Biodegradable elastomers for biomedical applications and regenerative medicine

Synthetic biodegradable polymers are of great value for the preparation of implants that are required to reside only temporarily in the body. The use of biodegradable polymers obviates the need for a second surgery to remove the implant, which is the case when a nondegradable implant is used. After implantation in the body, biomedical devices may be subjected to degradation and erosion. Understanding the mechanisms of these processes is essential for the development of biomedical devices or implants with a specific function, for example, scaffolds for tissue-engineering applications. For the engineering and regeneration of soft tissues (e.g., blood vessels, cardiac muscle and peripheral nerves), biodegradable polymers are needed that are flexible and elastic. The scaffolds prepared from these polymers should have tuneable degradation properties and should perform well under long-term cyclic deformation conditions. The required polymers, which are either physically or chemically crosslinked biodegradable elastomers, are reviewed in this article.

Keywords: biodegradable elastomer • elastic • flexible • polymeric biomaterial • regenerative medicine

Degradation & erosion of synthetic biodegradable polymers

Understanding the degradation and erosion behavior of synthetic biodegradable polymers is essential for the successful design of biomaterials. The process of polymer chain cleavage is referred to as degradation and the loss of material mass is referred to as erosion [1].

Degradation of polymers can occur by hydrolysis, thermolysis, radiolysis, or as a result of mechanical and oxidative stress. Most synthetic biodegradable polymers contain hydrolyzable bonds such as ester, anhydride, amide and carbonate bonds in their main chains that can be cleaved either enzymatically or nonenzymatically upon reacting with water. The rate of hydrolysis is influenced by the nature of the labile bond, the accessibility of the bonds to water or enzymes and by several other factors such as glass transition temperature, hydrophilicity, morphology, crosslinking, pH and the presence of proteins.

Erosion of polymers implies the loss of material as a result of diffusion and dissolution of monomers and other low-molecular-weight compounds that are formed upon degradation [1]. Polymer erosion is a complex process that depends on many factors including polymer degradation, swelling, changes in morphology, polymer molecular weight, and diffusion of water, monomers and oligomers [2].

Surface & bulk erosion

Biodegradable polymers can be classified as surface- or bulk-eroding materials. Both processes are schematically illustrated in Figure 1.

Surface-eroding polymers, among which are poly(anhydride)s, poly(orthoester)s, poly(trimethylene carbonate), poly(ethylene carbonate), poly(hydroxalkanoate)s and poly(glycerol sebacate), lose material from the surface only. The mass and dimensions of a device made of a surface-eroding polymer decrease proportionally to its surface area,
whereas the molecular weight of the polymer in the bulk of the material remains essentially unchanged. In the case of bulk-eroding polymers such as aliphatic polyesters, however, degradation and erosion occur throughout the bulk of the material. The mass and dimensions of a device made of such a material remain constant for a considerable part of its application time, while the molecular weight of the polymer starts to decrease essentially from the beginning of the bulk hydrolysis process. Mass loss usually sets in upon reaching a critically low molecular weight, leading to a rapid release of degradation products within a short period of time. It should be noted that loss of mechanical properties of the material precedes the loss of mass, leading to a dramatic mechanical failure of the device [3]. The change of properties in time for bulk- and surface-eroding polymers is schematically shown in Figure 2.

The predictability of the erosion process in the case of surface-eroding polymers is a great advantage in controlled release applications. This allows sequential release and delivery at a constant release rate (zero-order release) of bioactive compounds. In addition, the rapid formation and release of degradation products in the case of bulk-eroding polymers can be harmful to cells cultured in tissue-engineering scaffolds prepared from these materials or can evoke a severe tissue response after implantation of such scaffolds. Moreover, the structural integrity and mechanical properties of implants are better preserved in the case of surface erosion, which is especially desirable in tissue-engineering applications.

