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Polyesters and polyestercarbonates for controlled drug delivery

Part I. TAILORING OF THE DRUG RELEASE

Summary — A crucial factor in the design of safe and effective drug delivery systems is the development of biocompatible carriers, which offer the possibility to tailor the drug release kinetics for specific drugs. The determination of the factors controlling drug release, as well as the methods to adjust the properties of the polymer, is necessary. The influence of the copolymer chain microstructure on degradation, and thus the drug release profile, has been demonstrated; therefore, this factor cannot be neglected during the development of controlled drug delivery systems.
Keywords: polyesters, polycarbonates, drug, carriers.

POLIESTRY I POLIESTROWĘGLANY W SYSTEMACH KONTROLOWANEGO UWALNIANIA LEKÓW. Cz. I. KONTROLA UWALNIANIA LEKÓW
Streszczenie — Artykuł stanowi przegląd literatury dotyczący projektowania systemów kontrolowanego uwalniania leków, opartych na poliestrach lub poliestrowęglanach. Omówiono znaczenie rodzaju i właściwości opracowywanych do tego celu biokompatybilnych nośników, umożliwiających dopasowanie kinetyki uwalniania do określonego leku. Wskazano czynniki wpływające na szybkość uwalniania leków związane ze środowiskiem, postacią leku, rodzajem i właściwościami polimeru użytego w charakterze nośnika, a także z mikrostrukturą łańcuchów polimerowych.
Słowa kluczowe: poliestry, poliwęglany, nośniki leków.

Polymers that can degrade into biologically compatible components under physiologic conditions are advantageous for the preparation of drug delivery systems (DDS). The use of biodegradable polymers precludes the need for retrieval at the conclusion of the dosing regimen, thereby avoiding the potential complications associated with the use of non-degradable systems [1]. Homopolymers and copolymers, obtained from glycolide, lactide and ε-caprolactone and trimethylene carbonate (TMC), are the most commonly considered drug delivery vehicles. However, there are still few implantable drug delivery systems obtained from biodegradable polymers, as was presented in Part II of this article. The release of incorporated drugs from polymeric matrices is required to meet the therapeutic goal of releasing of the drug over time in order to allow for efficient treatment of the specific disease [2]. Tailoring the features of the drug delivery system requires the knowledge of all of the factors that control drug release and the methods that can be used to optimize the polymer properties. The desired properties of the drug delivery system may be obtained by modification of the copolymer chain microstructure. The microstructure's influence on degradation, and consequently drug release kinetics, has been determined.

ALIPHATIC POLYESTERS AND POLYESTERCARBONATES FOR MEDICAL AND PHARMACEUTICAL APPLICATIONS

Among the class of poly(a-ester)s, the most extensively investigated polymers used for medical and pharmaceutical applications are the poly(a-hydroxy acid)s, which include poly(glycolic acid) and the stereoisomeric forms of poly(lactic acid).

Polyglycolide (PGA) was one of the first biodegradable synthetic polymers investigated for biomedical applications and was synthesized for the first time in 1954. In the beginning, it was not considered for biomedical applications because of its thermal and hydrolytic instability. However, the ability to degrade inside the human body became a great advantage. The first synthetic resorbable sutures entered the market in 1960 under the trade name Dexon^{TM} [3, 4]. PGA is commonly synthesized by the ring opening polymerization of glycolide, as presented in Table 1 [4]. Glycolide monomer is synthe-

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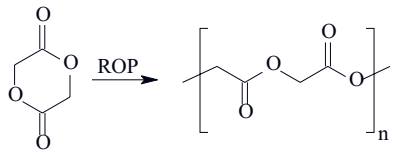
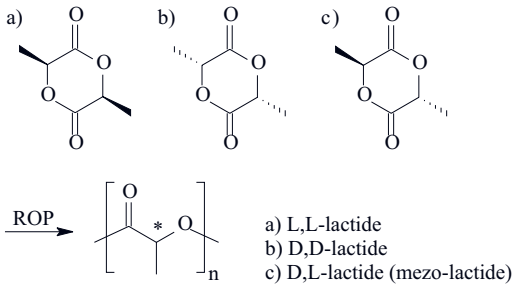
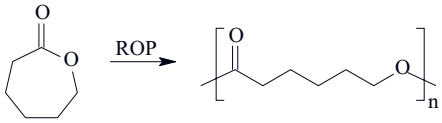
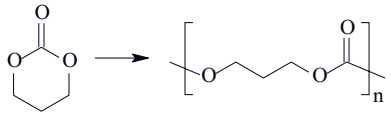
T a b l e 1. The most common monomers and polymers for pharmaceutical applications

