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Polymers in the Pharmaceutical Applications - Natural and Bioactive Initiators and Catalysts in the Synthesis of Biodegradable and Bioresorbable Polyesters and Polycarbonates

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1. Introduction

Biopolymers, synthetic polymers and their derivatives are commonly used in medicine and pharmacy. Significant progress attained in the polymer chemistry and technology has boosted the dynamic development of the medicinal engineering.

Recently, particular interest of scientists has been focused on biomedical polymers, especially those used for drug delivery systems, therapeutic systems and macromolecular prodrugs. The aforementioned applications have opened new exciting prospects for medicine, because specially designed polymers are capable of delivering medicinal substances to the target diseased tissues and cells together with dosing those drugs according to controlled specified pharmacodynamics. Particular attention has recently been paid to chemistry of biocompatiable and biodegradable polymers, because they have an advantage of being readily hydrolyzed into removable and non-toxic products, which can be subsequently eliminated by metabolic pathways. Furthermore, the biomedical polymers have to be synthesized now using friendly for the environment and safe for human health, effective natural initiators, co-initiators and/or catalysts.

Therefore, the main objective of this work is to discuss various polymers recommended for the pharmaceutical applications and then to describe natural compounds used as initiators, catalysts and co-initiators in the synthesis of biodegradable and bioresorbable polyesters and polycarbonates.

2. Polymers in the pharmaceutical applications

Macromolecules are applied in pharmacy as the pharmacological substances, blood substitutes, drug delivery and therapeutic systems, in the synthesis of macromolecular prodrugs and in the technology of prolonged release drug formulations.

2.1 Polymers with the pharmacological effects and polymeric blood substitutes

One of the most interesting polymers used in pharmacy, are those exerting a pharmacological effect. DIVEMA, copolymer of divinyl ether-maleic anhydride (Florjanczyk & Penczek, 1998; Papamatheakis et al., 1978) is an example of such compound with antitumoral and antiviral properties. Its action probably includes the stimulation of the glycoprotein production, which suppresses viral RNA translocation in cells and division of cancer cells.

Furthermore, the polymers are often applied as swelling, relaxation and sliding agents. Methylcellulose taken orally is not absorbed from the alimentary tract. However, it detains water on swelling and in consequence causes relaxation of the stercorous mass (Tonnesen & Karlsen, 2002; Zejc & Gorczyca, 2002).

A copolymer of ethylene and propylene glycols has found an application in the therapy of constipations (Tonnesen & Karlsen, 2002; Zejc & Gorczyca, 2002). This non-ionic, surface-active polymer is unable to penetrate through the gut walls because of large average molecular weight. However, it causes relaxation and hydration of the stercorous mass by the reduction of the surface tension.

A linear polymer of uronic acids - alginic acid (mannuronic acid conjugated β-1,4 and L-guluronoic acid glycosidically conjugated α-1,4) is mainly obtained from the *Laminaria algae*. This polymer neutralizes hydrochloric acid (Janicki et al., 2002; Zejc & Gorczyca, 2002). Its action relies on detaining of water in stomach followed by reduction of irritations and pain.

A polyvinylpyrrolidone has found an application as anti-diarrhoeal drug (Tonnesen & Karlsen, 2002; Zejc & Gorczyca, 2002). Its amphoteric properties normalize pH in stomach and intestines through acids or bases adsorption, which are usually raised as result of fermentation or putrefaction.

The synthetic hormones with the protein structure play an important role in the modern pharmacology (Zejc & Gorczyca, 2002). The Buserelin, Goserelin, Leuprorelin and Triptorelin are known as synthetic analogues of Gonadoliberin (the hormone of hypothalamus). These oligopeptides are obtained by exchanging of some amino acids in Gonadoliberin molecule and then are used to treat prostate and breast cancers or endometriosis. Another example is synthetic analogue of Somatoliberin used for treating children with some forms of GH deficiency. The synthetic analogue of Somatostatin - Octreotide is applied to treat the alimentary tract (Zejc & Gorczyca, 2002).

Corticotrophins are examples of synthetic hormones of the anterior pituitary, often applied in the therapy of rheumatoid diseases and severe asthma. Thus, Oxitocin, Vasopressin and Ornipressin are belong to the group of hormones of posterior lobe of the hypophysis (Zejc & Gorczyca, 2002). First of them causes uterine contractions, second can contract the smooth muscles of the blood vessels while Ornipressin is often added to the anaesthetics. Moreover causes the vessels contraction.

The peptide antibiotics are the relatively numerous group of the natural oligomers. They are composed of peptide-bounded amino acids to form cyclic, linear or cyclic-linear structures (Markiewicz & Kwiatkowski, 2001; Patrick, 2003; Zejc & Gorczyca, 2002). They may act the Gram-negative (Polymyxin) and Gram-positive (Gramicidin, Prostinamycin) bacteria as well as fungi and protozoa.

A cyclosporine A – branched and cyclic oligopeptide composed of 11 amino acids is an important macromolecular immunosuppressive drug (Markiewicz & Kwiatkowski, 2001; Zejca & Gorczyca, 2002). Cyclosporine A selectively inhibits lymphocytes T function, thus is widely used as an immune barrier tolerance agent in the transplantology.

Macromolecular inhibitors that absorb the cholesterol from the intestines are also known; form them insoluble in water polymers, which produce complexes with the bile acids. To this polymer group belongs: copolymer of divinylbenzene and styrene substituted with quaternary trimethylammonium group and copolymer of diethyltriamine and epichlorohydrin (Zejc & Gorczyca, 2002).

A heparin, obtained from the animal tissues (mainly livers and lungs) (Zejc & Gorczyca, 2002) is next example of the natural polysaccharide used as the therapeutic agent. The heparin effects on the all blood clotting phases. Usually is used to treat arterial embolism and thrombosis, heart failure and before surgical operations.

A very important group of the biomedical polymers is macromolecular blood substitutes. They are accountable for the regular osmotic pressure and viscosity, closed to the osmotic pressure and blood viscosity; usually used in the anaphylactic shock, heart failure, intoxication, burns, toxic diarrhoea, embolic-thrombotic complications as well as microcirculation impairment.