**In vivo tissue response & biodegradation**

*In vivo*, interactions of cells with implanted polymers are complex due to the presence of blood, other body fluids and multiple cell types. These interactions are very important, not only with regard to the biocompatibility of these materials, but also their functionality and biodegradation. Unlike biostable implants, degradable implants only have a temporary function, and are designed to be eliminated from the body after degradation. This implies that the degradation products should also be biocompatible and easily resorbable.

Once a biomaterial is introduced into the body of a patient, a sequence of events takes place in the tissue surrounding the biomaterial that leads to a foreign body reaction [4]. Upon implantation, proteins immediately adsorb to the surface of polymeric implants. These adsorbed proteins dictate the adhesion of inflammatory cells to the surface, as well as cell survival. In general, neutrophils are the predominant type of cells at the tissue–biomaterial interface in the first few days following implantation. Monocytes/macrophages extravasate and migrate to the implant site following the neutrophils and then become the predominant cell type. At later stages, lymphocytes and fibroblasts are
recruited and macrophages adhering to the surface of the biomaterial fuse to form foreign body giant cells. Macrophages are able to produce a large number of biologically active compounds such as chemotactic factors, reactive oxygen species, hydrolytic enzymes, cytokines and growth factors, among others. Therefore, they are regarded as highly influential cells in orchestrating the host response to biomaterials and their biodegradation.

Some biodegradable polymers have been shown to degrade faster in vivo than in vitro. This has been attributed to hydrolytic compounds secreted by macrophages. Polyurethanes intended for use in long-term applications, have been shown to be degraded by the action of hydrolytic enzymes and reactive oxygen species secreted by macrophages [5]. Several studies have demonstrated macrophage-mediated degradation and erosion of other polymers as well [6].

**Tissue engineering**

Every year, millions of people face health problems related to tissue loss and end-stage organ failure. Physicians have used surgical reconstruction, organ transplantation and artificial prostheses for the treatment of damaged tissues and organs. Although being a good alternative to organ restoration, organ transplantation has constraints regarding donor shortage and immune response [7]. Reconstructive surgery on the other hand, can cause serious problems in the long term because of abnormal reactions of the tissue at its new location [7]. Artificial prostheses also lack some requirements in treating organ failure such as durability and deficiency in fully performing all organ functions [8]. Therefore, tissue engineering has emerged as an alternative. The most common approach for the engineering of tissues, uses cells associated within a matrix or scaffold to guide tissue development [9,10]. Tissue-engineering research includes three main areas: scaffolds, cells, and signaling molecules and growth factors. For the purpose of this article, the desired properties of scaffolds for engineering of soft tissues are summarized after which biodegradable elastomers are discussed in detail.

**Scaffolds**

Cells in the body are in contact with a complex network of extracellular macromolecules that are physically and chemically crosslinked. This so-called extracellular matrix (ECM) can be considered as the actual difference between isolated cells and a tissue. The ECM serves to organize cells in space, to provide them with environmental signals to direct site-specific cellular regulation, and to separate one tissue part from another. The cells are constantly accepting information regarding their environment from cues in the ECM, and are frequently remodeling their ECM [11]. The ECM has roles in maintaining homeostasis, guiding development and directing regeneration. It provides adhesion signals, growth factor-binding sites and degradation sites to give way to migrating cells, which release enzymatic activity [12].

As most primary organ cells require anchorage sites and specific environments that provide support and act as a template for growth, a tissue-engineering scaffold that mimics the ECM is essential for cells to proliferate and form tissues [13,14]. Several fabrication techniques such as particulate leaching, gas foaming, phase separation, stereolithography and fused deposition modeling have been developed and applied to shape polymers into

![Figure 2. Change of properties in time for bulk- and surface-eroding polymers.](image-url)
complex architectures for the preparation of tissue-engineering scaffolds [14]. The requirements often depend on the intended application. However, to be considered for use in tissue engineering, some general properties must be fulfilled by a material [13,14]:

- The material and the degradation products of the scaffold must be biocompatible and completely resorbable;
- The material should allow cell adhesion, proliferation and migration, and the incorporation of bioactive compounds;
- To facilitate transfer of nutrients and biological waste products and to guide new tissue formation, the material should be processable into a porous scaffold with interconnected pores;
- The scaffold should have mechanical properties that suit the intended application.