Poly(glycolide)	
Poly(lactide)	 a) L,L-lactide b) D,D-lactide c) D,L-lactide (mezo-lactide)
Poly(ε-caprolactone)	
Poly(trimethylene carbonate)	

sized from the dimerization of glycolic acid [5]. Polyglycolide is a tough, highly crystalline polymer (45—55 % crystallinity) and therefore exhibits a high tensile modulus with very low solubility in organic solvents [6]. The poor solubility and high melting point ($T_m \approx 225$ °C and $T_g \approx 36$ °C) limits the application of PGA in drug delivery. However, due to its high crystallinity, polyglycolide shows excellent mechanical properties and has been investigated for bone internal fixation devices (Biofix®). Polyglycolide is a bulk degrading polymer and hydrolysis causes it to lose its strength in 1—2 months and mass within 6—12 months [6]. PGA degrades to glycolic acid [7] and is converted into glycine, which is either excreted in the urine or converted into carbon dioxide and water through the citric acid cycle [8].

Copolymers containing glycolidyl units are being developed to overcome the inherent disadvantages of polyglycolide, such as the high rate of degradation, acidic degradation products, low solubility and high melting point [6, 8].

Poly(lactide) (PLA) is obtained by polycondensation of lactic acid or by ring opening of the cyclic dimer of lactic acid, which exists as two optical isomers, D and L (Table 1). L-lactide is the naturally occurring isomer, and D,L-lactide is the synthetic blend of D-lactide and L-lactide [9].

The homopolymer of L-lactide, poly(L-lactide) (PLLA), is a crystalline polymer (approximately 37 % crystallinity), and the degree of crystallinity depends on the molecular weight and polymer processing parameters. The glass transition temperature of PLLA is 61 °C and the T_m is approximately 174 °C [5, 10]. Poly(L-lactide) degrades much slower than PGA, has good tensile strength, and has low extension and a high modulus (approximately 4.8 GPa); therefore, it is an ideal biomaterial for applications, such as orthopedic fixation devices (*e.g.* Phantom Soft Thread Soft Tissue Fixation Screws®, Phantom Suture Anchors®, Bio Interference Screws®, and Bio-Screw®). An injectable form of PLLA (Sculptra®) has been approved by the FDA for the restoration or correction of facial fat loss or lipoatrophy in people infected with human immunodeficiency virus [5]. The rate of PLLA degradation is very low because of its high hydrophobicity. It has been reported that high molecular weight PLLA can take between 2 and 5.6 years for total resorption *in vivo*. Therefore, copolymers of L-lactides with glycolide or D,L-lactide are currently under investigation for the development of polymers with improved properties [5].

Poly(D,L-lactide) [P(D,L-LA)] is an amorphous polymer due to the random distribution of L- and D-lactidyl units and has a glass transition temperature of 55—60 °C. Compared to poly(L-lactide) (PLLA), it shows much lower tensile modulus (approximately 1.9 GPa) and faster degradation; therefore, it is a preferred candidate for developing drug delivery vehicles or a low strength scaffolding material for tissue regeneration [5, 9].

It is possible to obtain drug delivery systems with different properties by choosing copolymers obtained from L-lactide or D-lactide. Analysis of poly(lactide-*co*-ε-caprolactone) (PLACL) microspheres with progesterone and β-estradiol revealed the influence that the microstructure of the lactidyl blocks in the copolymer chains had on the drug release rate. A more uniform release rate

was observed in the case of copolymers derived from D,L-lactide, compared to L-lactide. When L,L-lactide is used, the lactidyl blocks possess an isotactic microstructure, whereas in the case of D,L-lactide, the microstructure of the resulting lactidyl blocks can be described by pair-addition Bernoulli statistics. The chains containing L,L-lactide are more rigid, which is reflected by their higher glass transition temperature [11].

Polylactides undergo hydrolytic degradation *via* the bulk erosion mechanism. They degrade into lactic acid, a normal human metabolic by-product, which is converted to water and carbon dioxide in the citric acid cycle [8, 12].