A polyvinylpyrrolidone was the first synthetic polymer used as the blood substitutes. Its solutions were mainly used to treat the shock after the burns and, in the case when the blood transfusion was not indicated (Janicki et al., 2002; Florjanczyk & Penczek, 1998; Zejc & Gorczyca, 2002). Likewise, the solutions of polyvinyl alcohol have found the applications as the blood substitutes. However, they were withdrawn from the list of the blood substitutes as result of their undesirable side effects.

The blood susbstitutes with the therapeutic action has also been elaborated as result of incorporation of some therapeutic agents (e.g. penicillin, pelentanic acid, p-aminosalicylic chloride) into polyvinyl alcohol (Janicki et al., 2002; Zejc & Gorczyca, 2002).

Currently, the solutions of polysaccharides (e.g. dextran), modified starch derivatives and modified gelatin products (polygeline, oksopolygelin, liquid gelatin) are commonly used as the blood substititues (Janicki et al., 2002; Zejc & Gorczyca, 2002). The dextran with the average molecular weight ranged from 40 000 to 70 000 Da is used as 6 or 10% solution. This polysaccharide is produced by fermentation of the sucrose solutions in the presence of the *Leuconostoc mesenteroides* bacteria. Obtained glucose is polymerized to dextran in the presence of enzymes.

A hydroksyethyl starch is obtained by hydrolysis of high-amylopectine starch in acidic environment (Zejc & Gorczyca, 2002). The reaction products are neutralized followed by the reaction with ethylene oxide. The starch substituted with hydroxyethyl group is then produced in this reaction.

A polygeline is obtained from the reaction of diisocyanate with the gelatin. As result, linked urea groups are produced, whereas liquid gelatin is produced in the reaction with succinic anhydride (Janicki et al., 2002; Zejc & Gorczyca, 2002).

2.2 Macromolecular prodrugs

A prodrug is a modified therapeutic agent, which is metabolized into active precursor in human body (Janicki et al., 2002). Over the recent years, the conception of macromolecular prodrug has appeared as macromolecule that has therapeutic agents in the structure; the released drug becomes pharmacologically active during hydrolytic biodegradation of the polymer (Ouchi & Ohya, 1995). In general, the therapeutic agent could be incorporate into polymer chain, might be end-capped or may form a pendant group of the macromolecular chain (Figure 1).

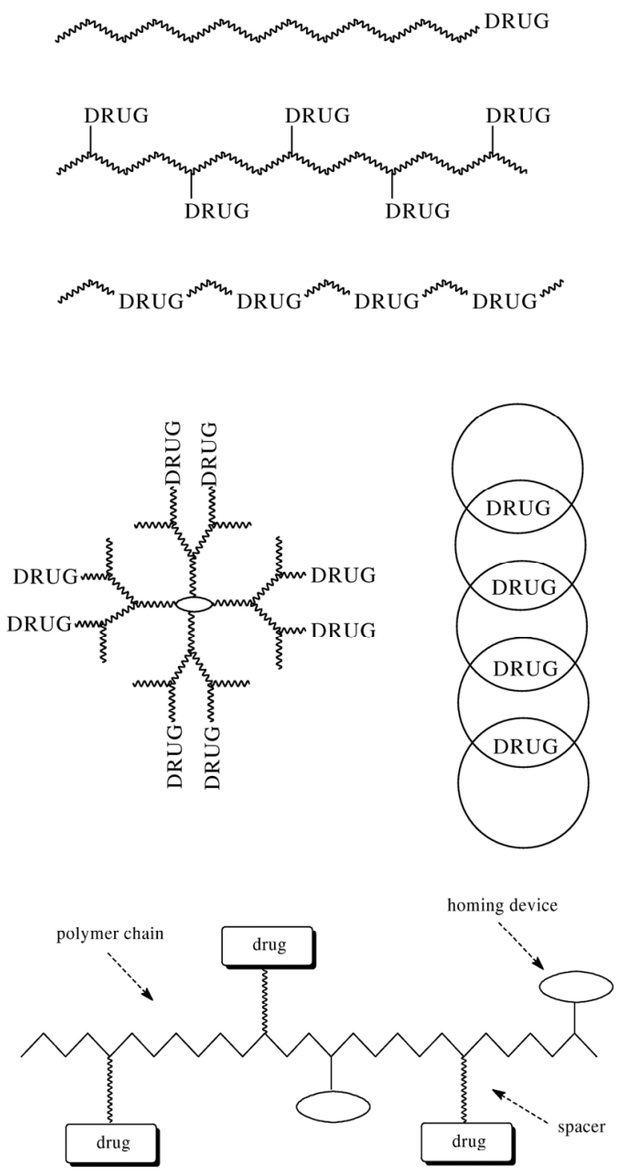


Fig. 1. Structure of the macromolecular prodrugs

Macromolecular prodrugs are mainly used in the cancer therapy. For example, 5-fluorouracil can be applied locally or orally in the therapy of the alimentary tract, urinary bladder and prostate gland cancers. The conjugations of this therapeutic agent as a pendant group to polyethylene glycol (Ouchi et al., 1986, 1992) or to vinyl polymer chain as substituent form examples of its macromolecular prodrugs (Ouchi et al., 1988).

The pharmacokinetics of the macromolecular prodrugs is mainly determined by the structure of the polymer (the rate of hydrolysis under the given conditions and the susceptibility to degradation in the presence of enzymes), its average molecular weight (the ability to the accumulation in blood, lymph, spleen, liver and other organs) or crystallinity (the rate of biodegradation).

The polymers must meet specific criteria to be applied in the synthesis of the macromolecular prodrugs. Namely, macromolecules and their metabolic decomposition products cannot be cumulate in the human body, to be toxic and the most important; the drug should be released from the macromolecule as result of the metabolic processes. The list of the macromolecular prodrugs developed so far is broadly presented in monograph (Ouchi & Ohya, 1995).

2.3 Polymers in the technology of prolonged release drug formulations

Macromolecules have also found the application in the technology of prolonged release drug formulations. They are mainly intended to ensure the constant concentration of the therapeutic agent in the certain time (e.g. 8-24 hours), in the patient body. The group of these drugs, therefore, can eliminate the drug multiple dosing during a day and reduce total daily dose of it. The prolonged drug forms are usually applied in the therapy of cardiac and alimentary tract diseases, coronary vessels, diabetics, and psychiatric disorders.

