Chapter 4
Biodegradable Polymeric Materials

Michael Schroeter, Britt Wildemann, and Andreas Lendlein

Abstract The ability of polymers to be degraded in physiological environments makes them interesting candidates for various medical applications. Degradation and metabolisation or excretion of polymeric implants can avoid a second surgery for the removal of an implant. They follow a distinct pathway for degradation, depending on their structure. Biodegradable materials can serve as a temporary substitute of the extracellular matrix or as matrix in controlled drug release systems, which both can be utilized in Regenerative Therapies.

This chapter gives an overview about polymeric materials established in clinical use such as polyesters, polyurethanes, polyanhydrides, or carbohydrates. It describes further their synthesis and exemplary applications such as surgical sutures. Finally the importance of a continuing development of novel materials for future applications is pointed out, since the number of potential applications in the medical field is expanding rapidly.

Keywords Biomaterial • Biodegradation • Surface erosion • Biodegradability of polymers • Biocompatibility

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G. Steinhoff (ed.), *Regenerative Medicine - from Protocol to Patient*,
DOI 10.1007/978-3-319-28274-9_4

4.1 Introduction

Many people experience biomaterials in the form of dental fillings, contact lenses or suture materials. Further applications are artificial joints, blood vessel substitutes or drug delivery systems. A biomaterial is defined as any material intended to interact with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body (The European Society for Biomaterials 1991). Biomaterials can be inorganic materials like bioactive glasses, ceramics or metal alloys as well as polymers including natural polymers (e.g. collagen), synthetic polymers and combinations of both. Biomaterials can be applied in permanent or temporary implants, depending on the particular indication. While all biomaterials must be biocompatible, their permanent application requires long term stability in physiological environments. An example for long term application is for the acetabular cup in artificial hip joints. These materials need to be integrated into the surrounding tissue after implantation and retain their function for a long time. For temporary applications, biodegradable materials are demanded, being degraded and eliminated or metabolized by the organism in the course of time (Lendlein 1999). Biodegradation is defined as the gradual breakdown of a material mediated in or by a biological system. The advantage of the bodies' capability for self-healing can be utilized by the use of degradable materials. A temporary implant is completely substituted by natural tissue in the best case. An overview about biodegradable polymers and natural materials, their synthesis and approved clinical applications will be given in this chapter.

The degradation of polymeric materials depends on their molecular structure and architecture. In copolymers the sequence structure (see Fig. 4.1) can substantially influence the degradation rate.

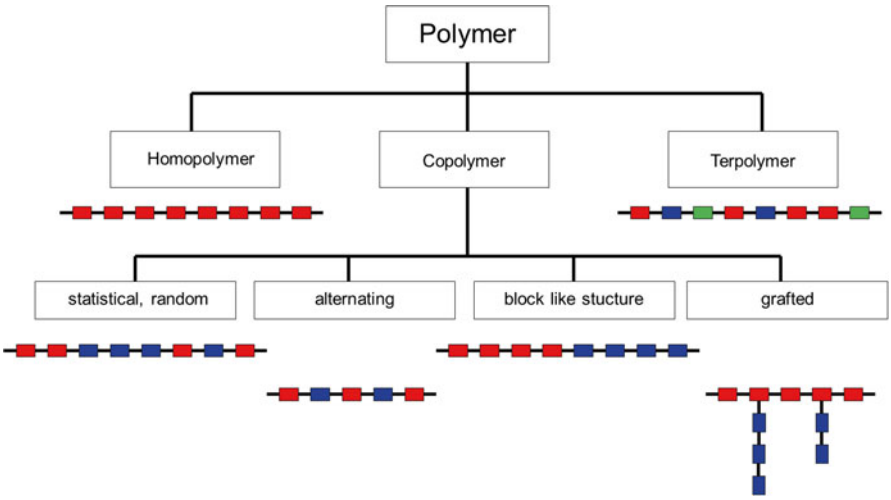


Fig. 4.1 Polymer architecture with different sequences of the monomers or building blocks. Each *rectangle* represents a repeating unit; different *colors* represent different types of repeating units which can form building blocks

Using different synthetic methods, such as polymerization, polycondensation or polymer analogous reactions, sequences and functional groups of the polymers can be systematically varied. In this way the properties can be adjusted e.g. from hydrophobic to hydrophilic.

In general, there are three main principles for degradable or removable materials (Fig. 4.2). Principle a demonstrates the degradation of crosslinks between mostly hydrophilic (water soluble) polymer chains to restore their solubility and ability to be removed from the implantation site. Principle b shows the transformation of a former hydrophobic side chain in a polymer into a hydrophilic group and makes the polymer water soluble and excretable via the renal or hepatic system. Principle c is used in the majority of cases for degradable polymers. The covalent bonds in the functional groups of the polymer backbone are degraded by hydrolysis or enzymatic degradation and finally yield monomers, which can be metabolized.

Degradable biomaterials must include linkages, cleavable under physiological conditions (see Fig. 4.2). One possibility is the incorporation of hydrolytically degradable bonds (see Fig. 4.3).

Hydrolytic degradation has the advantage that water is generally available in the body. Therefore degradation should occur at different locations of application / implantation. In contrast, concentrations of enzymes can differ locally. As the degradation rate of hydrolytically cleavable bonds can be increased by enzymes substantially, the degradation rate can differ significantly in different body parts or individuals. Chemical bonds whose cleavage is accelerated by enzymes can be used

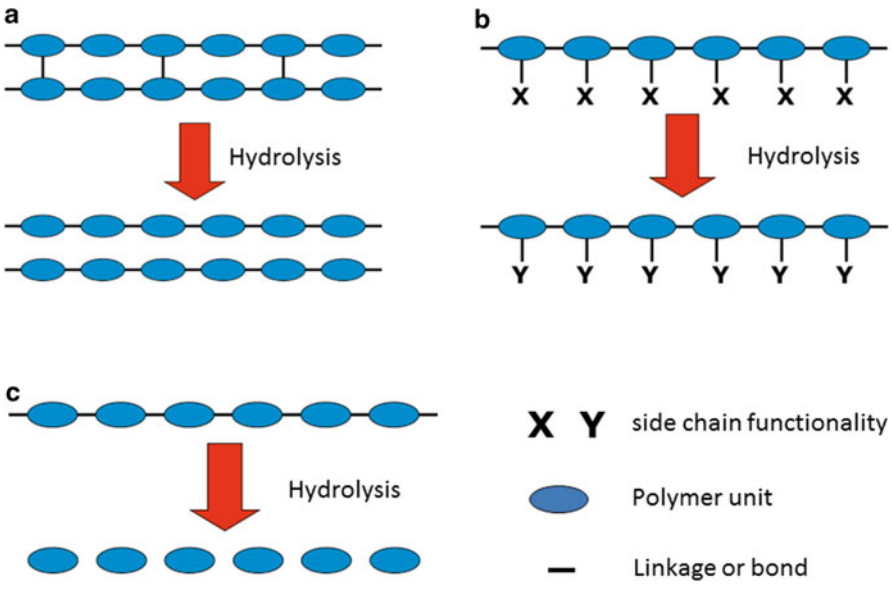


Fig. 4.2 Three general principles for hydrolytic degradation of polymers. *Blue circles* represent a repeating unit, *black lines* a covalent connection between the repeating units (**a**) Cross-linked material, where cross-links are degraded, (**b**) Transformation of side chains by hydrolytic or enzymatic degradation, (**c**) Degradation of the polymer backbone

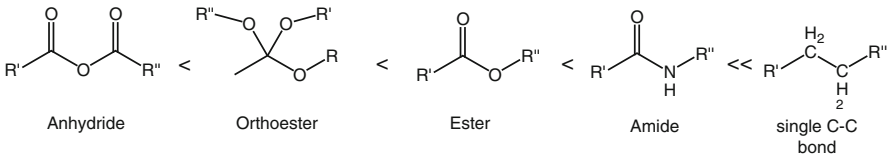


Fig. 4.3 Hydrolytically cleavable bonds in comparison to carbon-carbon bond in order of their hydrolytic stability

for the generation of local effects, such as the specific targeting of drugs or organ-specific processes. In general, the advantage of devices made from degradable polymers is that a second surgery for explantation can be avoided.

Two mechanisms for the hydrolytic biodegradation of polymers are discussed (i) bulk degradation and (ii) surface erosion. In case of bulk degradation the diffusion of water into a polymer matrix is faster than the hydrolysis rate. The hydrolytically cleavable bonds in the amorphous parts of the matrix can be degraded as water molecules are available because of fast diffusion (Brannon-Peppas 1997). Therefore, the average molecular weight of the matrix polymers decreases. In case of surface erosion the diffusion of water into the polymer is (much) slower than the degradation rate of the macromolecule. Hydrolysis is limited to a thin layer on the surface, while the molecular weight of the polymer in the bulk remains unchanged. In surface erosion the velocity of degradation depends on the shape of the sample. The higher the surface area is, the higher is the rate of degradation. The number of hydrolytically cleavable bonds in a macromolecule affects the hydrolysis rate (see Fig. 4.3).

Macromolecules containing orthoester or anhydride bonds as examples for easily hydrolysable bonds show a high tendency for surface erosion (Wu 1995). Many other parameters related to the polymer, the device (shaped body) or the environmental conditions can influence or determine the degradation behavior of polymers (see Table 4.1).