Many materials have been used to prepare scaffolds for tissue engineering. These are of biological or synthetic origin, or hybrid materials. Natural polymers such as collagens, starch, glycosaminoglycans, chitin and chitosan have been used [15]. Natural polymers may mimic the ECM quite well, but they often show large batch-to-batch variations upon isolation from biological tissues and poor mechanical performance. Moreover, it is challenging to control their degradation rates over wide periods of time. Polymers of biological origin may also provoke an immunological response [16].

Synthetic biodegradable polymers such as poly(α-hydroxy ester)s, polyorthesters, polyanhydrides and polyphosphazenes have been used as alternatives to natural polymers [11,12,15,17,18]. Polylactide (PLA), polyglycolide (PGA), poly(ε-caprolactone) (PCL) and their copolymers are the most widely used synthetic polymers for the preparation of biodegradable medical devices. The physical properties and degradation rates of PLA, PGA and PCL polymers can be tuned by copolymerization [15,19]. The synthetic polymers that were initially used for tissue-engineering applications were not designed for a specific application. Instead, the available aliphatic polyesters that were used in the preparation of degradable medical devices were used. These polymers served well in establishing the feasibility of the tissue-engineering concept. However, bulk hydrolysis of these polymers can lead to rapid formation of acidic products that can be proinflammatory [20]. Another drawback of their degradation by bulk hydrolysis is the dramatic deterioration of material strength. Moreover, these materials are very stiff (elastic moduli ranging from several hundred MPa to several GPa) and, as they are not crosslinked, deform plastically in time upon application of stress [15].

The mechanical properties of a scaffold are a function of the properties of the polymer itself, the geometry of the scaffold and the fabrication technique. Ideally, the mechanical properties of a scaffold closely resemble those of the tissue to be regenerated. Therefore, especially for soft tissue-engineering applications, novel materials need to be developed. Soft tissues such as skin, muscle and blood vessels are highly flexible and elastic in nature. The mechanical properties of several human tissues are presented in Table 1. Tissue cells feel the stiffness of their substrate and behave differently on substrates of different stiffness [21]. Many aspects

<table>
<thead>
<tr>
<th>Natural tissue</th>
<th>E-modulus (MPa)</th>
<th>σ_break (MPa)</th>
<th>ε_break (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth muscle</td>
<td>0.006–0.010</td>
<td>–</td>
<td>300</td>
<td>[25]</td>
</tr>
<tr>
<td>Articular cartilage</td>
<td>2.1–5.1</td>
<td>–</td>
<td>–</td>
<td>[26]</td>
</tr>
<tr>
<td>Carotid artery</td>
<td>0.084</td>
<td>–</td>
<td>–</td>
<td>[27]</td>
</tr>
<tr>
<td>Inferior cava vein</td>
<td>–</td>
<td>3.03†</td>
<td>51</td>
<td>[28]</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>0.1 ± 0.06†</td>
<td>1.07†</td>
<td>77</td>
<td>[28,29]</td>
</tr>
<tr>
<td>Aortic heart valve</td>
<td>2.0 ± 1.5†</td>
<td>–</td>
<td>30 ± 14</td>
<td>[30]</td>
</tr>
<tr>
<td>Myocardium</td>
<td>0.02–0.5</td>
<td>–</td>
<td>–</td>
<td>[31]</td>
</tr>
<tr>
<td>Pericardium</td>
<td>20.4 ± 1.9†</td>
<td>–</td>
<td>35 ± 1</td>
<td>[32]</td>
</tr>
<tr>
<td>Ulnar peripheral nerve</td>
<td>–</td>
<td>0.5–0.6</td>
<td>8–21</td>
<td>[33]</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>0.089</td>
<td>–</td>
<td>–</td>
<td>[34]</td>
</tr>
<tr>
<td>Cortical bone</td>
<td>6000–30,000§</td>
<td>–</td>
<td>–</td>
<td>[35]</td>
</tr>
</tbody>
</table>

†In radial direction.
‡At high strain.
§Included for comparison purposes.
of cell function have been shown to be mediated by the stiffness of the cell culture substratum or matrix, examples are: cell spreading, proliferation, migration, the formation of focal adhesions, and protein expression. As recently reported, the stiffness of the matrix also regulates the differentiation of stem cells [22,23], as well as gene delivery to cells [24].