COPOLYMERS OF LACTIDE AND GLYCOLIDE

Poly(lactide-*co*-glycolide) (PLGA) has been used in various areas for the controlled drug delivery of macromolecular therapeutics, such as proteins, peptides, genes, antigens, growth factors, *etc.*, and in tissue engineering or the healing of bone defects, mainly because of its biocompatibility and the fact that drug products containing PLGA have been approved for parenteral use by regulatory authorities around the world. PLGAs are commercially available with a variety of different physico-chemical properties, so the drug release profile can be tailored, and the duration of drug release can be varied from hours to several months [13, 14]. Copolymerization of lactide and glycolide is commonly used to modify the characteristics of PGA and PLA [PLLA or P(D,L-LA)]. Copolymers of glycolide with both L-lactide and D,L-lactide have been developed for both device and drug delivery applications. Copolymers of L-lactide with 25—70 % glycolide are amorphous due to the disruption of the regularity of the polymer chain by the other monomeric units. The increase in amorphicity is advantageous for drug delivery systems. The hydrophilicity of PLGA increases with the increase of glycolide content [4, 14, 15]. PLGA is of great interest in the development of matrices for drug delivery due to FDA approval for human use, its good processability, its biocompatibility and the fact that it undergoes degradation to resorbable products. PLGA has been shown to degrade by bulk erosion through hydrolysis of the ester bonds, and the rate of degradation depends on a variety of parameters, including the LA/GA ratio, its molecular weight, and the shape and structure of the matrix [6]. Copolymers of lactide and glycolide may also be useful in intracranial drug delivery due to the biocompatibility with brain tissue [16, 17].

Some PLGA products have entered the market (*e.g.* drug delivery systems, surgical sutures) [18, 19].

Poly(ε-caprolactone) (PCL) can be prepared by ring opening polymerization of ε-caprolactone using a variety of anionic, cationic and coordination catalysts. PCL is a semicrystalline polyester with a T_g of -60 °C and a T_m in the range of 55—60 °C, which enables easy formability at relatively low temperatures [20]. Moreover, it is soluble in a wide range of organic solvents. PCL is highly hydrophobic and crystalline (it crystallizes easily because of its regular structure), so its degradation rate is very low (2—4 years, depending on the initial molecular weight of the device or implant), and it is therefore appropriate for long-term applications [6, 20—22]. PCL was originally used in drug-delivery devices that remain active for over 1 year and in slowly degrading suture materials (Monocryl®) [20]. PCL is also useful for other applications, such as a coating for urethral stents or for tissue engineering of the muscle skeletal system. PCL materials can induce the good adhesion and proliferation of chondrocytes [23].

Hydrolysis of PCL leads to 6-hydroxycaproic acid, which is ω-oxygenated and β-oxygenated to acetyl-S-CoA. Acetyl-S-CoA is then metabolized into tricarboxylic acid [24].

There are some studies on the acceleration of PCL degradation, mainly by copolymerization with glycolide, lactide, or δ-valerolactone. It was determined that copolymers of ε-caprolactone and L-lactide have a greater degradation rate, better drug permeability, thermal and mechanical properties, and, thus, improved processability [15]. Copolymers of ε-caprolactone and glycolide are characterized by lower stiffness than products obtained from PGA [25]. Surgical sutures obtained from block poly(glycolide-*co*-ε-caprolactone) PGACL have entered the market (Monocryl®). PCL can be blended with other polymers to improve stress crack resistance, dyeability and adhesion and has been used in combination with polymers such as cellulose propionate, cellulose acetate butyrate, PLA and PLGA to manipulate the rate of drug release [4, 20, 26].

Poly(trimethylene carbonate) P(TMC) is an aliphatic polycarbon that has a T_g around -15 °C (so it is in rubbery state at room temperature) and a T_m in the range of 40—60 °C, which enables easy processability and the incorporation of labile drugs in mild conditions. The main degradation product is 1,3-propandiol. Acidic degradation products are not produced and released, which helps to avoid toxicity. P(TMC) undergoes surface erosion *in vivo* [27]. P(TMC) is characterized by a very slow *in vitro* degradation, which can be explained by the lack of autocatalysis reactions and absence of enzymes [4]. *In vivo* degradation occurs much faster than *in vitro* degradation, mainly due to enzyme activity observed in *in vivo* systems [4, 19]. It was observed that high molecular weight P(TMC) may not degrade even after 2 years, but a subcutaneous implantation of 10 mm diameter and 600 μm thick (pH = 7.4) discs caused rapid degradation. The discs underwent surface degradation, so a decrease of the diameter was observed, but the molecular weight remained unchanged. The enzymes that accelerate the degradation of P(TMC) are still under investigation; however, it is known that lipases play an important role in this process [28]. P(TMC) materials are characterized by a good tolerance in different cell lines, which gives the possibility for applications in tissue engineering [27]. Low molecular

weight P(TMC), on the other hand, has been investigated as a suitable material for developing drug delivery vehicles [6]. Copolymerization of TMC with ε-CL or L-lactide or making blends may be used for the modification of homopolymer features [4, 29]. P(TMC) has excellent flexibility but poor mechanical strength, so copolymerization with lactide may improve its mechanical features [27].