The biodegradability of polymers can be determined in vitro and in vivo. For in vitro experiments, the materials are exposed to an aqueous (buffer) solution which may contain ions or to cell culture medium, which may contain amino acids, sugar as well as serum. PH-value and temperature can be varied to mimic specific situations and environments. The partially degraded materials as well as the degradation products can be isolated and characterized. The addition of specific enzymes is also possible (Kulkarni et al. 2007). In vivo experiments are performed with different species e.g. mice or rats to investigate the biodegradation and biocompatibility.

Standards exist for biocompatibility testing of materials used in the human body. The American Food and Drug Administration (FDA), the Health and Welfare Canada, and Health and Social Services UK introduced 1986 the “Tripartite Biocompatibility Guidance for Medical Devices”. The guidance was developed to help FDA reviewers, but also manufacturers of medical devices, in judging and

Table 4.1 Parameters influencing the degradation rate of polymers

Structural parameters of macromolecules	Shaped body (device)	Environmental influence
Chemical composition	Processing conditions	Location of implantation
Sequence structure in copolymers	Shape of the sample	Adsorbed or absorbed molecules
Presence of ionic groups	Sterilization	Ion exchange, –strength, pH-value
Branches/chain defects	Thermomechanical "history" of the polymer	Changes of diffusion coefficient
Average molecular weight and distribution	Material inhomogenities and internal stress	Mechanism of hydrolytic degradation (H_2O, Enzymes)
	Surface roughness	Cracks due to hydrolytic degradation or mechanical tension

selecting appropriate tests to evaluate the biological responses to medical devices. Four different device categories of biomaterials were defined: Non-Contact Devices, External Devices, Externally Communicating Devices, Internal Devices. The biological test of the materials include: Sensitization Assay, Irritation Tests, Cytotoxicity Tests, Acute Systemic Toxicity Tests, Hemocompatibility Tests, Hemolysis Tests, Implantation Tests, Mutagenicity (Genotoxicity) Tests, Chronic Toxicity Tests, Carcinogenesis Bioassay, Pharmacokinetics, Reproductive and Developmental Toxicity Tests. To harmonize the biocompatibility testing, the International Standards Organization (ISO) developed a standard for biological evaluation of medical devices (ISO 10993). Until today, this standard consists of 20 parts and the first part "Biological Evaluation of Medical Devices: Part 1: Evaluation and Testing" provides guidance for selecting the tests to evaluate the biological response to medical devices. The appropriate methods to conduct the biological tests are described in most of the other parts. The ISO 10993 is under permanent actualization and covers aspects of biomaterial testing.

4.2 Polymer-Based Biomaterials

Biodegradable polymers can be divided in two main groups: materials based on natural polymers, and purely synthetic polymers, designed to meet different demands. Important groups of degradable polymers used in medical applications are: Polyesters, Polyesteramides, Poly(ortho ester)s, Polyurethanes, Polyanhydrides, Cyanoacrylates, Hydrogels (e.g. based on poly(ethylene glycol)). Carbohydrates and proteins form the basis for many biomaterials based on natural polymers. Synthesis or isolation and exemplary applications of such materials are presented in the following.

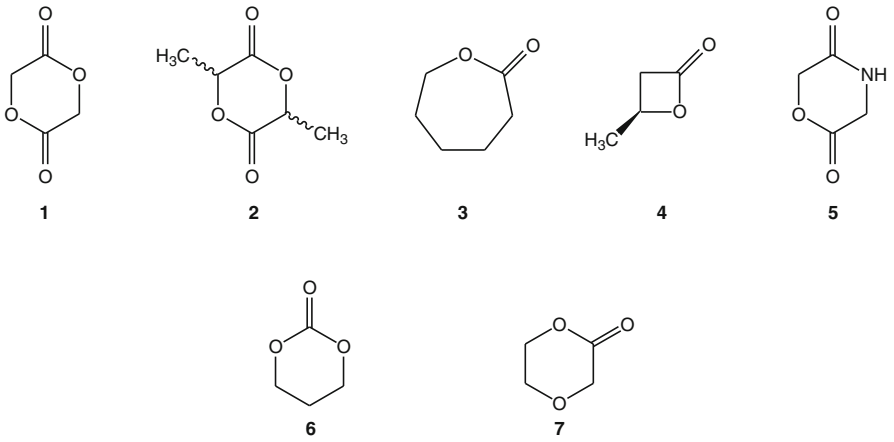


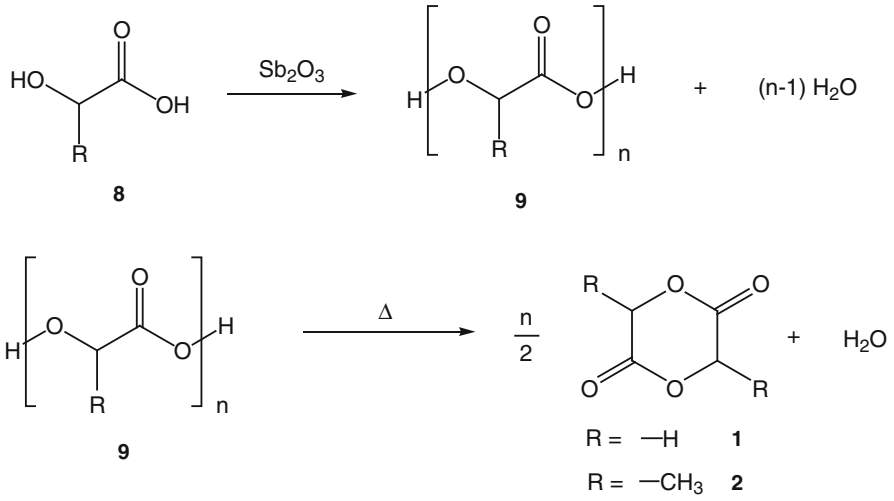
Fig. 4.4 Chemical structures of cyclic diesters and lactones used as (co)monomers for the synthesis of degradable (co)poly(ether)esters

4.2.1 Polyesters

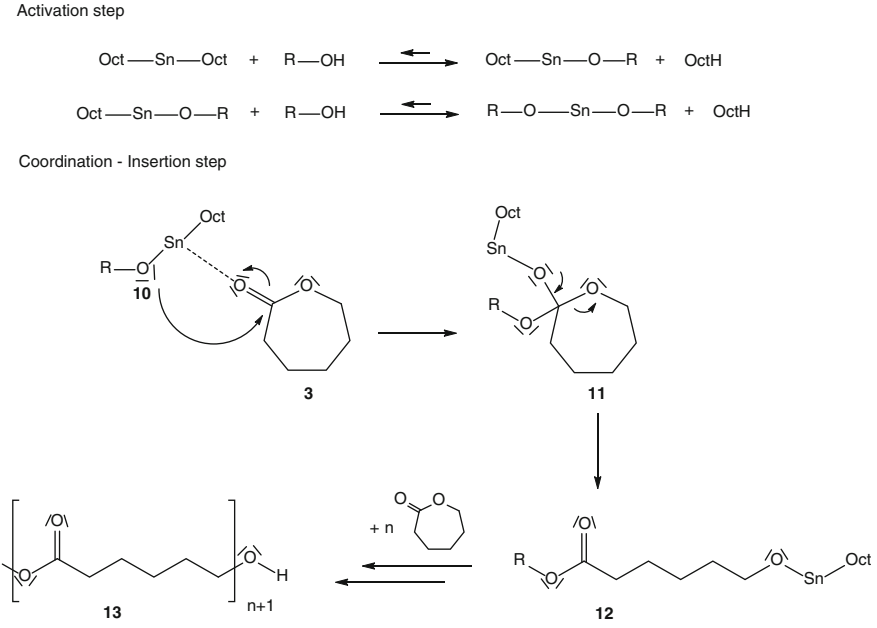
An important group of biodegradable biomaterials are (co)-polyesters used in surgical sutures. The degradation of ester bonds occurs under hydrolysis of the bond, forming a carboxylic acid and an alcohol. The rate of hydrolysis depends on the neighboring groups to the ester. They are typically prepared by ring-opening polymerization of lactones or cyclic diesters (Deasy et al. 1989; Piskin 1995; Vert 1986). A ring-opening polymerization proceeds in an anionic, cationic or coordination polymerization mechanism in the presence of catalysts and is started by initiators. Monomers like the cyclic diesters digylolide **1**, and dilactide **2**, as well as the lactones ε-caprolactone **3**, and β-butyrolactone **4** are frequently used. Further cyclic compounds, which can be polymerized in an analogue way, are cyclic carbonates (e.g. trimetylene carbonate **6**) dioxanone-compounds (e.g. *p*-dioxanone **7**), and compounds based on morpholino-2,5-dione **5** (see Fig. 4.4). Due to two stereo centres in dilactide **2** three different isomers exist: *L,L*-dilactide, *D,D*-dilactide and *meso*-dilactide.

Cyclic diesters are generated from the corresponding hydroxyl carboxylic acids (Scheme 4.1). Oligoesters are formed by elimination of water in the presence of catalysts (e.g. Sb_2O_3). In the case of poly(*L*-lactic acid) molecular weights of >100 kDa can be obtained by a solution condensation process with water removal by application of vacuum or by azeotropic distillation using diphenyl ether (Ajioka et al. 1995; Södergård and Stolt 2010).