In engineering of soft tissues that are subject to cyclic mechanical stresses in vivo, such as cardiovascular tissues and cartilage, the mechanical properties of the scaffold should also provide sufficient mechanical support to protect the cells from detrimental tensile or compressive forces. The scaffold should also allow transmission of mechanical stimuli to and from the cells upon culturing the constructs in a bioreactor or upon implantation. In this respect, flexible polymers of low moduli with an elastic nature, such as hydrogels or elastomers, are the most suited materials for the engineering of soft tissues.

As mentioned above, an important aspect of scaffolds is their degradation and erosion behavior. Preferably, the degradation and erosion should take place on an appropriate time scale. The newly formed tissue should replace the eroding scaffold. Degradation and erosion rates can also influence cell spreading and proliferation, as well as protein expression. When cells are encapsulated in hydrogels, degradation leads to an increasing porosity, which facilitates the diffusion and deposition of molecules secreted by the cells [36]. While rapid erosion can promote tissue in growth, rapid release of degradation products can adversely affect the viability of cells and their function [36,37]. Moreover, the mechanical integrity of the construct might be lost too quickly, leading to failure of the tissue-engineered construct.

### Biodegradable elastomers

#### Elastomers

Materials that show high extensibility and essentially complete shape recoverability are called elastomers [38]. The terms rubber and rubber-like material are also used. As these materials have very good elastic properties, they are currently used in many applications. For a material to exhibit such elastic properties, three criteria must be fulfilled: the material must be constituted of long polymer chains (for extensibility), these chains must have a high degree of flexibility and mobility (low glass transition temperature for deformability), and they must be joined into a network structure (for recovery).

A hypothetical perfect network may be defined as one having no free chain ends, in which all the chains contribute to the elasticity of the network. However, upon crosslinking of a polymer, several imperfections can be incorporated into the network structure and elastically ineffective structures might be formed as shown in Figure 3. If a chain is connected to a junction point at only one end, this will result in a dangling chain. If both ends of a chain are attached to the same junction point, a loop is formed. Chain contaminations result, for example, from the reaction of initiator molecules with the chains. There might also be some chains that are not incorporated into the network (sol), but remain trapped inside the network structure. Only trapped entanglements are elastically effective.

#### Biodegradable elastomers

Biodegradable elastomers are gaining increasing interest in the biomedical field, especially for the preparation of flexible and elastomeric tissue-engineering scaffolds and depots for controlled drug delivery systems [39,40]. These elastomers can either be physically or chemically crosslinked systems.

#### Physically crosslinked biodegradable elastomers (thermoplastic elastomers)

Phase separation of a block copolymer into hard and soft domains on a micron scale can result in polymers having an elastomeric nature. While the soft domains provide flexibility to the material, the hard domains constitute the physical crosslinks. The advantage of thermoplastic elastomers is that they can be processed thermally. On the other hand, phase separation leads to heterogeneous degradation of implants prepared from these materials. This can potentially lead to failure of implants due to loss of mechanical integrity. Biodegradable thermoplastic elastomers based on several polymers have been investigated.