The absorption of the therapeutic agent using prolonged release drug forms can be reduced by coating, incorporation, complexation or bonding on the ionites (Janicki et al., 2002). Polymers applied in this technology, could be generally divided into biodegradable and non-biodegradable. Biodegradable macromolecules are definitely more preferred from the toxicological point of view. In the technology of prolonged release drug formulation, natural polymers and their modified derivative (e.g.: starch, cellulose) as well as synthetic polymers are used e.g.: polyethylene, polypropylene, polyvinyl chloride, polyvinyl alcohol, polyvinyl acetate, polyacrylic acid, polycarbophile, polyacrylamides, polyacrylates, polyethylene glycol, poly(amino amide)s, polyurethanes, siloxanes, homo- or copolymers of lactide and glycolide, poly(ε-caprolactone), polyorthoesters (Cardamone et al., 1997; Ertan et al., 1997; Huang et al., 1994; Lan et al., 1996; Matthews et al., 1996; Merkli et al., 1998; Ouchi & Ohya, 1995; Schierholz 1997; Sintzel et al., 1996; Uhrich et al., 1999; Ulbrich et al., 1996).

The crystals, pellets and granules of the drug might be coated with several polymer layers, according to the expected release rate. The therapeutic agent is gradually released as result of the polymer erosion or diffusion or is rinsing out from the polymer coating (Figure 2) (Uhrich et al., 1999).

Methylcellulose, polyvinylpyrrolidone and polyvinyl alcohol are predominantly applied as the coating substances. The analogous effect can be obtained by coating of the

therapeutic agent with polymeric layers, soluble in different parts of the alimentary tract or under enzymes.

The drug release based on the diffusion takes place when polymers insoluble in the alimentary tract (e.g.: ethyl cellulose, nitrocellulose, cellulose acetate, acrylic and methacrylic ester copolymers) are applied as the coating agents. The coating tablets containing porophors (acrylic and methacrylic ester copolymers, starch, cellulose acetate phthalate or microcrystalline cellulose) are also used. The solubility of these tablets is increased as the effect of porophors dissolution and swelling.

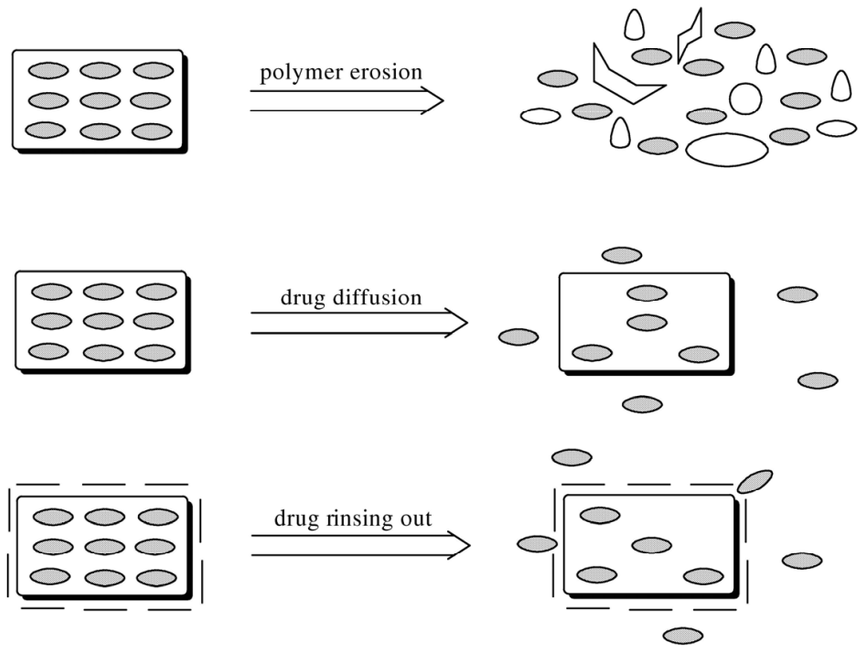


Fig. 2. The mechanism of the controlled release of the therapeutic agent

The incorporation method is relying on the suspension of the therapeutic agent on the prolonged released carrier. Most often as the carriers are used: hydrophobic polymers (e.g.: methylcellulose, acrylic acid polymers) as well as lipopholic polymers and some carriers insoluble in the alimentary tract (e.g.: polyvinyl chloride, polyethylene, cellulose acetate, ethyl cellulose, polystyrene, polyamide, silicone resin and acrylic and metacrylic acids ester copolymers). For instance, when the hydrophilic carrier is used, the tablet is consecutively swelled after passing the alimentary tract followed by creation of high viscous hydogels, which prolonged the drug release. The drug release suspended on the lipophilic carrier is dependant on pH and the presence of enzymes. Matrix tablets contained water-insoluble carriers, however, are stable in the alimentary tract environment. Therefore, the drug is gradually release via the capillaries.

The complexation method involves the creation of poor soluble, therapeutic agent-polymer complexes. The drug is released due to the gradual decomposition of this complex. This technique is also used to produce skin and mucosa antiseptics (iodophors). The iodophors

are the complexes of iodine with water-soluble polymers, which perform a role of carrier. They are high active against bacteria, viruses, fungi and protozoa.

The bonding of the drug on the ionites method is usually applied for acidic or basic drugs. It relies on release of the drug based on ion exchange in the alimentary tract.

2.4 Polymers in the therapeutic systems technology

The polymers used in the therapeutic systems are the drug forms that are dosing or releasing drug in the exact time with the controlled rate (Janicki et al., 2002; Müller & Hildebrand, 1998). They are designed to ensure constant concentration of the therapeutic agent in the body (Figure 3).