The ring-opening polymerization of cyclic diesters can be performed as anionic polymerization or as coordination-insertion polymerization (Scheme 4.2). Sn (II) compounds like Sn-dioctanoate are used as coordinative catalysts for the bulk polymerization (Leenslag and Pennings 1987). It has to be considered that such compounds catalyze transesterification reactions as well. Therefore side reactions



Scheme 4.1 Synthesis of cyclic diesters by depolymerization of oligoesters at elevated temperatures



Scheme 4.2 Mechanism of coordination insertion polymerization of ε-caprolactone

like inter- and intramolecular transesterification as well as depolymerization may occur. Heating of a mixture of two polyesters at 140 °C will change the sequence structure of both polymers (Kricheldorf and Serra 1985; Nieuwenhuis 1992). As alternative catalysts Zn (II) ethylhexanoate (Leenslag et al. 1984), and Zn-powder (Chabot et al. 1983) have been studied. The application of these catalysts leads to polyesters of high molecular weight. Catalysts based on Magnesium and other metals are under development with the aim to decrease toxicity of the catalyst or facilitate its removal from the reaction mixture (Kricheldorf and Stricker 2000). According to the actual literature the catalyst is first activated by the nucleophilic initiator and coordinates in the following to the carbonyl function of the lactone (Masutani and Kimura 2015). Several active catalytic species have been discovered depending on the conditions during polymerization reaction.

In addition to bulk polymerization, polymerization processes in solution and in suspension are possible. The lower viscosity of the reaction mixture compared to a bulk process enables a better heat transfer and by that a better control of the reaction temperature.

Homopolymers like poly(glycolic acid) (PGA), poly(*L*-lactic acid) (PLLA), or poly(*D,L*-lactic acid) (PDLLA) as well as copolymers of them with different amounts such as poly[(*rac*-lactid)-*co*-glycolide] (PLGA) were prepared by ring-opening polymerization. PGA and PLLA are semicrystalline polymers, whereas PDLLA is amorphous. PLGA has a glass transition temperature (T_g) close to body temperature ($T_g = 36$ °C), whereas PLLA and PDLLA have T_g values between 57–60 °C and 50–54 °C, respectively (Vert 1989). PLLA has been studied as degradable biomaterial extensively (Tsuji et al. 2003; Ye et al. 2008).

The discovery of so called stereocomplexes of poly(L-lactide) with its enantiomeric counterpart poly(D-lactide) in polymeric structures enables a better thermoplastic processing by increasing the melting point and glass transition temperature, higher degree of crystallinity, and increased resistance towards hydrolytic degradation (Ikada et al. 1987). The enantiomers are forming strong complementary interactions between the chain structures; they build crystallites in a 3_1 helix form. This results in stereocomplex crystallites which will act as cross-links. The melting temperature of PLLA can be increased by 40–50 °C by physically blending the polymer with PDLA due to stereocomplex formation. The temperature stability is maximised when a 1:1 blend is used, but even lower concentrations of 3–10 wt% PDLA improve the properties substantially (Bao et al. 2012; Tsuji et al. 2012). Applications of the polymer e.g. in 3 D – printing applications with high resolution of PLA-based scaffolds become possible (Serra et al. 2013). Due to the higher crystallinity the hydrolytic resistance of the polymer is higher (Tsuji 2003). The 3D – printing or rapid prototyping technology developed into a tool in the field of biomaterials that enables fabrication of three dimensional structures with well-defined and reproducible geometries and architectures. The use of degradable polymers in electrospinning for tissue engineering applications (Pham et al. 2006) and membranes (Ahmed et al. 2015) is a further improvement for processing and tailoring polymers for biomedical application. The degradation speed of electrospun fibres can be controlled by their crystallinity between 23 and 46 % via their spinning parameters (Ero-Phillips et al. 2012).

Poly(ε-caprolactone) (PCL), prepared from ε-caprolactone **3**, is a semi-crystalline degradable polymer with sufficient mechanical strength and thermal stability for application as scaffold material or matrix material for drug delivery. Its melting point is in the range of 59–64 °C and its T_g is around −60 °C. The homopolymer is slowly degradable, due to high hydrophobicity and relatively low hydrolysis rate (Little et al. 2009).

Poly(p-dioxanone) (PPDO), synthesized from *p*-dioxanone **7** (Fig. 4.4), is a semi-crystalline degradable polymer with a melting point of 115 °C and a T_g in the range of −10 – 0 °C. Above its melting point this polymer depolymerizes to *p*-dioxanone **7** (Shalaby and Johnson 1994).

Several medical devices based on (co)polyesters are applied in the clinic. The main products made out of polyester are sutures, orthopaedic implants and scaffolds (Nair and Laurencin 2007; Weigel et al. 2006). The FDA approved a suture called DEXON®, based on polyglycolide (Table 4.2) in 1969.

(Co)polyesters degrade mainly by bulk erosion. Due to water uptake random scission of polymer chains occurs in the amorphous domains. Oligomers and hydroxy acids are obtained as water soluble degradation products. The generated carboxy groups may induce an autocatalytic process.

Despite the good results of the resorbable suture materials, concerns exist regarding the use of (co)polyesters in ligament reconstruction surgery. A review article published in 2009 by Konan and Haddad summarized adverse reactions due to the use of resorbable screws in anterior cruciate ligament reconstruction surgery (Konan and Haddad 2009). They concluded that the resorbable materials offer advantages compared to metal screws, but also possible disadvantages, such as potential adverse biological responses resulting in the worst scenario, in a failure of the surgery. Further long term studies and the improvement of the material are necessary.

If polyesters are used as matrix material for drug delivery the bulk erosion must also be considered (Li and Jastri 2006). The water uptake into the bulk material and the acidification might potentially interact with the drug. Several drug releasing implants have been developed (Table 4.2).

Injectable local drug delivery systems were developed based on in situ forming implants. For this method a biodegradable, water insoluble polymer and the drug are dissolved in a non-toxic organic solvent. After injection the solvent dissipates into the tissue and water permeates into the polymer solution resulting in a precipitation and consequently the polymer forms an implant with the enclosed drug (Li and Jastri 2006). Atrigel uses this principle and two products are FDA approved: Eligard® (leuprolide acetate for injectable suspension) as a prostate cancer product that provides systemic release of leuprolide acetate for 1–4 month, and Atridox® (8.5 % doxycyline) for localized subgingival delivery of doxycycline.

A just recently published meta-analysis including over 18,000 patients showed better results regarding very late in-stent late loss and stent thrombosis when using degradable polymer drug-eluting stents compared to permanent polymer drug-eluting stents. No difference between the drug-eluting stents was seen for target-lesion revascularization, myocardial infarction or death (Wang et al. 2014).

Table 4.2 Examples for devices – approved or in clinical trials – made of polyester

Implant material	Polymer	Name	Application
Sutures	PGA	Dexon®	All kinds of sutures (Gunatillake et al. 2006)
	PLGA	Vicryl®, Polysorb®	
	PDO	PDS®	
	PGATMC	Maxon®	
	PHA	TephaFLEX®	(Shrivastav et al. 2013)
Screws	PLLA	Absolute®	ACL reconstruction (Purcell et al. 2004)
	ß-TCP/PLA	Biocryl®, Intrafix®	
	PLLA	Sheathed Femora® BioScrew® Bio-Cortical® Bioabsorbable Wedge®	
	PLA	BioRCI®	
	PLLA/PGA	Gentle Threads®	
Plates and screws	PLGA	RapidSorb®	Craniomaxillofacial surgery (Peltoniemi et al. 2002; Pietrzak and Eppley 2000)
	SR-PLDLA	Biosorb®	
	Copolymers of L-lactide, D,L-lactide, glycolide and TMC	Inion CPS® Fixation	
Skin and cartilage	PLGA (Vicryl mesh)	Dermagraft®	Artificial skin
		NeoCyte®	Engineered cartilage (Ueda and Tabata 2003)
Anastomotic ring	PGA and barium sulphate	Valtrac®	Anastomoses in the gastrointestinal tract surgery (Kaidar-Person et al. 2008)
Membranes/ meshes	PLGA	ResoIut® Vicryl Mesh®	Guided tissue regeneration, wound support
	PHA	TephaFLEX® Absorbable Monofilament Mesh, Surgical Film	(Greenstein and Caton 1993; Wolff and Mullally 2000)
Facial surgery	PLLA	Sculptura®	Correction of facial fat loss
Nerve conduits	PGA	Neurotube®	(Meek and Coert 2008)
	PDLACL	Neurolac®	

(continued)

Table 4.2 (continued)

