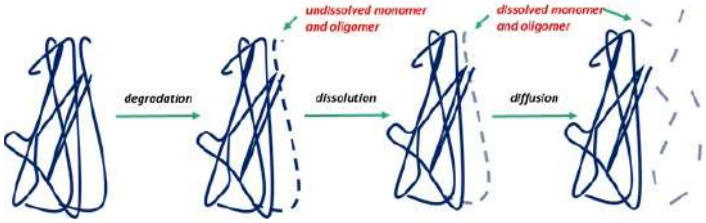


Figure 6: Process of polymer bio-degradation and erosion.

Chemical erosion

Chemical erosion or biodegradation is a chemical breakdown of polymer chains into smaller fragments (oligomers) that occurs in polymer matrix. This degradation process can be hydrolytic or enzymatic. Although for most biodegradable polymers involvement of the enzymes in vivo is questionable especially in parenteral conditions because enzymes are bulky molecules and cannot entered into DDS easily. There is possibility that enzymes impacts degradation rate of polymers at later stage of in vivo degradation and more likely on the surface not in the bulk of the DDS [27].

Heller has defined three mechanisms of polymer bioerosion in 1980 [28]. Mechanism I or crosslinked degradation concerns crosslinked water insoluble macromolecules that contain hydrolytically unstable cross-links. These polymers are mainly used for the release of sparingly water-soluble drugs. Mechanism II or side chain degradation includes water insoluble macromolecules that are solubilized by ionization or protonation of a pendent group without any backbone cleavage.

Transformation or cleavage of side chains leads to formation of polar or charged group. Mechanism III or backbone degradation refers to water insoluble (hydrophobic) macromolecules with hydrolytically labile bonds that can be converted to small soluble molecules by backbone cleavage of bonds between repeating units of the polymer chain. Most of the biodegradable synthetic polymers undergo type III mechanism.

Physical erosion

Their bio-erosion or process called physical erosion can be classified into two erosion patterns: bulk erosion and surface erosion [29]. In bulk erosion, the entire area of polymer matrix is subjected to chemical or enzymatic reaction; thus, erosion occurs homogeneously through the entire matrix. Bulk eroding polymers degrade all over their cross-section, have erosion kinetics which are non-linear, and are usually characterized by a discontinuity. In bulk erosion, the size of a device will remain constant for a considerable portion of time during its application.

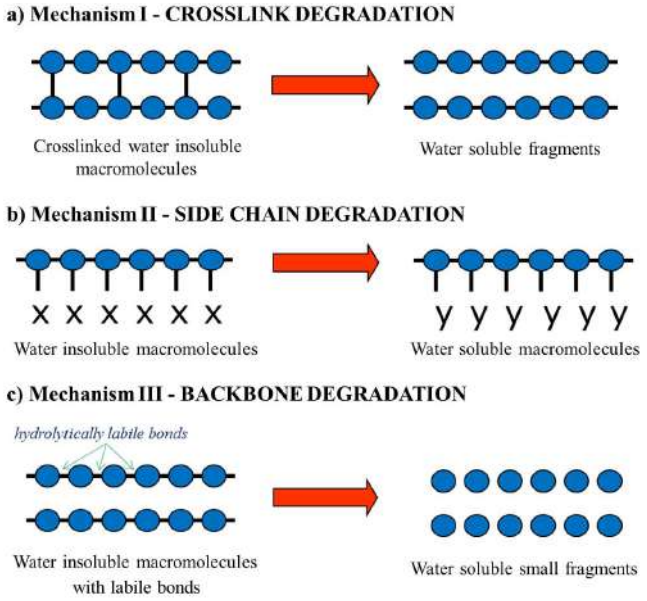


Figure 7: Schematic representation of three pathways of polymer breakdown: a) crosslink degradation, b) side chain degradation and c) backbone degradation.

In surface erosion, polymer degradation is limited to the surface of an implant exposed to a reaction medium. Erosion therefore starts at the exposed surface and works downwards, layer by layer. The advantage of surface-eroding polymers is the predictability of the erosion process. Thus, a drug distributed homogeneously in a surface-eroding matrix implant, of which the surface is invariant with time, shows constant release with time over the period of implantation.