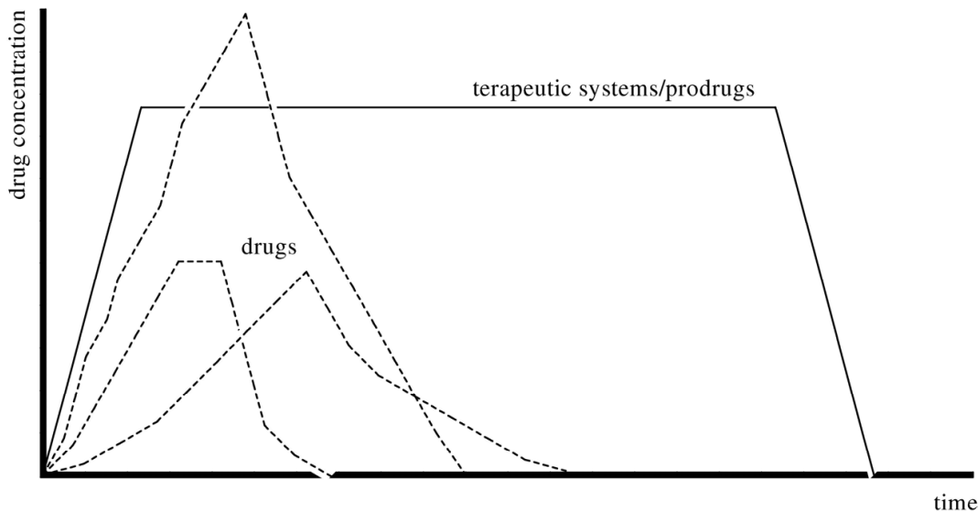


Fig. 3. Drug release profile from the conventional tablets and polymeric therapeutic systems

Therapeutic systems are commonly used in medicine due to their high efficiency in comparison to the conventional drug forms and prolonged release tablets. Considering the way of administration and the location of the drug absorption there are: oral, transdermal, ocular, intra-uterine, implantation and infusion therapeutic systems (Table 1). According to the construction of the element dosing the drug, there are: membrane, matrix and microvessels transdermal therapeutic systems (Knoch & Merkle, 1987; Müller & Hildebrand, 1998), usually used to treat stenocardia, inflammations, motion sickness, chronic hypertensive disease, in the hormonal and anti-nicotinic therapies (De Mey et al., 1989; Fagerström et al., 1993; Hadgraft, 1996; Ho & Chien, 1993; Liedtke et al., 1989; Lin et al., 1993; Man et al., 1993; Monkhouse & Hug, 1988; Sanders, 1996). The novelty comprises the ultrasonic transdermal therapeutic systems and the microelectronics transdermal therapeutic systems, where the drug is released from the polymer carrier under the frequency electric field influence (Prausnitz et al., 1994; Santus & Baker, 1993; Simonin, 1995).

In the ocular therapeutic systems, the drug is released to the lachrymal fluid through the membrane. The intra-uterine therapeutic systems are mostly used in the contraception, whereas implantation therapeutic systems are usually applied under the skin. In their case, the drug release is carried out through the slow diffusion from the polymeric systems to the tissue.

Therapeutic system	Polymer	Drug
Transdermal therapeutic system	copolymers of acetate vinyl and ethyl, poliacrylate, silicone, polyurethanes, polyolefines, polyethylene glycol	Acetate Noretisterone, Buprenorphine, Clonidyne, Estradiol, Fentanyl, Flurbiprofen, Hyoscine, Isosorbide dinitrate, Nicotyne, Nitroglycerin, Testosterone
Oral therapeutic system	polyvinyl alkohol, polyacetale vinyl, polyamides, polyethylene glycol, poliacrylate, silicone, homo- or copolymers of lactide, glicolide and ε-caprolactone	Acetazolamide, Glipizide, Metoprolol, Nifedipine, Okseprenolol KCl, Li_2SO_4, $FeSO_4$
Ocular therapeutic system	copolymers of acetate vinyl and ethyl	Pilocarpina
Uterus therapeutic system	silicone	Progesterone
Implantation therapeutic system	copolymers of lactide and glicolide, silicone	Estradiol, Goserelin

Table 1. The therapeutic systems examples

3. Natural and bioactive initiators and catalysts in the synthesis of biodegradable and bioresorbable polyesters and polycarbonates

Biodegradable and bioresorbable polymers such as polyglycolide (PG), polylactide (PLA), poly(ε-caprolactone) (PCL), poly(trimethylene carbonate) (PTMC) and copolymers of glycolide (GL), L-lactides (LA), *rac*-lactide (*rac*-LA), ε-caprolactone (CL), trimethylene carbonate (TMC) or others cyclic esters and carbonates are very often used as polymeric prodrugs, drug delivery or therapeutic systems. Aliphatic polyesters and polycarbonates are degraded *in vivo* by hydrolytic deesterification into glycolic, lactic or other acid monomers. The latter species become involved in the carboxylic acid cycle and are subsequently excreted as carbon dioxide and water. Furthermore, biodegradable and bioresorbable drug forms exhibit unique pharmacokinetics, body distribution and pharmacological efficacy.

There are two methods of the synthesis of aliphatic polyesters or polycarbonates, namely polycondensation of diols, dicarboxylic acids or hydroxycarboxylic acids and ring-opening polymerization (ROP) of cyclic monomers (Platel, 2009; Labet & Thielemans, 2009). The polycondensation is hampered by typical limitations of step polymerization. The polymers obtained in this process are characterized by a high polydispersity. ROP gives polymeric products with the higher molecular weight and lower polydispersity. Therefore, is more preferred route to obtain aliphatic polyesters or polycarbonates (Platel, 2009).

The ROP of cyclic esters, carbonates or ether-esters initiated or catalyzed by the metal complexes or organic compounds yields high molecular weight polymers with the excellent conversion. The metal compounds are used commercially due to their selectivity, rate and lack of side reactions. On the other hand, for some biomedical or pharmaceutical applications, metal residues (Zn, Al, Sn) are undesirable (Albertsson & Varma, 2003; Albertsson & Srivastava, 2008; Varma et al., 2005).

3.1 Natural catalysts of ring-opening polymerization of cyclic esters and carbonates

The application of enzymes as catalysts of ROP seems to be a perspective direction in the polymer research. Macromolecules with well-defined structures can be formed by enzyme-catalyzed processes. On the other hand, the use of enzymes has some disadvantages, such as high cost, large quantity of enzymes required for ROP and relatively low molecular weight of the obtained polymers. However, the metal-free method of polymerization and suitable molecular weights of the resulted polymers are desirable conditions for the pharmaceutical applications, especially for the design of new drug delivery systems.