Implant material	Polymer	Name	Application
Stents	PLLA	Igaki-Tamai® stent	Peripheral artery (Commandeur et al. 2006)
Drug delivery:			
Drug eluting stents	PLLA plus PDLLA coating and Everolimus	BVS everolimus-eluting stent	Coronary artery disease (Ormiston and Serruys 2009)
	Metal stent with degradable coating releasing specific drug	Axxess BioMatrix® Cardiomind ELIXIR JACTAX MAHOROBA NEVO OSIRO® Supralimus SYNERGYTM	Coronary artery disease or acute coronary syndromes (Commandeur et al. 2006; Sun et al. 2014)
Drug delivery	PLGA	LUPRON DEPOT® Eligard® Zoladex® Decapeptyl® Telstar® Pamorelin® Profact Depot®	Release of gonadotropin releasing hormone agonist or goserelin acetate, benign gynaecological disorders; prostate/breast cancer (Sinha and Trehan 2003)
		Posurdex®	Release of dexamethasone, retinal vein occlusion (Kuppermann et al. 2007)
		Risperdal Consta®	Schizophrenia
		Sandostatin® LAR®	Acromegaly
		Bydureon®	Type 2 Diabetes
	PLGA plus triclosan	Vicryl®plus	Antimicrobial sutures (Leaper et al. 2011)
	Titanium coated with PDLLA and Gentamicin	Expert Tibial Nail PROtect	Prevention of bacterial colonization on the implant (Schmidmaier et al. 2006)

PGA poly(glycolic acid), *PLA* poly(lactide acid), *PLLA* poly(L-lactide acid), *PDLLA* poly(D,L-lactic acid), *PLGA* poly[(rac-lactid)-co-glycolide], *PCL* poly(ε-caprolactone), *PDLACL* Poly[(rac-lactide)-*co*-(ε-caprolactone)], *TMC* trimethylene carbonate, *PDO* polydioxanone, *β-TCP* beta-tricalciumphosphate, *PGATMC* poly(glycolide-co-trimethylcarbonate)

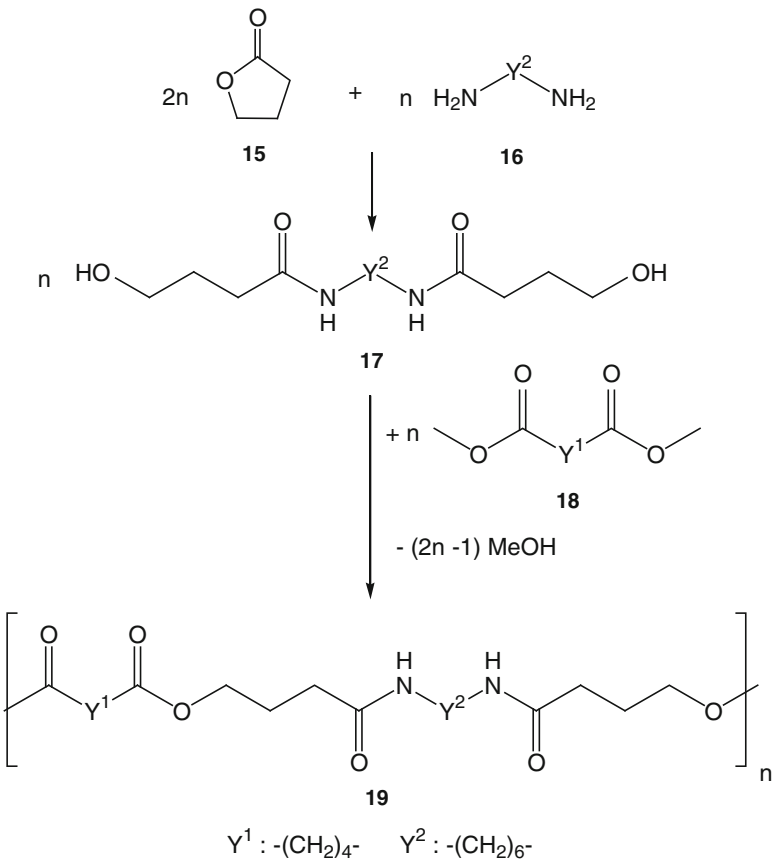
A multi-center randomized controlled trial in maxillofacial surgery showed disappointing results on the use of degradable implants. In contrast to the expectations, the 2-year follow up of 230 patients either treated with a titanium or a degradable plate showed a higher rate of plate removal in the group treated with the degradable plate comparted to the titanium implant (van Bakelen et al. 2013). Therefore, further research is necessary towards a higher biofunctionality of degradable implants.

Very successful are degradable synthetic suture materials, which are in clinical use since the early 1970s (Dexon®) with a huge market exceeding 1.3 billion dollar annually (Pillai and Sharma 2010). In general, degradable suture materials should be easy to handle, evoke only minimal tissue reaction, must not support bacterial growth, degrade after serving its function, and have an appropriate mechanical strength also during degradation. A challenge in the development of suture materials is tailoring of the degradation time period and the change of the mechanical strength as well as suture elasticity during degradation, which needs to be adjusted to the clinical needs. Newly developments of suture materials are focusing on self-knotting actions by usage of shape-memory polymers (Lendlein and Kelch 2002) and bioactive materials, which have e.g. an antimicrobial activity (Vicryl Plus, approved material) or inhibit matrix degradation (Pasternak et al. 2008).

4.2.2 Poly(Ester Amide)s

Poly(ester amides) (PEAs) can be prepared by different synthetic routes, which yield polymers with segmented, statistical distribution of chain segments. A random copolymer can be derived from 1,4-butanediol, adipic acid and ε-caprolactame (Grigat et al. 1998). The mechanical properties of segmented PEAs (and also of polyurethanes) are interesting because of the microphase separation of their hard and soft segments. In PEA soft domains were formed by the ester-rich domains, and hard domains are formed by the amide-rich domains acting as physical crosslinkers determining the shape of a sample body. A segmented PEA could be synthesized by reaction of an alternating ester-amide oligomer, obtained from the reaction of adipic acid with a bisamide diol derived from 1,6-diaminohexane (**16** with Y^2=C6) and γ-butyrolactone (**15**), with an oligoester prepared from 1,2-ethanediol and dimethyl adipate (see Scheme 4.3) (Bera and Jedlinski 1993).

There are four types of biodegradable PEAs: (a) Polydepsipeptides, which combine properties of poly(α-hydroxy acids) and poly(α-amino acids). These polymers can be prepared by ring-opening polymerization of morpholine-2,5-diones (see **5** in Fig. 4.4) (Feng and Guo 2009). (b) Derivatives of α-hydroxy acids obtained by reaction of an acid dichloride with a bisamide diol prepared from glycolic acid and diaminoalkanes. The polymers showed promising results in mechanical properties, degradability, and biocompatibility (Horton et al. 1988); (c) Derivatives from α-amino acids: Poly(ester amides) containing α-amino acid units have been developed and extensively studied (Guo and Chu 2007). These polymers can be obtained by polymerization of an acid dichloride and the p-toluenesulfonic salt of a bis (α-amino acid) α,ω-alkylene diester (Paredes et al. 1998). This polymer type has the



Scheme 4.3 Synthesis of a PEA

disadvantage of relatively high production costs, insolubility in common organic solvents, and thermal instability (Vera et al. 2006); (d) Polymers made from carbohydrate derivatives: carbohydrates like arabinose, xylose and tartaric acid have been used for the formation of polymers by reaction with amines and esters and their degradation properties were investigated (Martinez et al. 1997). The degradation is strongly influenced by the chain microstructure of the resulting polymer. The ester moieties degrade faster than the amide moieties, so the degradation rate is adjustable by the amount of ester moieties used.

4.2.3 Poly(ortho ester)s

Poly(ortho ester)s (POEs) were developed for drug delivery applications. Four types of POEs have been developed, which are shown in Fig. 4.5.

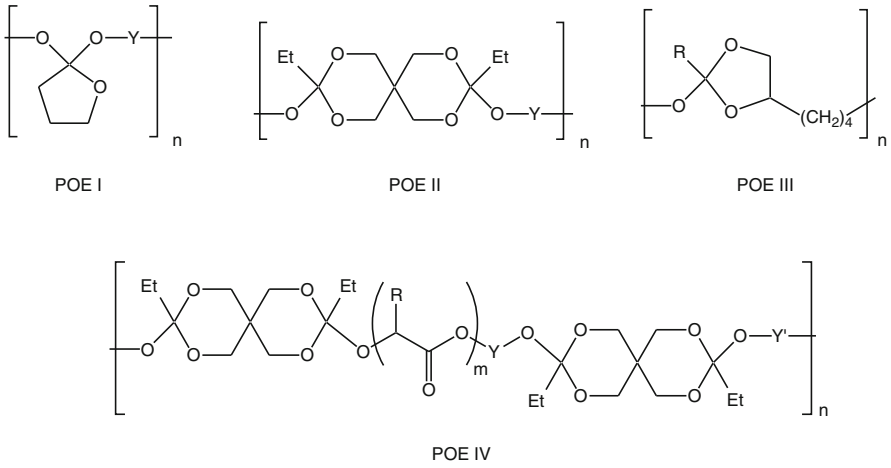
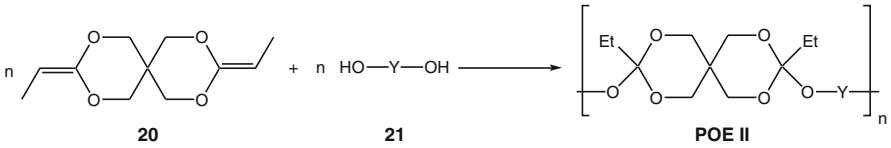