REQUIREMENTS AND CRITERIA FOR SELECTING A POLYMER FOR DRUG DELIVERY APPLICATIONS

Polymers used in a biodegradable delivery system must be tailored to meet a number of requirements [5, 6, 30—32]:

1. Biocompatibility (not only of the final product but also of the degradation products that are metabolized and cleared from the body):

— No or acceptable toxicity, lack of a sustained inflammatory or toxic response upon implantation in the body;

— No immunogenicity (unless desired);

— No mutagenicity;

— No thrombogenicity.

2. Biofunctionality:

— Stability in storage, an acceptable shelf life. Degradable materials need to have a controlled service-life during which their properties and performance should not significantly deteriorate. Afterwards, they should degrade in a predictable fashion without harmful degradation products or polymer fragments;

— The degradation time of the material should match the healing process;

— Adequate material properties (chemical, physical, physico-chemical, thermal, and biological);

— Appropriate mechanical properties for the indicated application; the variation in mechanical properties with degradation should be compatible with the healing process;

— Appropriate permeability and processability for the intended application;

— Easily processable into the final product form;

— Sterilizability.

Chemical and physical properties, biocompatibility, purity, and reproducibility of the product must be maintained through all steps of the scaled-up manufacturing process, packaging, and storage. Moreover, regulatory requirements of the design, performance, and safety must be considered throughout the development phase of medical devices [4]. Commercial polymers rarely meet all of the desired specifications. Moreover, because of the wide range of applications of currently used polymeric biomaterials, multiple different polymeric system are necessary, which underlines the need for developing a wide range of biodegradable materials that can appropriately match the specific and unique requirements of each individual medical application [6, 33]. Progress in the development of biodegradable polymers, especially related to the methods of their synthesis, is advantageous for obtaining the correct polymer for a particular use [4]. However, when developing the drug carrier, all of the factors that control drug release must be taken into consideration to achieve complete drug efficacy.

FACTORS AFFECTING DEGRADATION AND THE DRUG RELEASE PROCESS

In controlled drug delivery, bioactive agents are entrapped within a biodegradable polymer matrix from which they are released in an erosion- or diffusion-controlled fashion or a combination of both. The release characteristics of the bioactive agents can be effectively modulated by suitably engineering the matrix parameters [6, 13]. Knowledge regarding these more detailed processes is necessary for understanding drug release in detail and for controlling the release rate.

Large particles or DDS often exhibit a tri-phasic release profile due to heterogenous degradation [13]:

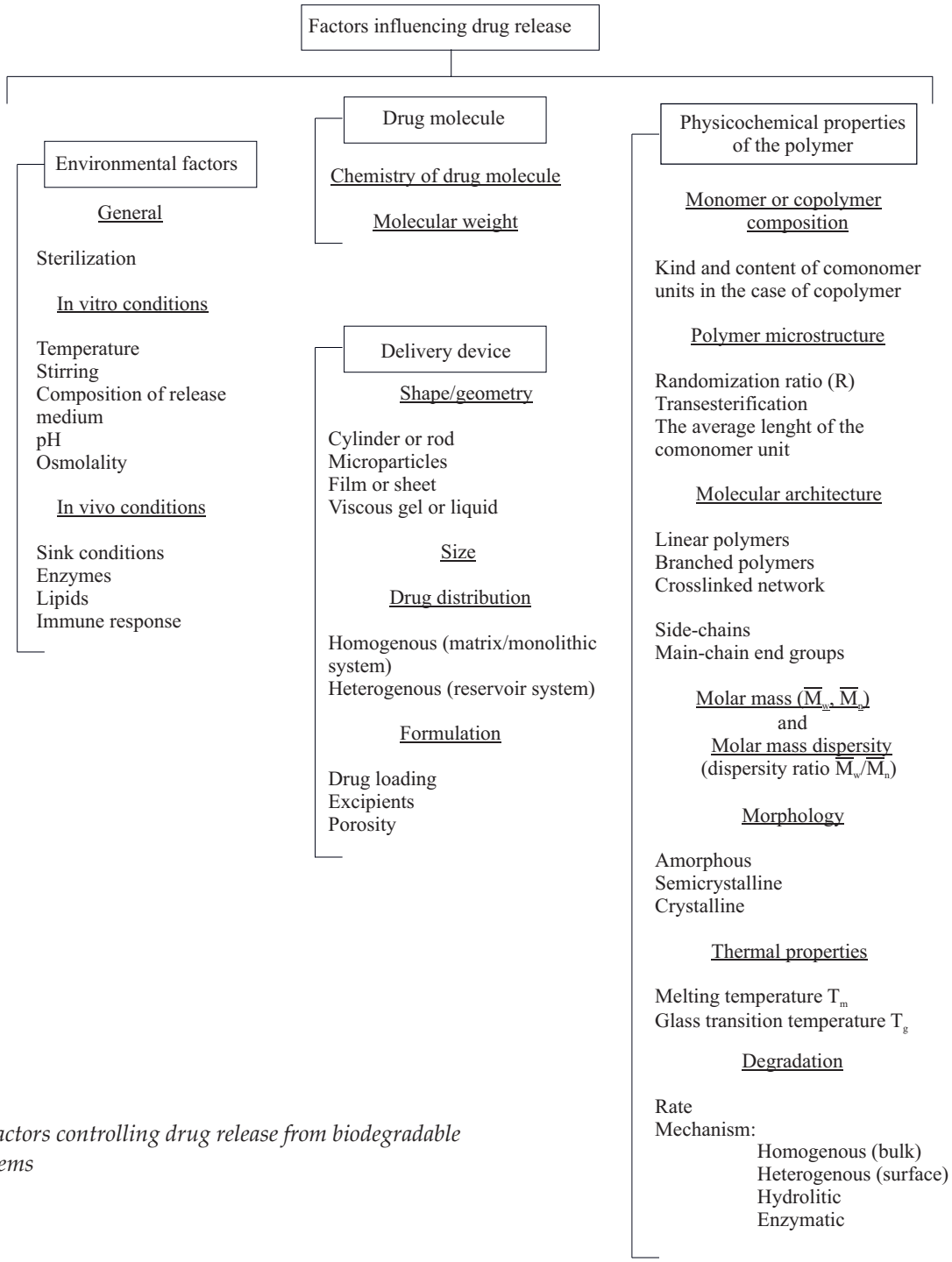
— Phase I is usually described as a burst release, leads to a higher initial drug delivery and reduces the effective lifetime of the device [34]. The initial burst release has been attributed to not incorporated drug particles on the surface or drug molecules close to the surface with easy accessibility by hydration. Other reasons for the burst release may be the formation of cracks and the disintegration of particles [13]. Sometimes, the initial burst stage may be utilized in certain drug administration strategies. For example, in the case of drugs used at the beginning of wound treatment, an initial burst provides immediate relief followed by a prolonged release to promote gradual healing. On the other hand, the burst effect can be pharmacologically dangerous and economically inefficient; therefore, the burst effect is typically considered a negative effect of the drug delivery process. One of the main difficulties with burst release is its unpredictability, and even when the burst is desired, the amount of burst cannot be significantly controlled [34]. Therefore, the knowledge of tailoring drug release may also be used to modify or eliminate the burst effect.

— Phase II is often a slow release phase, during which the drug diffuses slowly, either through the relatively dense polymer or through the few existing pores, while polymer degradation and hydration proceed.

— Phase III is usually a period of faster release, so it is sometimes called the second burst or rapid phase. This phase is commonly attributed to the onset of polymer erosion; however, it may also be caused by cracks or the disintegration of the drug carrier.

However, not all the release profiles follow the traditional tri-phasic pattern. Small particles and particles coated with a thin PLGA film often exhibit a bi-phasic release profile with a relatively rapid second phase [13].

Among the factors influencing drug release kinetics, the drug — drug and drug — polymer interactions must



Scheme A. Factors controlling drug release from biodegradable polymer systems

also be taken into account. The drug may be bound or crosslinked to the polymers. This phenomenon was found to be less significant for higher M_w PLGA (because there are fewer polymer chain end groups) or higher drug load (there are more drug molecules than polymer end groups) [13]. The potential interactions of the drugs with the matrix polymer may result in incomplete drug release [2]. Drug-drug interactions, such as forming of physical or covalent aggregates, have been suggested to cause slower and incomplete drug release. Such aggregates are also a result of an acidic environment [13].