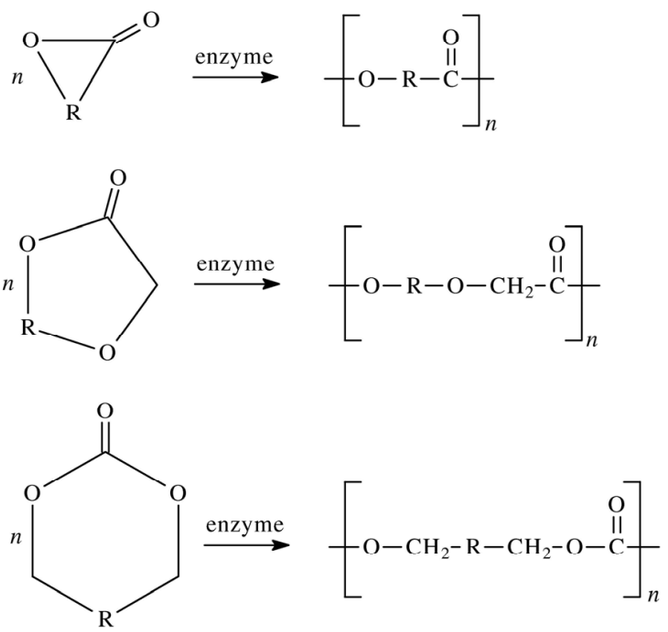


Fig. 4. e-ROP of cyclic esters, ether-esters or carbonates

The primary research on the enzyme ring-opening polymerization (e-ROP) has been carried out for CL. Currently major works concern ROP of six- and seven-membered cyclic esters, cyclic ether-estres or carbonates.

Lipases could also catalyze ROP of cyclic monomers, with different ring sizes as well as monomers containing substituents in the ring: α-methyl-β-propiolactone (1), β–butyrolactone (2), γ-caprolactone (3), α-methyl-valerolactone (4), 1,4-dioxan-2-one (5), δ-caprolactone (6), γ-ethyl-ε-caprolactone (7), ε-heptanolactone (8), δ-decalactone (9), δ-dodecalactone (10), α-methyl-12-dodecanolide (11), α-methyl-15- pentadecanolide (12), L-lactide (13), D-lactide (14), D,L-lactide (15), 1,4-dioxepan-2-one (16), 1,5-dioxepan-2-one (17), 2-methylene-4-oxa-12-dodecanolide (18), 1,3-dioxan-2-one (19), 5-methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one (20), 5-benzyloxy-1,3-dioxan-2-one (21), 1-methyl-1,3-dioxan-2-one (22), cyclobis (hexamethylene carbonate) (23), 2,2′-dimethyl-1,3-dioxan-2-one (24) (Figure 5) (Albertsson & Varma, 2003; Albertsson & Srivastava, 2008; Labet & Thielemans, 2009; Platel, 2009; Varma et al., 2005).

Many families of enzymes were used in ROP of cyclic esters or carbonate: *Aspergillus niger*, *Pseudomonas species*, immobilized *Pseudomonas species*, *Candida rugosa*, *Candida antarctica* (Novozyme-435), *Candida cylindracea*, thermophilic *Esterase lipase* CloneZyme ESL-001, cutinase from *Humicola insolens*, immobilized *Pseudomonas species* on celite, *Porcine pancreatic lipase*, immobilized *Porcine pancreatic*, Lipozyme IM or immobilized lipase from *Thermomyces lanuginose*, *Mucor javanicus*, *Mucor meihei*, *Pseudomonas aeruginosa*, *Pseudomonas cepacia*, *Pseudomonas fluorescens*, *Porcine pancreatic* lipase, *Penicillium roruefortí*, *Tritirachium alkaline proteinase*, *Rhizopus delemer*, *Rhizopus japonicus*, surfactant coated Lipase from *Aspergillus niger,* surfactant coated Lipase from *Pseudomonas species*, surfactant coated Lipase from *Candida rugoza*, surfactant coated Lipase from *Mucor javanicus*, surfactant coated *Pseudomonas species* (Barrera-Rivera et al., 2009; Córdova et al., 1999; Divakar, 2004; Dong, 1998, 1999; Gorke et al., 2007; Henderson et al., 1996; Kobayashi, 2001a, 2001b, 2009; MacDonald et al., 1995; Marcilla et al., 2006; Matsumoto et al., 1999; Mei et al., 2003; Namekawa et al., 1999; Rokicki, 2000; Sivalingam & Madras, 2004; Van Der Mee et al., 2006).

Lipases can accommodate a wide variety of synthetic substrates and still be able to show stereo- and regio-selectivity. They have evolved unusually stable structures that may survive effect of the organic solvents. The lipase-catalyzed hydrolysis in water can be easily reversed in non-aqueous media or bulk into ester synthesis or transesterification (Albertsson & Varma, 2003; Albertsson & Srivastava, 2008; Labet & Thielemans, 2009; Platel, 2009; Varma et al., 2005).

The e-ROP can be carried out in bulk, in organic media and at various interfaces. Enzyme-catalyzed reactions proceed under different reaction conditions (i.e. temperature, pressure, time). As an example, e-ROP of cyclic monomers was performed using lipase as catalyst for 2-720 h. M_n of the resulting polymers was ranged from 1000 to 90 000 Da, when M_w was in the range from 6 000 to 170 000 Da. The yield of the obtained polymers varied from 10 to 100%. The preferred lipase system generally used is a physically immobilized form of *Candida Antarctica*, commercially available as Novozyme-435 (Barrera-Rivera et al., 2009; Córdova et al., 1999; Divakar, 2004; Dong, 1998, 1999; Gorke et al., 2007; Henderson et al., 1996; Kobayashi, 2001a, 2001b, 2009; MacDonald et al., 1995; Marcilla et al., 2006; Matsumoto et al., 1999; Mei et al., 2003; Namekawa et al., 1999; Sivalingam & Madras, 2004; Van Der Mee et al., 2006).