Fig. 4.5 Chemical structures of the four types of poly(ortho ester)s



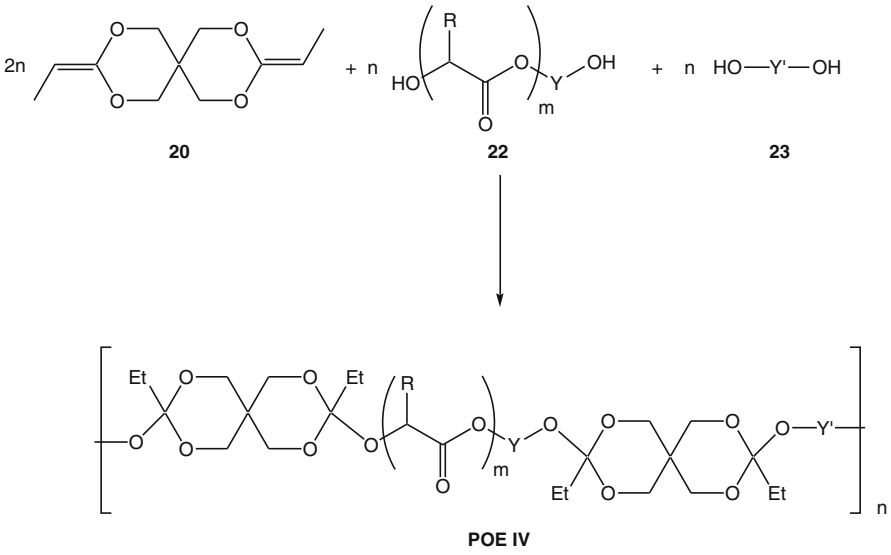
Scheme 4.4 Synthesis of POE type II

POE II is prepared by reaction of diketene acetal **20** (DETOSU) with an appropriate diol **21** (see Scheme 4.4) (Heller et al. 1992). DETOSU was synthesized from the corresponding ketene acetals (Crivello et al. 1996).

This type of poly(ortho ester) was investigated as a drug delivery system for ivermectin containing strands to prevent heartworm infestation in dogs using a cross-linked matrix containing a trivalent alcohol as cross-linker (Shih et al. 1993). The degradation behavior was not sufficiently predictable.

POE IV is prepared by the reaction of DETOSU (**20**), a mixture of diols (**23**) and a poly α-hydroxyacid (**22**) as shown in Scheme 4.5 (Ng et al. 1997). The concentration of the α-hydroxyacid segments in the polymer chains controls the degradation rate.

The mechanical properties of the polymers (POE II and IV) can be influenced by using rigid diols such as trans-cyclohexandimethanol and flexible diols like 1,6 hexanediol. The glass transition temperature (T_g) is determined by the ratio of such diols in the polymer (Heller et al. 1983; Heller et al. 1995). For drug delivery systems the drug has to be uniformly distributed over the polymer matrix. POE IV can be processed by melt extrusion at 100 °C without significant change in molecular weight. POE II and IV are soluble in solvents like methylene chloride, ethyl acetate, or THF, enabling formation of microspheres by conventional procedures.



Scheme 4.5 Synthesis of POE type IV

Poly(ortho ester)s are stable when stored under water-free conditions at room temperature and can be sterilized (Heller et al. 2002).

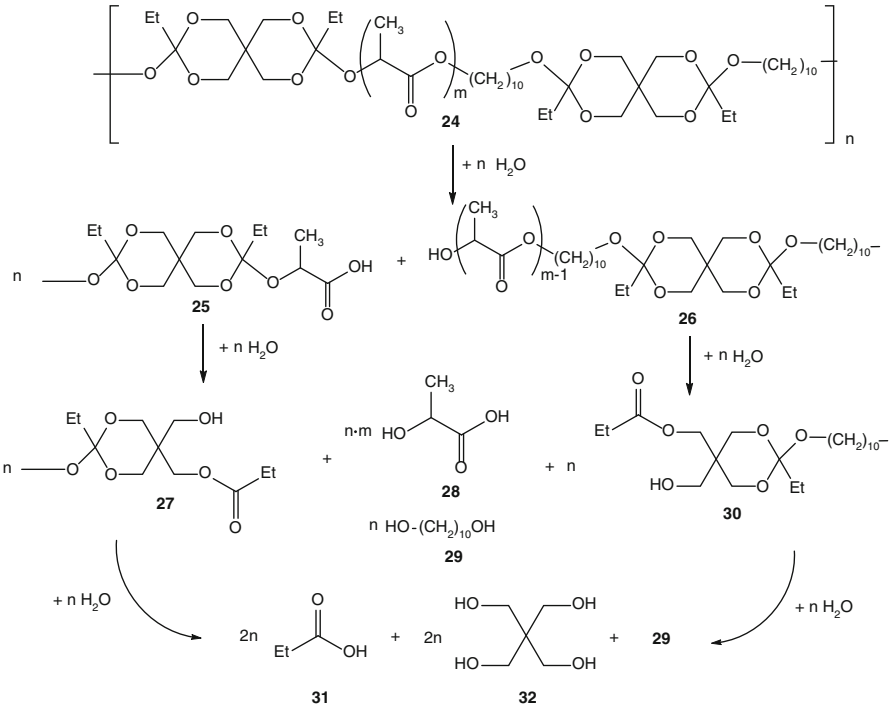
The hydrolysis of the POE IV proceeds in three consecutive steps (see Scheme 4.6).

The weight loss during degradation is linear for POE Type IV. First the ester bonds were cleaved in the polylactide moiety of the polymer (**25**, **26**) and as a second step the orthoester moiety degraded. This resulted finally in the release of lactic acid (**28**), propionic acid (**31**), pentaerytritol (**32**) and decandiol (**29**). The process is predominatly confined to the surface layers of the polymer matrix (surface erosion). Only a small amount of bulk erosion occurs, which is in contrast to the poly(lactide-*co*-glycolide) copolymers or poly(lactic acids) (Vaccaro et al. 2002).

Hydrolytically labile poly(ortho ester amide) (POEA) copolymers were developed to overcome the drawbacks of the traditional methods of POE synthesis by solution polycondensation between an acid labile diamine with a build-in ortho ester bond and fatty diacid esters of different chain-length (Tang et al. 2009).

4.2.4 Polyurethanes

Polyurethanes (PURs) are used for industrial applications since the 1940s, but development of biocompatible polymers based on urethanes started in the 1960s. These polymers are often used for long-term applications because of their beneficial characteristics like toughness, durability and biostability. Also polyurethanes with a



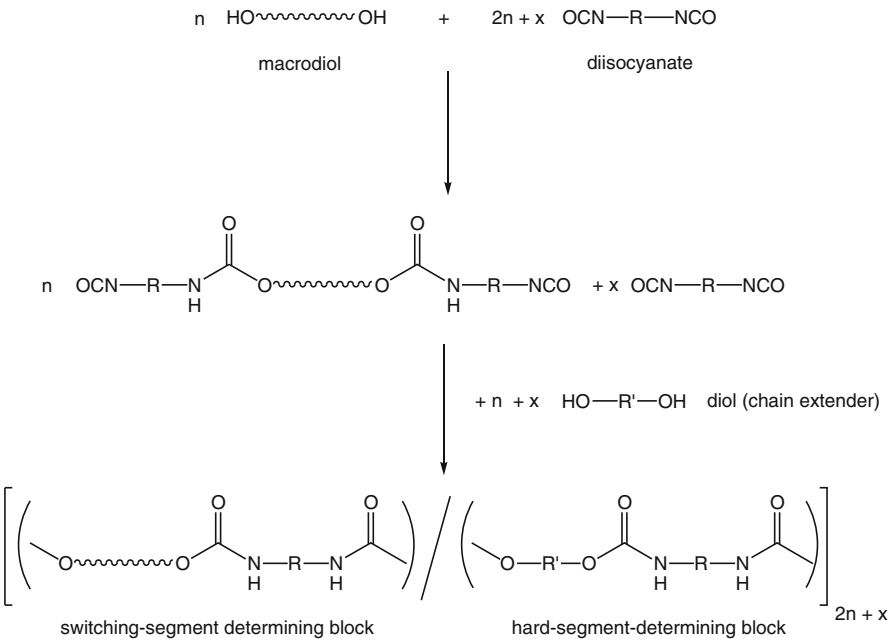
Scheme 4.6 Degradation mechanism of POE type IV in the presence of water

controlled degradation rate have been developed due to a high demand on degradable biomaterials (Lendlein et al. 1998).

PURs are basically synthesized using a diisocyanate, a diol and a chain-extender as main components (Syzcher 1999). In these cases aromatic diisocyanates were substituted by an aliphatic compound such as 1,6-hexamethylene diisocyanate (HDI), 1,4-butylene diisocyanate (BDI), lysine methylester diisocyanate (LDI), or trimethyl hexamethylene diisocyanate (TMDI) (Cardy 1979).

The diol in degradable PURs is commonly an oligomer with hydroxyl end groups, so called macrodiol, with a backbone corresponding to polyester or polycarbonate. Polyester urethanes are the most common degradable polymers of this type. The macrodiols can be prepared by ring-opening polymerization of a cyclic lactone (see under polyester). The reaction between the diol and the isocyanate is carried out with an excess of diisocyanate to obtain a reactive prepolymer with isocyanate end groups. To obtain a thermoplastic PUR with a segmented architecture the prepolymer is further reacted with a chain extender, which is a short chain diol (see Scheme 4.7).