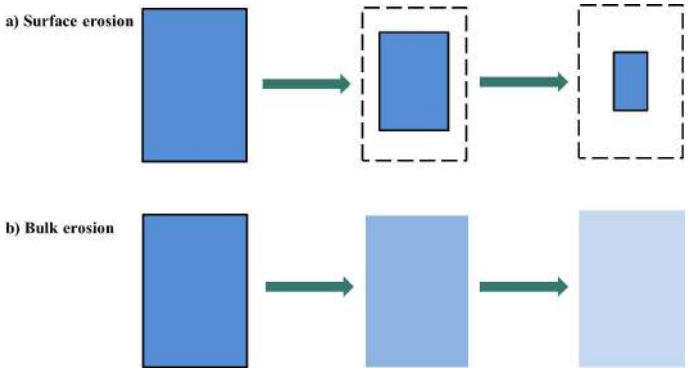


Figure 8: Schematic representation of a) surface and b) bulk erosion of polymer matrix.

Factors that affects polymer degradation rate

Most important chemical and physical factors that affects polymer degradation rate will be discussed in text below. Most important chemical factors are chemical stability of the bonds between monomer units along main polymer chain, hydrophobicity of the polymer composition, structural arrangement of the side groups and possible steric effects. Important physical factors that will be discussed are polymers microstructure (crystallinity) and production of autocatalytic breakdown fragments mainly in bulk-eroding polymer systems [30].

Chemical factors

The chemical bonds between monomer units along polymer chain for most commonly used biodegradable synthetic polymers can be ranked based on their stability against hydrolysis [31].

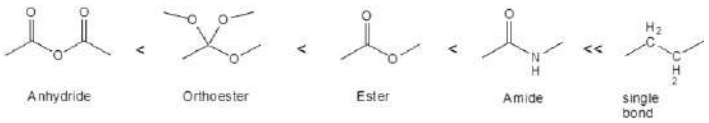


Figure 9: Type of chemical bonds and their stability against hydrolysis of the biodegradable synthetic polymers.

Figure 9 shows that anhydride and orthoester linkages are less stable in comparison to the ester or amide bonds. Based on these predispositions, DDS based on polyanhydride or polyorthoester linkages are a system that erodes predominantly by surface erosion mechanism because the rate of polymer hydrolysis is relatively rapid and mass loss is faster from the surface than from the bulk. In comparison to the DDS that are based on polyester polymers, water penetrates faster than the rate of degradation and those polymer systems undergo predominantly bulk erosion [32].

Local structure of the polymer molecules has notable impact on polymer hydrolysis rate which is mainly related to the size and structural arrangement of side groups along main polymer chain. Side group reduces hydrolytic activity of carbons via steric effect and for that reason lactic acid units in polylactide (PLA) is more reactive than glycolic acid unit in polyglycolide (PGA) – methyl group is more bulky than one hydrogen atom (Figure 10a). Then, polymer rich in lactide results in a highly hydrophobic polymer which absorbs less water and consequently degrades slowly. On the other hand, polyorthoester's (POE's) reacts with water very fast – this is due to the high bond tension caused by the three RO-groups around the carbon atoms (Figure 10b) [33].

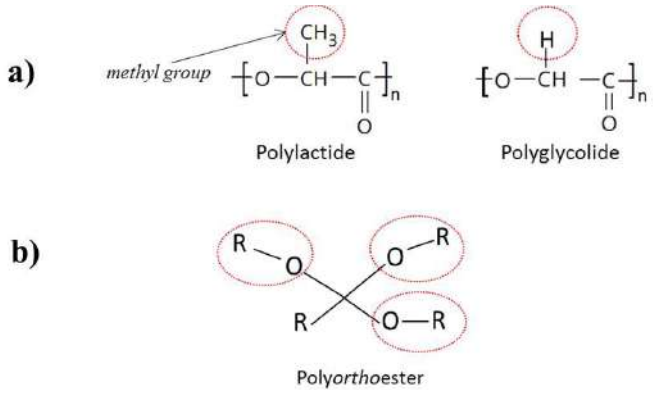


Figure 10: Impact of local structure of the polymers on the hydrolysis rate: a) lactic acid unit in polylactide (PLA) vs. glycolic acid unit in polyglycolide (PGA) and b) polyorthoester's (POE's).

Solubility of the monomers is a key concept in the design of degradable polymeric drug delivery systems (DDS) – it will have major impact on the erosion mechanism of the polymers and consequently rate of drug release. It is dependent on the chemical composition, structure, and degree of crystallinity within the polymer.