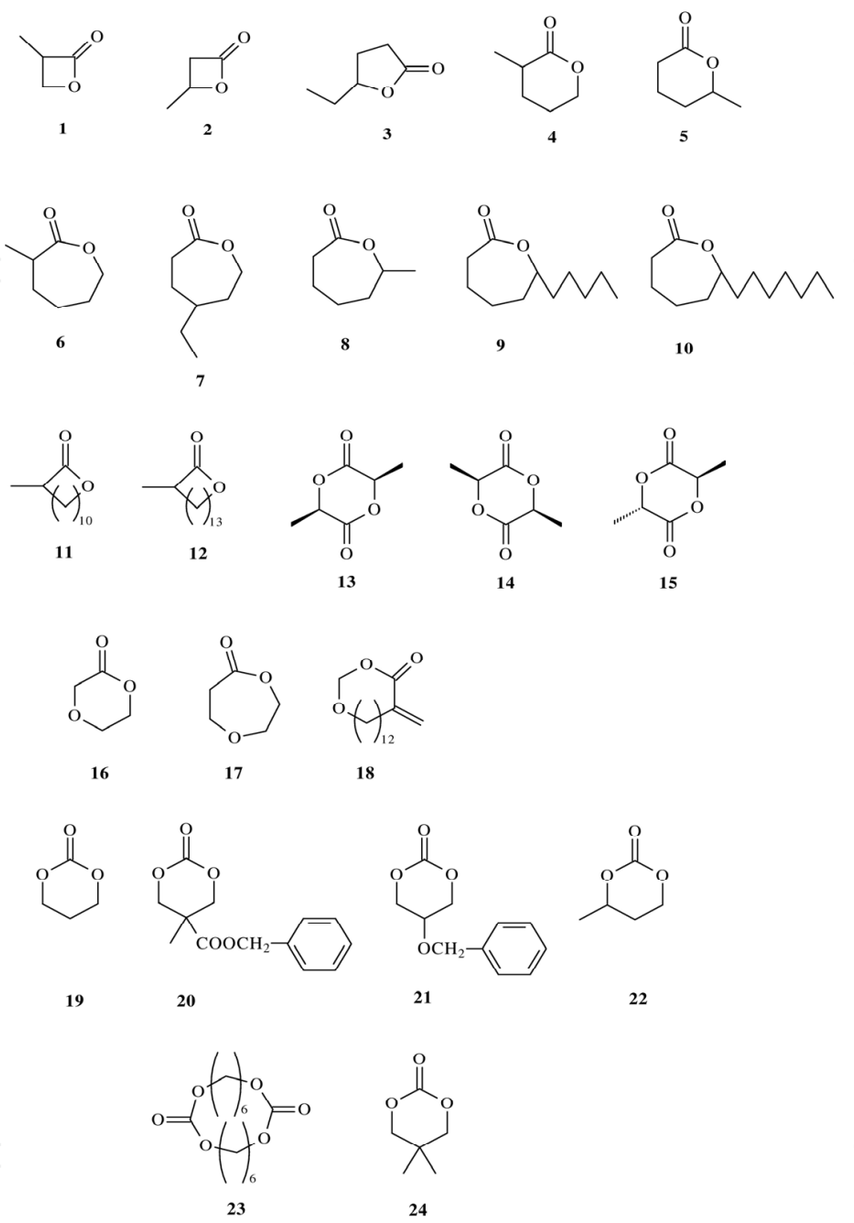
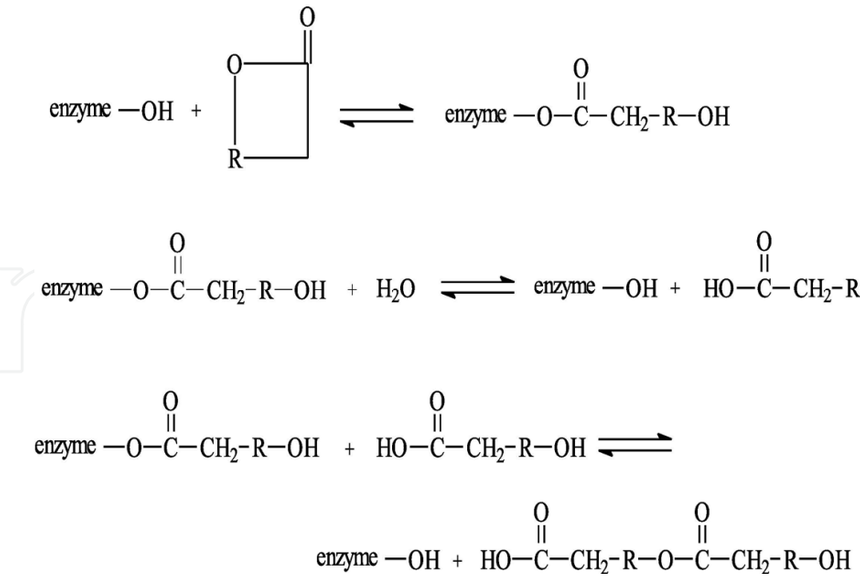


Fig. 5. Representative monomers for e-ROP

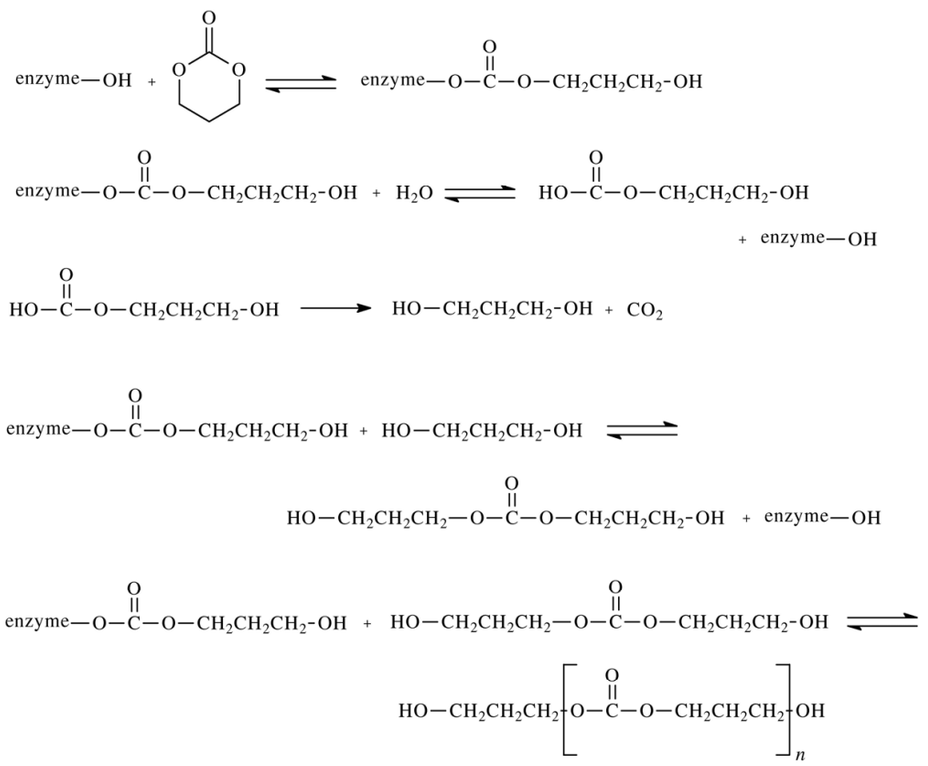
The mechanism of e-ROP of cyclic esters using lipases as catalyst has been proposed by several authors. Monomer activated e-ROP (Scheme 1) involves the activation of the monomer molecules by an enzyme followed by the attack of the activated monomer onto the polymer chain end (Albertsson & Srivastava, 2008; MacDonald et al., 1995; Namekawa et al., 1999).