PURs are multi-block copolymers, which show microphase separation. This phase separation comparable to PEAs allows another functionality beside degradability in the materials: these polymers show shape-memory properties. Using poly(ε-caprolactone)diol and poly(p-dioxanone) together with TMDI a degradable



Scheme 4.7 Synthesis of a polyurethane using a macrodiol, a diisocyanate and a short chain diol as a chain extender

shape-memory polymer can be generated (Lendlein and Kelch 2002; Lendlein and Langer 2002; Spaans et al. 1998). Shape-memory polymers are materials which can be deformed and fixed in a temporary shape, from which they recover their original shape only when exposed to an appropriate stimulus (Behl and Lendlein 2007). They show at least two separated phases. The phase with the highest thermal transition acts as a physical cross-link and is responsible for the so called permanent shape of the polymer. A second phase serves as a molecular switch and enables the fixation of a temporary shape. The transition temperature T_{trans} for the fixation of the switching segments can either be a glass transition (T_g) or a melting temperature (T_m). After deforming the material above the switching temperature, the temporary shape can be fixed by cooling the polymer below the switching temperature. Heating up the material above T_{trans} again cleaves the physical cross-links in the switching phase. As a result of its entropy elasticity the material is forced back to its permanent shape. Potential applications are intelligent degradable sutures and degradable shape-memory-stents. Degradation is controlled by the amount of degradable bonds (e.g. ester bonds) in the used macrodiols for synthesis.

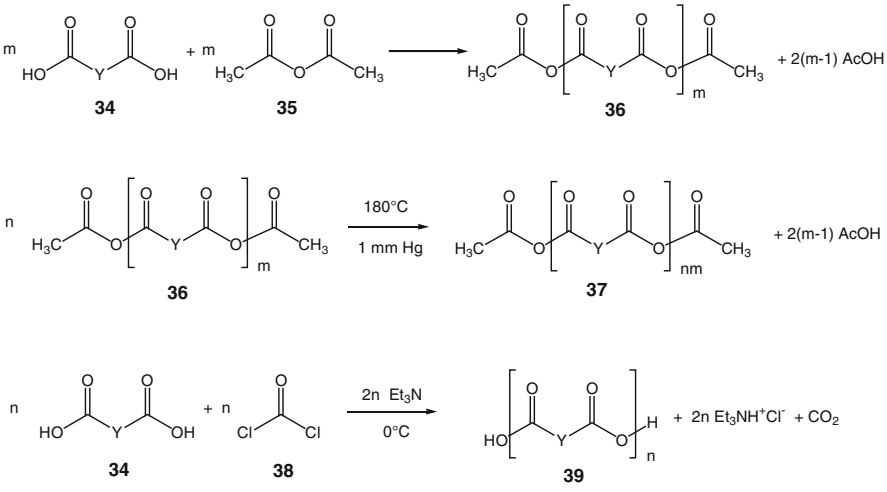
Degradable PURs are of interest in the design of scaffolds for in vivo tissue engineering as well as for cardiovascular applications. Elastic materials are required for soft tissue engineering due to mechanical conditions during the development of the new tissue. For cardiovascular tissue engineering the material should have sufficient elasticity and high tensile strength.

4.2.5 *Polyanhydrides*

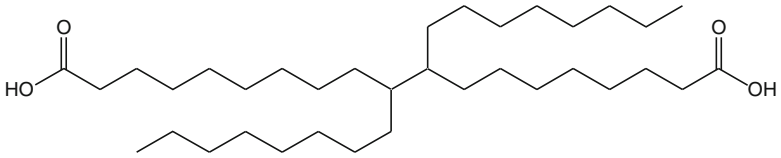
A group of polymers showing surface erosion are the polyanhydrides (Bucher and Slade 1909; Carothers and Hill 1932; Domb et al. 1994; Laurencin et al. 1995). Since beginning of the 1980s polyanhydrides are developed for biomedical applications. The easily cleavable anhydride bond is introduced into a hydrophobic polymer, such as aliphatic long chain diacids (such as **34**). For variation of the mechanical properties by adjusting the crystallinity, sebacinic acid is often used as a comonomer.

Aliphatic diacids can be polycondensated to polyanhydrides by reaction with acetic acid anhydride (**35**, Scheme 4.8). The reaction proceeds in two steps. First, oligomeric polyanhydrides with terminal acetate groups are received (**36**), further reaction to a high molecular product occurs at elevated temperatures under vacuum. When glutaric acid (y = C10) and succinic acid instead of sebacic acid are used under the same conditions, they form cyclic compounds. The reaction between dicarboxylic acids and dicarboxylic diacidchlorides results in low molecular weight products. To gain higher molecular weight products phosgene (**38**) is used as condensation agent. Et_3N is used as a proton acceptor and precipitates the evolving hydrochloride.

While polysebacinic acid is semi-crystalline (T_m = 82 °C) the homopolymer of the oleic acid dimer (**40**) is liquid. Copolymers of them are partly crystalline with melting points between 30 °C and 78 °C having average molecular weights between 24.000 and 280.000 g·mol^{-1}. Sebacinic acid (**41**) can be condensed with benzoic acid derivative (**42**) to form the drug delivery matrix Septacin® for curing chronic bone infections (Fig. 4.6, see applications).



Scheme 4.8 Synthetic routes for the synthesis of polyanhydrides



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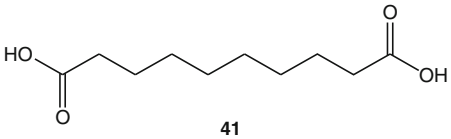

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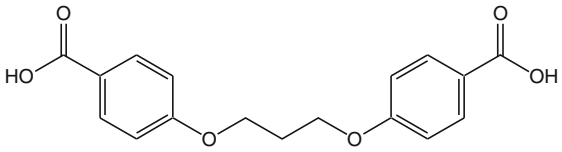

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Fig. 4.6 Different diacids used as monomers in the preparation of polyanhydrides

It is assumed that polyanhydrides degrade by surface erosion mainly driven by two processes: (a) the easily hydrolysable anhydride bonds at the surface, and (b) the restriction of water permeability into the bulk due to hydrophobicity (Jain et al. 2005). These two processes allow a control of the release and a protection of the drug within the bulk material until release. In addition, the release of the drug is timely correlated to the material degradation. The duration of the polymer degradation can be controlled by varying the type of monomer and the comonomer ratio. Various polyanhydrides have been used experimentally as drug delivery systems (Table 4.3). As a localized drug delivery system for chemotherapeutic agents GLIADEL® is used in brain cancer treatment. The first approval in 1996 was for its limited use as an additive therapy in patient with recurrent Glioblastoma multiforme (GBM) for whom surgical resection is indicated. In 2003, the approval was expanded for use of GLIADEL® in patients with newly diagnosed high-grade malignant gliomas, as an adjunct to surgery and radiation. SEPTACIN® is a Gentamicin delivering product for osteomyelitis treatment (Li et al. 2002).

4.2.6 Polycyanoacrylates

Cyanoacrylate is a generic name for fast acting glues based on various cyanoacrylates such as methyl-2-cyanoacrylate, ethyl-2-cyanoacrylate, n-butyl-2-cyanoacrylate, and octyl-2-cyanoacrylate (see **44**, Fig. 4.7). These polymers are suitable for bonding tissue, and have been exploited for the benefit of suture-less surgery.

Table 4.3 Experimentally used polyanhydrides for drug delivery

Delivery System	Polyanhydride	Drug	Disease
Matrix	Ricinoleic acid based	Methotrexate	Cancer
	P(RA- SA)	Cisplatinum	Cancer
	P(FAD-SA)	Cisplatin, 5-FU, methotrexate, paclitaxel	Cancer
	P(FAD-SA)	Bupivacaine HCL	Local anesthesia
	P(OA/LAD-SA)	Gentamicin	Osteomyelits
	P(DDDA-TA)	Ciprofloxacine hydrochloride	Local infection
Implant	P(CPP-SA)	BrdU & N-(phosphonacetyl)-l-aspartic acid; 5-fluorouracil or Camptothecin	Cancer
	P(CPP-SA)	Dibucaine, bupivacaine	Local anaesthesia
	P(CPP-SA)	Etoposide	Glaucoma
	P(FAD-SA)	Taxol	Cancer
	P(EAD-SA)	Heparin	Restenosis
Injectable paste	P(RA-SA)	Paclitaxel	Cancer
Microspheres	Poly(anhydride-esters)	Aminosalicylates	Inflammatory bowel disease
	PLA-PSA-PLA	Triamcinolone	Inflammation
	P(FAD-SA)	GnRHa	Hormone therapy
	SA copolymers	Bethanechol	Alzheimer disease

Taken from Jain et al. Copyright 2005, with permission from Elsevier
P(BA-PA) Poly(brassylic acidpentadecandioic acid), *P(CPP-SA)* Poly[1,3-bis(p-carboxyphenoxy) propane-co-sebacic anhydride], *P(DDDA-TA)* Poly(dodecane dioic acid-*co*-tetradecanedioic acid), *P(EAD-SA)* Poly(erucic acid-*co*-dimersebacic acid), *P(FAD-SA)* Poly(fatty acid dimer-*co*-sebacic acid), *PLA-PSA-PLA* Poly(lactic acid)-poly(sebacic acid)-poly(lactic acid), *P(OA/LAD-SA)* Poly(Oleic acid/linoleic acid dimer-*co*-sebacic acid), *P(RA-SA)* Poly(ricinoleic acid-*co*-sebacic acid), *SA* Sebacic acid