When the polymers used in DDS are hydrophobic in nature, drug release is controlled by surface erosion (ex. POE's). When there is a balance between hydrophobic and hydrophilic functionalities in the polymer backbone, degradation can occur from within the bulk of the polymeric system (ex. PLGA). Furthermore, the blending of hydrophilic polymers with hydrophobic polymers can increase pore formation along with an increase in the rate of polymer degradation and drug release [34,35].

Figure 11 shows schematic representation how change in chemical composition between hydrophilic and hydrophobic constitutes can change polymer solubility in water and consequently its degradation rate. For example, increasing the glycolic acid portion of PLGA, which renders the polymer more hydrophilic, can result in faster degradation rates. The solubility of the monomer is therefore a critical factor in the rate of drug release from polymeric drug delivery systems. Additionally, for polymers that have identical percentage of lactide and glycolide units in copolymer but differ only in their end group (-OH or ester group), release of the drug can be notably different [36].

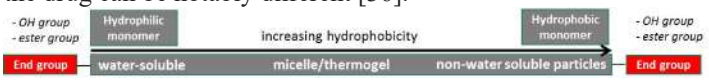


Figure 11: Relation between hydrophilic and hydrophobic constitutes in the polymer structure and their impact on their solubility in water and consequently their degradation rate.

Physical factors

During hydrolysis of biodegradable polyesters, degradation by-products with carboxylic end groups can be formed and they have ability to accelerate ester hydrolysis. This phenomenon is more pronounced in DDS where accumulation of hydrolysis by-products occurs like in bulk-eroding systems. As a consequence, faster degradation occurs inside of the polymer matrix in comparison to the surface due to this autocatalysis. Figure 12 shows schematic presentation of the formation of autocatalytic product during degradation process. Penetration of water into polymer matrix leads to hydrolytic cleavage of ester bonds and degradation occur in the bulk of the matrix (step 1). Then hydrolysis degradation by-products (soluble oligomeric compound with carboxylic acid end) accumulate in large extent in the interior (step 2). Hydrolysis by-products at the surface of the matrix can easily diffuse out from the matrix while those accumulated in the interior cause acceleration of the internal degradation (step 3). As a consequence, hollow structures can be formed when the internal material, which is totally transformed to soluble oligomers, dissolves in aqueous medium. Hollow structure was observed for amorphous polymers while in case of crystallizable polymers, no hollow structures were obtained due to the crystallization of degradation products (step 4) [37-40].

Synthetic polymers can be classified as amorphous or semi crystalline depends on the structural arrangement of the monomer units and side-groups along macroradical chain. Physical properties and degradation rate depends on degree of crystallinity in the polymer structure. It is well-known phenomena that crystalline regions resist hydrolysis more in comparison to the amorphous since water molecules penetrate more easily into amorphous region [41].

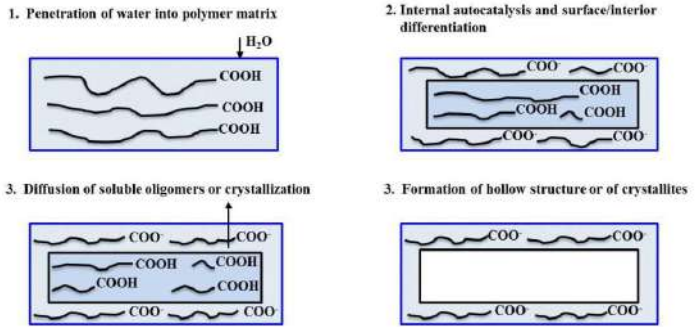


Figure 12: Schematic presentation of the internal degradation mechanism in bulk-eroding polymer systems due to autocatalysis [40].

During degradation study of the polymers in vitro- spontaneous change of the degree of crystallinity was observed. This is well-known phenomena for optically active polylactide PLLA but also possible for initially amorphous PDLA. Spontaneous recrystallization in amorphous region can occur during the polymer degradation [42] Several literature findings confirmed that during degradation process of initially amorphous polyesters after 6 months aging in the PBS buffer at 37 °C, recrystallization in amorphous region occurs and degree of crystallinity increased from 0 to 50 % [43,44]. This is due increased chain mobility of the formed oligomers that can lead to their reorganization to crystals or stereo complex formation [45].

These phenomena can have adverse effect on the drug release kinetics from the DDS because those subsequently formed crystals can push out drug molecule from the polymeric matrix and that can be reflected in uncontrolled release of the active compound at later stage (late burst occurrence) especially if the release of the drug is in several-weeks' time frame. Therefore, dynamic of stereo-complex formation and diffusion of the oligomers are significant component of polymers degradation process.