The ROP of cyclic carbonates catalyzed by enzyme or enzyme derivatives, in which polyesters, poly(ether-ester)s and polycarbonates terminated by hydroxyl groups are obtained, seems very attractive from the pharmaceutical or medical point of view.



Scheme 1. The mechanism of e-ROP of cyclic esters

Bisht and coworkers proposed a mechanism for chain initiation and propagation for lipase-catalyzed trimethylene carbonate polymerization, based on the symmetrical structure of these products and the end-group structure of high molecular weight chains (Scheme 2) (Bisht et al., 1996).



Scheme 2. The mechanism of e-ROP of cyclic carbonates

3.2 Natural initiators and organocatalysts of ring-opening polymerization of cyclic esters and carbonates

Recently, many modification approaches on biodegradable and bioresorbable polymers were carried out to meet the requirements of specific medical and pharmaceutical applications. Between them, incorporation of bioactive or biocompatible compounds such as lipids, amino acids into polymer chain or using of natural products as organocatalysts has received considerable attention.

The guanidine is a natural base, existing in human body and some vegetables. Some guanidine derivatives are the components of the therapeutic agents (Kinnel et al., 1998; Ramarao et al., 1993). Application of guanidine derivatives as organocatalysts for the synthesis of biodegradable polymers is an attractive way in the materials science technology. Li and coworkers reported the use of hexabutyl guanidinum acetatae in the living ROP of lactides (LAs) (Li et al., 2004). The polymerization was performed in bulk, producing polylactides (PLAs) with moderate molecular weight and narrow polydispersity. Strong guanidine bases: TBD (1,5,7-Triazabicyclo[4.4.0]dec-5-ene), MTBD (7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) and DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) were applied as effective organocatalysts for ROP of LA, δ-valerolactone (VL) and CL by Lohmeijer`s and coworkers (Lohmeijer et al., 2006). They found that TBD was polymerized LA, VL and CL in the controlled manner while MTBD and DBU polymerized only LA. For VL and CL the addition of thiourea co-catalyst was required. Wang and coworkers were used creatinine as catalysts of ROP of LA, examining the influence of temperature, time and creatinine dosage on the polymerization and properties of the produced biodegradable polymer (Wang et al., 2003). Based on the obtained results they proposed that creatinine is initiated ROP of LA according to the coordination-insertion mechanism. The biogenetic guanidine carboxylates: creatinine acetate (CRA) and creatinine glycolate (CRG) were synthesized and then effectively utilized as single-component initiators of ROP of LAs (Li et al., 2009). The mechanism of ROP was proposed based of the experimental investigation. In our laboratory, other guanidine derivatives: arginine and citrulline were successfully applied as initiators of ROP of LA and CL (Oledzka et al., 2011). The incorporation of α-amino acid molecules into the polymer chain was confirmed using ^{1}H, ^{13}C NMR and FT-IR spectroscopy and MALDI TOF MS spectrometry.

Various carboxylic acids (lactic, tartaric, hexanoic, propionic and citric acids) and natural amino acids (glycine, proline and serine) were engaged as catalysts in living ROP of CL and VL (Casas et al., 2004). The reactions were performed without solvent with the efficient way of recovering of the catalysts. Moreover, the authors found that the order of catalytic efficiency of the organic acid catalysts in ROP was as follows: tartaric acid (pKa=2.98)>citric acid (pKa=3.08)>lactic acid (pKa=3.14)>proline (pKa=1.95).

The fatty acids are found naturally in the human body. They are considered biologically safe and are generally considered suitable candidates for the preparation of biodegradable polymers (Teomim & Domb, 2001).

ROP of CL by organic acids catalyst and oleic acid derivatives initiator systems was investigated by Oledzka and coworker (Oledzka & Narine, 2001). They have found that the polymerizations were efficiently catalyzed by succinic and fumaric acid. The incorporation of fatty acid molecules resulted in less crystallinity and lower melting points of the obtained

polymer samples. Furthermore, the degradation rate of the received polymers was slower when compared to CL homopolymer, but increase in porosity of the polymers was observed over time.

Natural amino acids are essential components in human nutrition. The studies performed by Liu and coworkers showed that they are also effective as initiators of ROP of CL (Liu & Liu, 2004). Authors found hat the number-average molecular weights of the obtained polymers did not exceed 5700 Da and that used amino acids were incorporated into macromolecule chain (Figure 6). In our laboratory, more detailed studies, involving an extended range of amino-acid initiators applied to ROP of CL and *rac*-LA were previously performed (Sobczak et al., 2008). The polymerization of CL and *rac*-LA was carried out in bulk, at 120–160 ^{o}C. L-alanine, L-cysteine, L-leucine, L-methionine, L-phenylalanine, L-proline, L-threonine, L-aspartic acid, L-glutamic acid, L-histidine, L-lysine were used as initiators of ROP. Aliphatic polyesters have synthesized with high yield (even ca. 100 % in some cases).