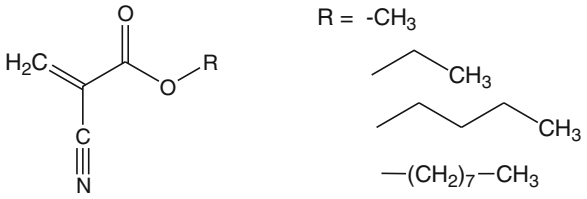

Fig. 4.7 Chemical structure of cyanoacrylates

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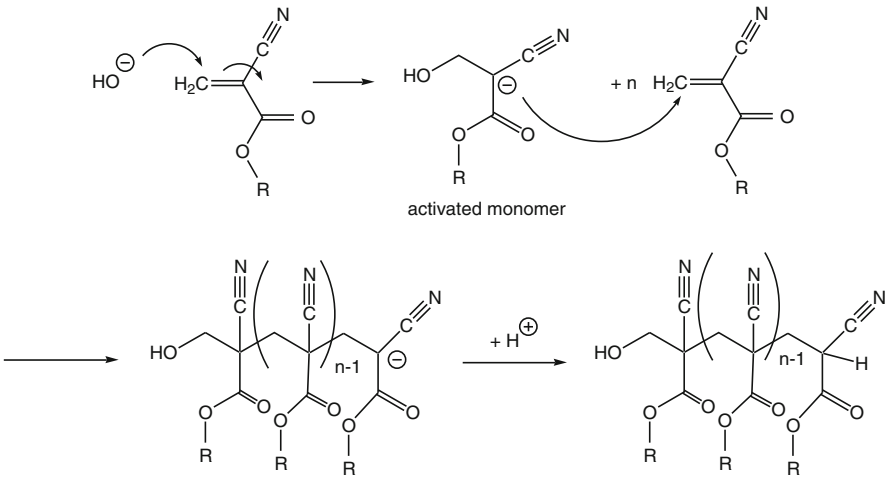
Cyanoacrylates rapidly polymerize in the presence of traces of water (specifically hydroxyl ions), forming polymers with chain length sufficient for the demanded physical properties (see Scheme 4.9). Such polymers are able to join surfaces of different roughness.



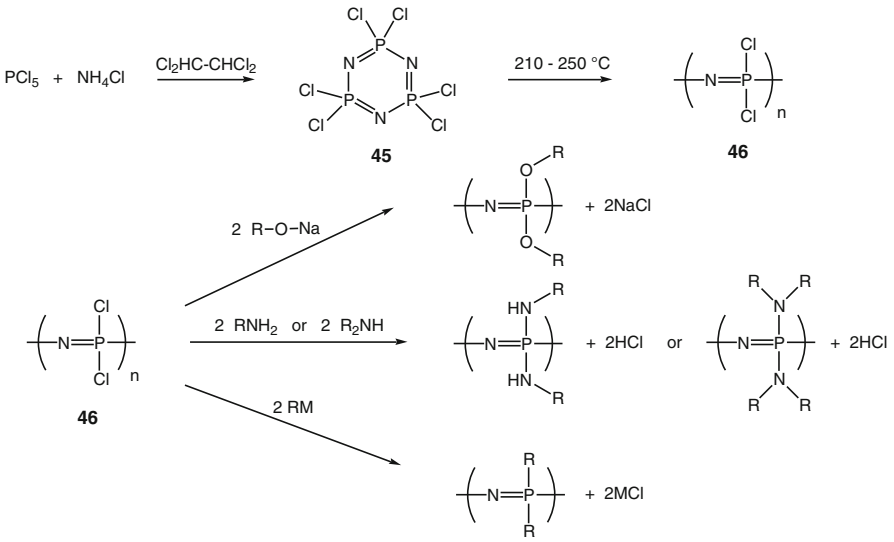
Scheme 4.9 Polymerization mechanism of cyanoacrylates in the presence of water

N-butyl, isobutyl, and octyl ester derivatives of the cyanoacrylates were used In medical and veterinary applications. They are considered bacteriostatic. Polymers made from n-butyl monomers are rigid; octyl ester containing polymers provide more flexible materials. The polymer generated from octyl-2-cyanoacrylate degrades more slowly compared to formulations from shorter alkyl ester chains. Degradation products remain below the threshold of tissue toxicity, if the polymers degrade slowly. The degradation of the cyanoacrylates happens via an unzipping mechanism of the polymer, which proceeds by a retro Knoevenagel reaction after elimination of the hydroxyl group. The ester bonds in the structure can be cleaved under acetic or basic pH (Han et al. 2008).

Cyanoacrylate based products are: Dermabond®, LiquiBand®, SurgiSeal™, or Nexaband® (all 2-octyl cyanoacrylate) and Indermil® and Histoacryl® (both are *n*-butyl-cyanoacrylates). All products are approved for topical use only. They serve as adjuncts to closure of skin incisions and Dermabond® and Indermil® are also indicated as barrier to bacterial skin penetration (Spotnitz and Burks 2008).

4.2.7 Polyphosphazenes

Polyphosphazenes are a class of biocompatible polymers (Andrianov 2009), which are prepared by reaction of phosphorus pentachloride with ammonium chloride in tetrachloroethane forming hexachlorocyclotriphosphazene (**45**) in a first step. After heating to 210–250 °C the chlorine substituted polymer (**46**) forms by thermal ring-opening polymerization (Allen 1981). In a second step the polymer is functionalized by nucleophilic attack on the phosphor (see Scheme 4.10) in solutions with



Scheme 4.10 Synthesis and chemical functionalization of polyphosphazenes

benzene, toluene or tetrahydrofurane. A high variety of functional groups can be introduced such as amines, amino acids, poly(ethylene glycol)s or aliphatic chains. The hydrophilic substituted polymers are able to degrade to phosphate, ammonia and an organic residue depending on the functionalization of the backbone. Phosphate and ammonia create a pH buffer system during degradation.

The properties of the polymers depend on the nature of the side groups. With side groups derived from trifluoroethanol ($-O-CH_2-CF_3$) the polymers show high flexibility and a low glass transition temperature, in this respect the polymers resemble the commercial significant siloxanes.

Polyphosphazenes are explored as degradable scaffolds for bone regeneration in tissue engineering and drug delivery (Lakshmi et al. 2003). Here, the polymers are functionalized with amino acid ethyl esters and can be electrospun to generate a non-woven scaffold. Introduction of carboxylic groups enable ionic cross linking with calcium ions. They are also intended as temporary substrates that accommodate moderate cell infiltration and tissue in-growth in regenerative medicine. The 3D scaffold built from polyphosphazene with glycylglycine dipeptide and 4-phenylphenoxy group as side chains and blended with a polyester (PLAGA) allows the formation of an interconnected porous structure out of a solid coherent film to an assemblage of microspheres (Deng et al. 2010).

The degradation products are aside of phosphate and ammonia, the amino acid ethyl esters. The same type of polyphosphazene can be used as a drug delivery device in the form of nano- or microparticles (Sethuraman et al. 2011). They show a long blood circulating life time and are PEG coated. Furthermore bioerodable blends of the polyphosphazenes with e.g. PLGA have been developed (Krogman et al. 2007).

4.2.8 Hydrogels

Hydrogels are three dimensional networks from hydrophilic polymer chains, which are able to take up high amounts of water under retention of their shape. The networks can be based on physical or covalent cross-links. Potential applications include matrices for cell culturing or drug delivery systems (Hoffman 2002; Peppas 1987). Hydrogels suitable for long term applications are approved as soft contact lenses, made from 2-hydroxyethylmethacrylate and a cross-linker or poly(ethylene glycol) with reactive end groups. Hydrogels can be designed to be stimuli-sensitive by introduction of specific functional groups or segments (Qiu and Park 2001).

Degradability can be established by introduction of degradable blocks like poly(lactic acid) in the main chain of the hydrogel.

Examples for approved products are CoSeal™, Baxter, Fremont, CA (for vascular sealing) and DuraSeal™, Covidien, Waltham, MA (for dural sealing). Both of these sealants are synthetic and form hydrogels that seal tissues. It is indicated as an adjunct to blood vessel hemostasis by mechanically sealing areas of leakage. DuraSeal™ consists of two solutions. The first is a PEG ester and the second contains trilisine amine with a blue dye for visualization. Following normal dura suturing the use of DuraSeal™ allows a true watertight closure.

4.3 Biomaterials Based on Natural Products

Carbohydrates are isolated from different natural sources. Hyaluronic acid, a non-sulfated glycosaminoglycan and one of the main components of the extracellular matrix, was isolated e.g. from cock's combs (Boas 1949), or isolated by gel filtration on agarose together with the protein complex (Barker and Young 1966) and is nowadays isolated from various sources. The repeating unit is a disaccharide composed of D-glucuronic acid and D-N-acetylglucosamine, linked together via alternating β-1,4 and β-1,3 glycosidic bonds (4GlcUAβ1-3GlcNAcβ1) (see Fig. 4.8). Hyaluronic acid is degraded enzymatically by hyaluronidases. In humans, there are at least seven types of hyaluronidase-like enzymes.