Advanced Drug Delivery Systems Based on Synthetic Biodegradable Polymers

One of the parenteral pharmaceutical product approved by FDA (Food and Drug Administration, US) that contains biodegradable synthetic polymers as functional excipients is ELIGARD®. ELIGARD® is a sterile polymeric matrix formulation of leuprolide acetate, a GnRH agonist, for subcutaneous injection. It is designed to deliver leuprolide acetate at a controlled rate over a one-, three-, four- or six-month therapeutic period. ELIGARD® is administered subcutaneously, where it forms a solid drug delivery depot. It is a drug delivery system based on ATRIGEL® technology. This technology is based on polymeric (non-gelatin containing) delivery system consisting of a biodegradable poly(DL-lactide-co-glycolide) (PLGA) polymer formulation dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (NMP) [46]. Different release rate of the drug is accomplished by changing the composition of the PLGA copolymers and also

their terminal groups. In the Table 2 it is presented composition of the PLGA copolymers together with their terminal groups that are used in ATRIGEL® drug delivery systems with different drug release period (1, 3, 4 and 6 months).

ELIGARD®		1 month	3 months	4 months	6 months
ATRIGEL® delivery system	Polymer type	PLGA	PLGA	PLGA	PLGA
	Lactide to glycolide ratio in the copolymer	50:50	75:25	75:25	85:15
	Terminal group type	Copolymer containing carboxyl endgroups	Copolymer with hexanediol	Copolymer with hexanediol	Copolymer with hexanediol

Table 2: Composition of the PLGA copolymers together with their terminal groups that are used in ATRIGEL® drug delivery systems with different drug release period (1, 3, 4 and 6 months).

Atrigel® technology is based on in situ precipitation of polymers. Polymers are dissolved in biocompatible solvent, NMP (N-methyl pirolidone), in which the drug is suspendended. Upon exposure to an aqueous environment, the water-miscible organic solvent diffuses from the drug-polymer suspension into the surrounding media, while water diffuses into the organic solvent phase. Due to the water-insolubility, polymer precipitates into a solid or semi-solid depot trapping or encapsulating a drug within polymeric matrix at the site of injection. Drug release is controlled by polymer matrix biodegradation kinetics via hydrolysis over time [47]. Copolymer composition is the most important factor to determine hydrophilicity of the polymer matrix which influences its degradation rate. Different lactide to glycolide ratio in the PLGA copolymers influences hydrolysis rates. By increasing the lactide comonomer ratio decreases hydrolysis rates by reducing the hydrophilicity of the PLGA polymer matrix [48].

Solvent exchange process between water and biocompatible solvent at site of administration it is a critical and crucial step during depot formation that has major impact on depot's morphology [49]. Schematic representation of the depot formation is presented at Figure 13.

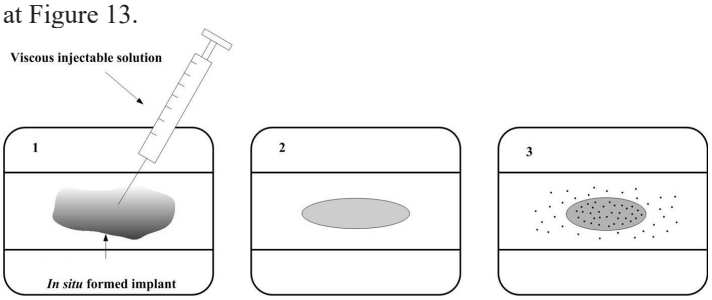


Figure 13: Mechanism of in situ forming depot and release of the drug from polymer matrix (1- injection of viscous polymer solution with the drug at specific site of administration; 2 – in situ formation of biodegradable implant in which the drug is dispersed; 3 –drug release from the polymer matrix by diffusion and gradual erosion of polymer chains) [12].

PLGA copolymers forms 3D-hydrogel network of specific size and porosity. Since the water penetration into the PLGA-based hydrogel is faster than the hydrolysis of the ester bonds, PLGA undergoes predominantly bulk erosion.