Other factors that control the drug release process, including environmental conditions and factors related to the drug molecule, polymer, and drug delivery system, are presented below and summarized in Scheme A [1, 6, 13, 35—37].

Environmental factors

Among the environmental factors that affect drug release are the flow rate, buffer concentration, temperature, and the presence of enzymes. There are some contradictory results about the influence of the release medium. It has been shown that PLLA microcapsules exhibit rapid weight loss in alkaline media (pH = 8—9) [38]. In contrast, studies conducted on PLGA revealed that the rate of deg-

radation increased in acidic media (pH = 5), but slowed down in alkaline media (pH = 9.24). Thus, it was concluded that both alkaline and strongly acidic media may accelerate the degradation rate [39]. Salts, plasticizing agents and surfactants in the release medium may affect the processes in the same way as if they were incorporated, with the exception that a high osmolality in the release medium would decrease the rate of water absorption by the DDS. Increased temperature not only accelerates all chemical reactions but also increases the mobility of the polymer chains and, thus, the possibility of pore closure. Faster polymer degradation and drug release have been reported *in vivo* and have been mainly attributed to the effects of enzymes and immune responses [13].

Factors related to the drug carrier

Selection of the shape and size of the drug carrier depends on the flexibility with which the polymer can be processed, the desired route of administration, the duration of action and the stability of the drug under processing conditions. The drug distribution in the dosage form can be either homogenous (monolithic or matrix system) or heterogenous (reservoir system) [1]. In the reservoir system, the polymer membrane serves as the barrier, and the drug release is controlled by Fickian diffusion. However, biodegradable polymers are chemically unstable, so they are generally not used to prepare reservoir delivery systems. Most often, they form monolithic systems in which the drug is dispersed or dissolved homogenously throughout the polymer. The drug is initially released from the outer surface and then from deeper regions of the dosage form. Thus, the diffusional path increases during the release process, so diffusion-controlled release from matrix systems is not zero-order. Typically, low-molecular-weight drugs can be released from monolithic system at rates that are consistent with a diffusion controlled mechanism. High-molecular-weight drugs, such as peptides and proteins, need an additional mechanism that can facilitate drug transport, *e.g.* degradation, which causes the formation of pores and channels and thus, enhances the drug release [1, 2].

Large drug delivery systems are more susceptible to autocatalytic degradation because the degradation products do not leach out easily from the network, which causes a decrease in pH [40]. The shape of the DDS, in particular the ratio of surface area to volume, affects the release of the drug and the polymer degradation products [13].

The amount of incorporated drug (drug loading) is an important factor because the space left vacant after drug release will most likely constitute pores, facilitating further drug release [13]. Thus, high drug loading (>10—20 %) often results in a faster release of the drug. This fast release can also be attributed to the smaller amount of polymer that acts as a diffusion barrier [2].

Factors related to the drug molecule

The incorporated drug or the co-incorporated additives may affect drug release in several ways [13]:

— Enhanced or inhibited water absorption and hydrolysis due to an increased hydrophilicity/hydrophobicity, osmolality, or due to surface active substances;

— Increased or decreased rate of hydrolysis due to acid or base catalysis, or acid neutralization. Basic compounds can catalyze ester-linkage scission and, thus, accelerate the degradation. On the other hand, basic compounds can neutralize carboxyl end groups and, thus, decrease the degradation rate as a result of reduced acid catalysis [38, 39];

— Plasticization of the polymer;

— Constitution of crystalline parts of the DDS.

Factors related to the polymer

One of the important factors that regulates drug release is drug carrier chemistry. Copolymers offer several possibilities to change polymer properties, *e.g.* by manipulating the types and relative ratios of different comonomers [40]. Composition can directly dictate many of the physicochemical polymer properties, such as bulk hydrophilicity, morphology, structure and the extent of drug-polymer interactions (*e.g.* drug solubility in the polymer) [1].

In addition to copolymer composition, thermal properties, polymer processing characteristics and the stability of the dosage form also affect the transport rates of the polymer. When exposed to temperatures above the T_g, the polymer will exhibit an increase in free volume that permits greater local segmental chain mobility and faster drug transport. On the other hand, the greatest stability during the storage of a polymer device may be obtained at temperatures below the T_g [1, 41]. The presence of plasticizers, such as residual solvents or solutes including the drug or other additives, will tend to lower the polymer glass transition temperature. Factors that decrease segmental mobility, such as greater chain rigidity, bulky side groups and ring structures, tend to increase the T_g [1].