In the human body the polysaccharide hyaluronic acid (HA) is found in almost every tissue and half of the total HA content in the body is present in the skin. The main clinical application is the use of esterified HA as a wound dressing (HYAFF®)

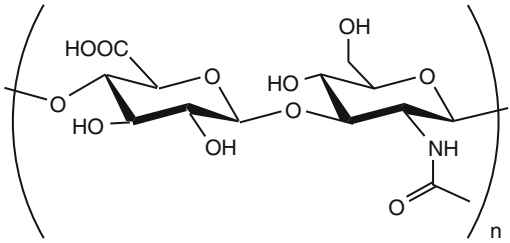


Fig. 4.8 Chemical structure of hyaluronic acid

(Little et al. 2009). In orthopaedic surgery, hyaluronic acid scaffolds are used experimentally and in clinical trials as carrier for stimulating factors and cells (HYAFF®11, HYALOGRAFT C®). Viscous HA is used as a synovial substitute in osteoarthritis patient for pain relief and to improve joint mobility (SYNVISC® ORTHOVISC®).

Chitin and Chitosan are carbohydrates, which are FDA approved as food additives. Two other products are approved as medical device: CHITOSKIN® is a wound dressing and CHITOSTYPE® is used to reduce bleeding.

Polysaccharide spheres are the basis of the absorbable haemostat Vitasure®. Natural haemostasis is enhanced by the spheres that act as hydrophilic molecular sieves concentrating blood solids (platelets, red blood cells, and blood proteins) on the particle surfaces to form a gelled matrix. This gel matrix reduces further blood loss and is formed regardless of the patient's coagulation status.

Alginic acid is a polysaccharide of brown algae. As an alternative bone grafting material, ALGISORB™ is available. After cleaning and manufacturing, the algae is transformed into calcium phosphate a major inorganic component of bone.

4.3.1 Other Natural Materials

Natural materials have been used for centuries and have a broad range of applications in human medicine. In addition to autologous (patient's own) material, allogenic (human donor) and xenogenic (animal donor) transplant material, including various collagen products are currently used (Table 4.4). Furthermore non-animal materials, for example from algae, are also approved for human application (see carbohydrates).

4.3.2 Examples for Approved Natural Materials

Collagen is the main protein of connective tissue and the most abundant protein in mammals (Di Lullo et al. 2002). 29 types of collagen have thus far been identified and described in literature. Over 90 % of the collagens in the body are of so called type I, II, III, and IV. Different methods are used to isolate collagen from tissues (for example see Xiong et al. 2007).

A large number of collagen products are on the marked. Collagen is clinically used, for example as a nerve conduit NeuraGen® and NeuroMatrix™ (bovine) and received FDA approval in 2001 (Purcell et al. 2004).

In combinations with osteoinductive growth factors (BMP-2 or BMP-7), bovine collagen is used as a carrier in the form of a sponge (InductOs®) or as granules with a particle size of 75–425 μm (Osig raft®) (Friedlaender et al. 2001; Govender et al. 2002).

Table 4.4 Overview on tissue grafts

	Source/organ	Application	
Autograft	Bone	Defect filling	
	Mesenchymal stem cells	Various applications	For detailed information see Part II
	Tendon	Tendon repair	
	Skin	Wound repair	
	Cartilage	Cartilage repair	
	Vessels aorta; coronary artery	Vessel replacement	
Allograft	Bone: spinal fusion grafts, cortical and dense cancellous bone, demineralized bone matrix	Defect filling, Spinal fusion, Periodontal Surgery	From tissue banks, processed materials
	Tendon	Tendon repair	
	Split Thickness Skin	Wound repair	
	Acellular dermis	Hernia repair and abdominal wall reconstruction.	
	Liver	Liver transplantation (TX)	Live donations, unprocessed
	Kidney	TX	
	Heart	TX	
	Lung	TX	
	Pancreas	TX	
	Skin, cornea	TX	
	Bone Marrow, stem cells	Leukemia	
Xenograft	Cardiac valve	Heart surgery	Mainly porcine, processed
	Collagen	Various applications	Bovine, porcine, equine, processed
	Bone	Defect filling	Mainly bovine, processed
Mixed	Fibrin human fibrinogen and human thrombin	Tissue sealant	
	Gelatine	Haemostatic	

KOLLAGEN-resorb®, GENTA-COLL resorb®, GentaFleece® and Septocoll® for example have several indications in surgery and are used for hemostasis, as a wound dressing, defect filler, and for bone regeneration. The supplementation of the collagen by adding gentamicin allows for protection against infections.

A product group based on natural porcine small intestinal submucosa (SIS) is marketed under the name Surgisis (SIS®) (Hodde 2006) for the treatment in: congenial diaphragmatic hernias (CDH), colon and rectal surgery, gastroenterology, general surgery, obstetrics & gynaecology, otolaryngology, plastic surgery, thoracic surgery, urology, vascular surgery. Surgisis is an acellularized matrix mesh composed of collagen, proteins, and glycosaminoglycans proteoglycans.

A gelatinous protein mixture secreted by Engelbreth-Holm-Swarm sarcomosa cells (EHS) is commercialized under the name BD Matrigel™. This mixture resembles the complex extra cellular environment found in many tissues and contains laminin, entactin, and collagen. These proteins self-assemble to a structure which enables coating of glassware and 3D scaffolds for tissue engineering (Hughes et al. 2010).

Open porous collagen scaffolds under the name Optimax® are available for a drop in or drop on cell seeding. They are stable in cell culture for several weeks and are used for drug production in bioreactors, cell expansion, and tissue engineering application in preclinical development. Their oriented pore structure in the scaffold enables directed growth of e.g. muscle cells in cell cultures (Kroehne et al. 2008). The pores are generated from controlled freezing of a water suspension of collagen, where the collagen molecules orient on the surface of finger like ice crystals. In the final step the ice is removed by freeze drying.

Remaix® is a resorbable dental barrier membrane for applications in guided bone regeneration (GBR) and guided tissue regeneration (GTR). It is used to cover the space filled with bone graft material. This secluded space assists bone regeneration by protecting the slowly growing bone from infiltration with cells from the surrounding soft tissue. The membrane is composed of a network of purified porcine collagen fibers intermingled with purified porcine elastin fibers, by providing a barrier against migration of unwanted cells from the soft tissue and allows the ingrowth of osteogenic cells in the space of the bone defect.

Several materials of natural origin are available as hemostats to reduce or stop bleeding due to surgery. Sponges or meshes made from porcine gelatine (Gelfoam sponge®, Surgifoam sponge/powder®) or bovine collagen (Avitine sponge/flour®, Helistat® & Helitene®, Instat®) function as a mechanical barrier. To actively stop bleeding, active substances based on thrombin are approved. These materials can be of bovine origin (Thrombin JMI®), made from human thrombin (Evithorm®) or be recombinant (Recothrom®) (Han et al. 2008).

Fibrin is also used as a hemostat and sealant (Tisseel®, Evicel®). It is a combination of plasma fibrinogen and thrombin from human or bovine origin. A dual chamber syringe separates the thrombin and the fibrinogen and after mixture of thrombin with the fibrinogen, a fibrin clot forms. Cryoseal® Fibrin Sealant System is a semi-automated product designed to produce an autologous fibrin sealant during surgery. Vitagel® is a combination product of microfibrillar collagen and thrombin in combination with the autologous plasma (fibrinogen and platelets).

A further very interesting biomaterial is spider silk. The product (SERI®) is approved as a surgical scaffold for plastic, reconstructive and supportive treatment of soft tissue. An interim report from 2015 documents the first results of a prospective single-arm study using SERI® scaffold for breast reconstruction with a high satisfaction of the patients and investigators but no results regarding the performance of the scaffold (Fine et al. 2015).

4.4 Conclusion and Outlook

For each application of degradable polymers a specific set of properties e.g. mechanical properties such as degradability or a certain modulus is demanded. With increasing number of potential applications a greater extend of various materials with different property combinations is required. It is still only a limited amount of materials in clinical application, which are not able to fulfil all the new requirements. Therefore a substantial need of novel degradable biomaterials with tailored properties exists. Additional to the purely synthetic materials, biomimetic approaches are integrated into material design.

Emerging fields of modern medicine, e.g. regenerative medicine require materials with a variety of several functionalities (e.g. shape-memory effect or other stimuli sensitive functions) combined in one material. Hence multifunctional materials are an important research topic. One example is a degradable shape-memory polymer with the additional ability of controlled drug release.

Multifunctional materials will be designed to mimic the microenvironment of cells, e.g. of mesenchymal stem cells, which is of high significance for regenerative therapies.

For a successful development of new materials a solid knowledge of existing applied polymers in clinical use it is necessary to avoid old pitfalls and enable new combinations.

Acknowledgements We would like to thank the Deutsche Forschungsgemeinschaft (DFG, SFB 760) and the Bundesministerium für Bildung und Forschung (BMBF, FKZ1315848A) for supporting the interdisciplinary research in the field of tissue regeneration.

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