One of the main characteristics of advanced drug delivery systems is that they can be delivered at specific site [7]. This is huge advantage for many cancer drugs. Usually cancer drugs can cause enormous toxicity if they are dosed by systemic route; therefore, the opportunity to deliver them locally creates the possibility of improving both the safety and efficacy of cancer chemotherapy. The drug itself becomes more effective when placed next to, and delivered directly to, its targeted tissue and much higher local drug concentrations can be achieved compared to traditional approaches [49]. GLIADEL® is a brain tumor targeting drug delivery system based on biodegradable polyanhydride copolymer poly[bis(p-carboxyphenoxy)propane – sebacic acid] (PCPP – SA copolymer in 80:20 ratio). GLIADEL® drug delivery system was designed in the form of wafers and has been used to locally deliver chemotherapeutic drugs such as carmustine (BCNU) to treat brain cancer [50]. In these patients, the surgeon resects as much of the tumor as possible at the time of the operation and then places small polymer drug wafers at the surface of the brain in the tumor resection cavity (Figure 14).

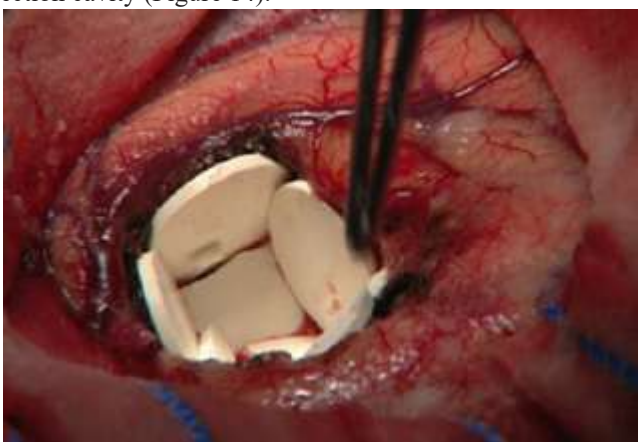


Figure 14: GLADEL® drug delivery system based on biodegradable synthetic polyanhydride copolymers in a form of wafers.

The drug is slowly released from these wafers for approximately three weeks to destroy any remaining tumor. Because the drug is delivered locally, rather than systemically, harmful side effects that normally occur are minimized. Polyanhydrides are the polymer systems that 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 (Figure 15).

From the presented examples of advanced drug delivery systems that contains biodegradable synthetic polymers it can be conclude that degradation process of the applied polymers is a complex process involving several different phenomena such as water absorption, chemical bond stability against hydrolysis, dissolution and diffusion of the small oligomeric fragments that are formed as a consequence of chemical breakdown. These phenomena depends

on many factors such as matrix morphology, chemical composition of the polymers and their configurational structure, size, molecular weights, distribution of the drug molecule within the matrix, and composition of the degradation media. All of these factors have major impacts on the drug release kinetics in controlled drug delivery systems.

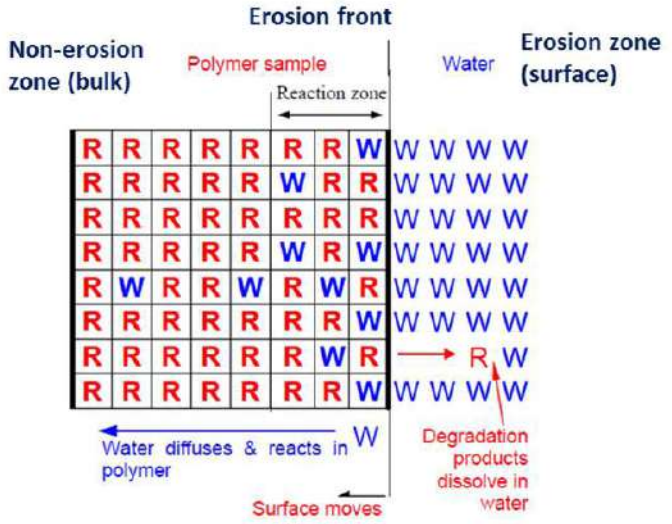


Figure 15: Schematic presentation of surface eroding mechanism [31].

Concluding Remarks

The importance of advanced drug delivery has increased over the past decades, and significant progress have been made in the development of novel technologies based on synthetic biodegradable polymers as drug carrier. Extensive applications of polymers in advanced drug delivery have been realized because polymers offer unique properties which so far have not been attained by any other materials. Polymers are macromolecules having very large chains, contain a variety of functional groups, can be blended with other low- and high-molecular-weight materials and can be tailored for any applications. The future development of biodegradable and bioresorbable synthetic polymers will be based on discovering macromolecules with not only appropriate chemical, physical and mechanical properties but also suitable biological properties. Focus should be on development of environmentally friendly, non-toxic and safe raw materials (monomers, catalysts, solvents, initiators) utilized from renewable resources (2nd generation of waste) that can be used for their polymerization processes.

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