Chain length is also important in the dissolution and diffusion steps, as both solubility and diffusivity in polymers can be dependent on molecular weight [42]. The degradation rate increases as the molar mass decreases. The presence of low molar mass species and/or monomers leads to a faster degradation rate, in agreement with the presence of more carboxylic acid-catalyzing groups [40].

Many factors are known to influence the biodegradation rate of a polymer: polymer chemistry, molecular architecture, molecular weight, morphology, size, geometry, and porosity of the device, as well as the surrounding conditions (*e.g.* pH and temperature) or additives. Consequently, the mechanism and rate of polymer degradation

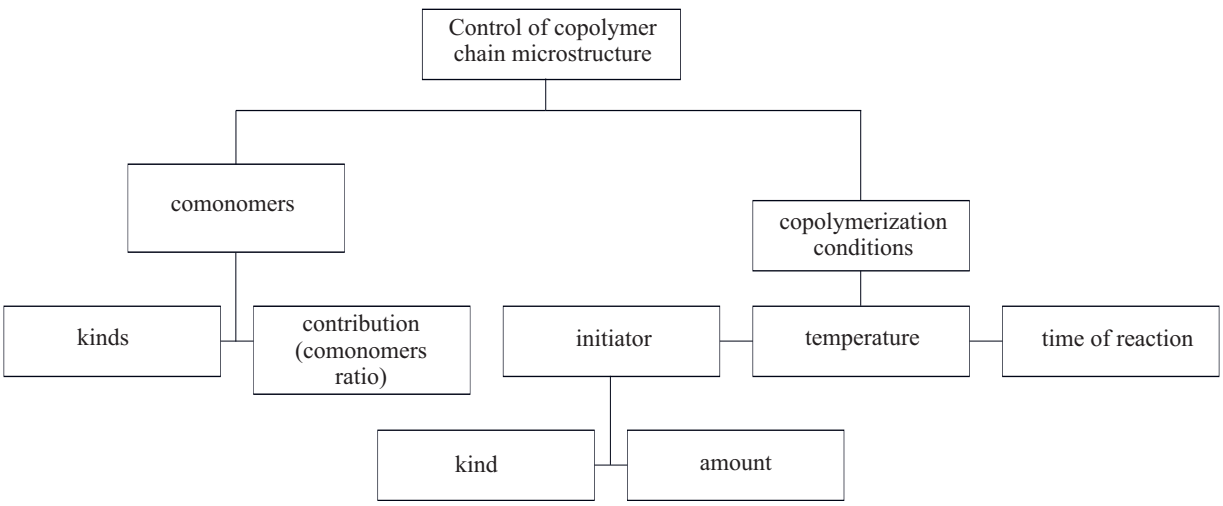
will also influence the drug release and its stability after administration [1, 10, 38]. As was mentioned previously, aliphatic polyesters are susceptible to hydrolytic degradation. The reaction rate depends on the ability of the polymer to absorb water. Erosion is defined as the physical disintegration of a polymer matrix as a result of degradation. Depending on the erosion mechanism, the polymer is classified as either a bulk-eroding or a surface-eroding polymer [4]. In the case of bulk degradation, the internal concentration of autocatalysis products can produce an acidic gradient as the newly generated carboxyl end groups formed during ester bond cleavage accumulate, which in turn accelerates the internal degradation compared to the surface, leaving an outer layer of higher molecular weight skin with a lower molecular weight, degraded interior. The degradation mechanism thus becomes defined by a bimodal molecular weight distribution [20, 35]. Surface-eroding devices are hence often preferred over bulk-eroding materials for the sake of predictability [4].

Microstructure of the polymer chain

The microstructure of the polymers may be controlled by several factors used during synthesis (Scheme B).