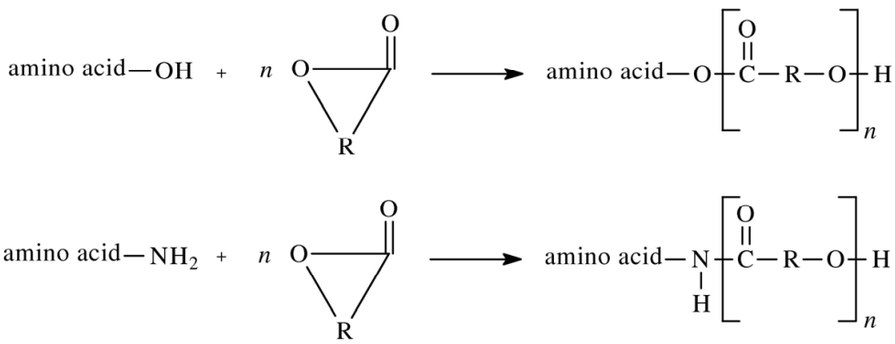


Fig. 6. ROP of cyclic esters using natural amino acids as initiators

ROP of aliphatic cyclic carbonates using natural amino acids was also investigated by Liu and coworkers (Liu et al., 2008). The biodegradable polymers with incorporated amino acids molecules were effectively obtained. The presence of natural amino acids in the polymer chain was proved by nuclear magnetic resonance spectroscopy.

Polyamidoamine (PAMAM) dendrimers are highly hyperbranched synthetic polymers with well-defined structure that allows accurate control of shape, size and functionality of terminal groups (Tomalia et al., 1985). The PAMAM dendrimers have useful applications in pharmaceutical technology e.g. as carriers in drug delivery systems, which can cross cell walls by both paracellular and transcellular pathways (Jevprasesphant et al., 2003). In our laboratory, novel star-shaped biodegradable polyesters were synthesized by ROP of CL using PAMAM dendrimer initiator without any metal catalysts (Oledzka et al., 2011). The nonlinear structure as well as physicochemical properties of the obtained biodegradable polymers were confirmed by nuclear magnetic resonance, gel permeation chromatography, thermal gravimetric analysis and differential scanning calorymetry.

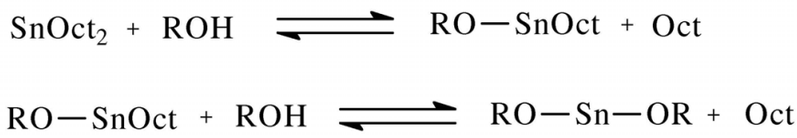
3.3 Natural co-initiators of ring-opening polymerization of cyclic esters, ether-esters and carbonates

Metal catalyzed ROP of cyclic esters, ether-esters or carbonates has become the object of intensive studies with respect to their practical applications in the synthesis of biomaterials.

Tin(II) 2-ethylhexanoate ($SnOct_2$) is commonly used as a commercial catalyst for the ROP of cyclic monomers. It is effective, relatively cheap, non-toxic, soluble in the most commonly used organic solvents (Labet & Thielemans; 2009). $SnOct_2$ is considered to have a toxicity much lower than other metal compounds, and it is allowed to be used as a food additive in a number of countries.

$SnOct_2$ must be used together with a nucleophilic compound (generally an alcohol) to initiate the reaction if a controlled synthesis of the polymer is to be obtained. The main drawback of $SnOct_2$ is that it requires high temperature, which leads inter- and intra-molecular esterification (Labet & Thielemans; 2009).

According to Kowalski's hypothesis, the first step of the polymerization consists of the production of the active species by reacting the alcohol with the catalyst. The more alcohol is added, the more the equilibrium is displaced towards the right and the more active species are created. With increasing carboxylic acid concentration, the equilibrium shifts to the left and less active species are present in the medium (Scheme 3) (Kowalski et al., 1998). Mechanism of CL and LA polymerization initiated with $SnOct_2/C_4H_9NH_2$ system has also been described (Duda et al., 2005).



Scheme 3. The formation of active centres in the reaction of $Sn(Oct)_2$ with alcohol (co-initiator)

$SnOct_2$ has also been combined with ureidopyrimidinone-alcohol (UPy) compounds. Using the good soluble alcohols, bearing a 1-ethylpentyl moiety, the ROP was significantly more controlled (Celiz & Scherman, 2008).

Sobczak and Kolodziejski have studied $SnOct_2$/L-carnitine (CA) catalytic system. CA is a hydrophilic amino acid derivative, naturally occurring in human cell. Low-molecular weight PCL, PLA and copolymers of CL and *rac*-LA were obtained by the ROP of cyclic esters in the presence of $SnOct_2$/CA. The molecular mass values averaged over the obtained polyesters were roughly in agreement with the theoretical molecular weights calculated from the feed ratio of the cyclic esters to CA (Sobczak & Kolodziejski, 2009).
Zhang and coworkers used cholesterol (CHL) as an initiator and $SnOct_2$ as a catalyst of ROP of CL (Zhang et al., 2005). The polymerization was carried out under rigorously anhydrous conditions. The optimized ring-opening polymerization conditions have been identified to be 8 h at 140 ^{o}C. The molecular weight of CHL-PCL has increased with decreasing cholesterol/CL feed ratio. Incorporation of the cholesteryl moiety into polymer chain has leaded to a slower enzymatic degradation rate. Whereas, Cai and coworkers utilized PAMAM dendrimer as initiator of ROP of LLA (Cai et al., 2003). The star-shaped biodegradable polymers with the average molecular weight about 70000 Da were successfully obtained in that work. The authors also found that the synthesized polymers showed a faster degradation rate than linear homopolymer because of its shortened polymer chains.

4. Conclusions

The pharmaceutical technology is one of the most important fields of using of polymers. From this review, it is clear that macromolecules have been extremely active research area over the last years. In addition is worth to note, that the progress of modern pharmaceutical technology is not feasible without utilization of natural and synthetic polymers. The discovering of new drug forms, e.g.: new therapeutic systems and macromolecular prodgrugs is simply demanded by the market and industry presently. The elaboration of new medical and pharmaceutical specimens will also require intensive investigations in chemistry and biomedical polymer areas.

As is also evident from this discussion, the spectacular improvement has been achieved with natural compounds applied as initiators, catalysts, organocatalysts or co-initiators of polymerization of cyclic esters, ether-esters and carbonates. The utilized compounds are primarily friendly for environment, safe, non-toxic and irreplaceable for the synthesis of polymers for the pharmaceutical applications. Promising avenues of research have also emerged for the enzymatic approach. Increasing interest has also been dedicated to the polymers containing natural compounds in macromolecules that have been incorporated into though the polymerization process. Clearly, the future development of biodegradable and bioresorbable polymers will be based on discovering macromolecules with not only appropriate chemical, physical and mechanical properties but also suitable biological properties.

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