Ring Opening Polymerization (ROP) of heterocyclic monomers, such as lactide, glycolide, ε-caprolactone and trimethylene carbonate (TMC), is considered the most effective polymerization method to obtain high-molecular-weight homo- and copolymers. The advantages of ROP over the polycondensation route as a commercially viable process are as follows: milder reaction conditions, shorter reaction times, the absence of reaction by-products and the ability of using even six- or seven-membered lactones [6, 15, 43]. Indeed, this mechanism allows quite good control of the polymer characteristics (*i.e.* predictable molecular weight and narrow molecular weight distribution) and is particularly well suited for macromolecular engineering with the production of homo- and copolymers of various architectures (*i.e.* palm-tree, diblock, multiblock, star) [15, 44]. A broad range of anionic, cationic and coordinative initiators or catalysts has been reported for ROP [44]. Although stannous octanate [$Sn(Oct)_2$] is still one of the most widely used initiators, the contamination of the aliphatic polyesters by potential residues is of particular concern as far as biomedical applications are envisioned, so the possibility of replacing it with more biocompatible initiators has been studied [44, 45]. Thus, another approach for producing aliphatic polyesters free from toxic metallic residues is the use of bioresorbable salts for the ROP of polyesters. Lactide polymerization at 180 °C has been studied for a wide range of cations (Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, and Fe^{2+}) with a variety of counter-ions (chloride, iodide, oxide, hydroxide, carbonate, acetate and higher fatty acids, lactate, tartrate, citrate, α-amino acids and peptides) [44]. Zirconium derivatives have been investigated for polyester synthesis because they are 10 times less toxic than tin counterparts, and Zr-containing drugs and cosmetics have been approved by the Food and Drug Administration [45]. Moreover, it was determined that the copolymers obtained with zirconium(IV) acetylacetonate and chloride could successfully replace the ones obtained in the presence of tin compounds as far as medical applications are concerned [46—48].

Polymer microstructure may be described by the average lengths of the blocks; the randomization ratio, which describes the randomness of the copolymer chain (and has value of 0 in case of a diblock copolymer of AB type and 1 in the case of a completely random distribution of copolymer sequences); and transesterification of the second mode ratio [49]. The increase of interest in block copolymers is a consequence of searching for amphiphilic copolymers that can be used as drug delivery vehicles. Block copolymers can be used to prepare nano- and micro-particles, hydrogels, micelles or polymerosomes [50]. Random copolymers possess a statistic distribution of copolymer sequences. Random copolymers are



Scheme B. Methods of copolymer chain modification for obtaining polymers with tailored physicochemical features

formed by transesterification, which causes a redistribution of the sequences along the polymer chains leading to changes in the chain structure and the lengths of microblocks [15, 51]. There are some factors that favor transesterification reactions, such as the type of initiator [*e.g.* $Sn(Oct)_2$] and an increased temperature or reaction time [15, 24]. Two modes of transesterification may change the sequences in the resulting polyester. In the first mode, the ester bond opening occurs exclusively between monomeric units or their multiples, and in the second mode, monomeric units undergo bond cleavage [52].

It has been determined that polymer degradation depends on its microstructure [25, 53]. In the case of poly(glycolide-*co*-ε-caprolactone), the copolymers with a higher C-G bond content or a higher degree of randomness exhibit higher degradation rates. Sequences with odd numbers of glycolyl units, such as -CGC- and -CGGGC-, which result from the second mode transesterification, appear to be more resistant to hydrolysis [25]. Consequently, the effect of the polymer chain microstructure on the kinetics of this process has been shown.

The influence of the microstructure of the immunosuppressive drug's (cyclosporine A or rapamycine) carrier has been demonstrated. Analysis of three types of poly(L-lactide-*co*-TMC) (PLATMC), two semiblock and one random, revealed that matrices without drugs obtained from semiblock copolymers degraded differently than matrices containing cyclosporine A or rapamycine, whereas all types of matrices obtained from the random PLATMC degraded in a similar way. Based on the obtained results, correlations between the copolymer degradation and the drug release process were proposed. According to the outcome, a regular drug release process may be obtained from highly randomized copolymers ($R \approx 1$) that remain amorphous during degradation [54]. Based on these results, poly(L-lactide-*co*-trimethylene carbonate) 74:26 with a tailored chain microstructure (randomization coefficient $R = 0.7$) was synthesized and used to prepare matrices with cyclosporine A (CyA). A regular degradation was determined, which also caused a uniform CyA release profile [55].

The influence of the PLAGA and PLACL chain microstructure on the release process of doxorubicine has also been observed [56].

CONCLUSIONS

The increase in interest of biodegradable polymers for pharmaceutical and medical applications requires the tailoring of physico-chemical proper-

ties of polymers in the aim of adjusting their features for particular and sometimes unique applications. As was shown in this article, drug release is a very complicated process that is influenced by many factors related to the polymer, drug, drug carrier and release environment. In the case of polymers for drug delivery applications, the comonomer composition and ratio are the most commonly used for modification of polymer characteristics. However, it was determined that copolymer chain microstructure influences polymer properties as well as degradation, which has an impact on the drug release kinetics, and, thus, it should be considered during the designing and development of new drug delivery vehicles.

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