Segmented polyurethanes are thermoplastic elastomers that have been used in the preparation of implants for several decades [41]. The general structure of a polyurethane is shown in Figure 4. The biodegradation behavior and the physical properties of polyurethanes can be tailored by the choice of hard segments (diisocyanate and chain extender), soft polyol segments (hydroxyl-terminated low-molecular-weight polymer such as polyester, polyether or polycarbonate) and their weight ratio. Several chemical processes such as passive hydrolysis [42], enzymatic hydrolysis [43] and oxidative degradation [44] have been shown to be involved in the biodegradation of polyurethanes. Biodegradable polyurethane elastomers have been used for the preparation of scaffolds for soft tissue engineering [45]. As an example, aliphatic poly(ester urethane) s containing random 50/50 ε-caprolactone/ε-lactide copolymer segments, 1,4-butanediol and 1,4-butandiol isocyanate were used to prepare porous structures for meniscus reconstruction [46].
Poly(ether ester) block copolymers consist of a polyether soft segment and a polyester hard segment. Often-investigated poly(ether ester)s are block copolymers of poly(ethylene oxide) and poly(butyleneterephthalate). These poly(ether ester) elastomers have been used as antiadhesion barriers [47] in controlled release systems [48] and to prepare scaffolds for tissue engineering [49].

Copolymers containing lactide or glycolide hard segments and ε-caprolactone or trimethylene carbonate (TMC) soft segments also show elastomeric behavior [50]. The structure of a TMC–lactide copolymer is shown in Figure 5. Block copolymers composed of poly(TMTC) (PTMC) soft blocks and polyester rigid blocks are expected to have a microphase-separated morphology, allowing the preparation of thermoplastic elastomers. As an example, diblock and triblock copolymers composed of PGA segments and PTMC (inner) segments were synthesized via sequential polymerization of the monomers, yielding semi-crystalline, fiberforming materials. These block copolymers are used for the preparation of degradable sutures, commercialized under the trade name Maxon™ (Covidien, MA, USA).

Recently, thermoplastic elastomers were obtained by stereocomplexation of D-lactide- and L-lactide-based triblock copolymers containing PTMC as a soft segment [51]. Trimethylene carbonate and ε-caprolactone are used to obtain polymers of low glass transition temperature, which are thus flexible at physiological conditions. To make use of the elastic properties of these polymers, cells were cultured under mechanical stimulation in scaffolds prepared from lactide/caprolactone copolymers for the engineering of cartilage and blood vessels [52,53].

**Chemically crosslinked biodegradable elastomers**

Polyester elastomers prepared by polycondensation of polyols and multifunctional carboxylic acids are of interest for controlled release and tissue-engineering applications. Poly(polyol sebacate)s [54] and poly(polyol citrate)s [55] have been much investigated, as sebacic acid and citric acid are metabolic intermediates. Drawbacks of preparing elastomers by a polycondensation approach are the high temperatures and long reaction times required for curing. In vivo, networks of poly(polyol sebacate) show surface erosion and a favorable tissue response, although their relatively high erosion rate limits their use to short-term applications [56]. To slow down the erosion rate of these networks, amino alcohol-based poly(ester amide) networks have recently been developed [57]. The suitability of poly(polyol sebacate) elastomers has been assessed for several applications such as drug delivery [58], the engineering of cardiac muscle [59] and blood vessels [60], and as nerve guides [61]. Poly(polyol citrate)s have also demonstrated cell and tissue compatibility and have been used as scaffolding material in the tissue engineering of blood vessels [59].

Network formation by free radical polymerization is an often-used method to obtain biodegradable elastomers. Crosslinking of prepolymers that contain unsaturated groups can be achieved by either thermal- or photo-initiated polymerization reactions. Methacrylate-functionalized prepolymers based on D,L-lactide (DLLA), ε-caprolactone and TMC were thermally cured to obtain elastomeric networks [62]. Thermal initiation usually requires relatively high temperatures and long reaction times. In addition, the biocompatibility of the initiators used for this purpose such as benzoyl peroxide and 2,2´-azobis(2-methylpropionitrile) is a concern.

Photo-initiated crosslinking is more advantageous compared with thermal initiation. Relatively rapid and efficient crosslinking reactions at low temperatures reduce the risk of denaturation of biological compounds and allow the development of minimally
invasive injectable systems. This method has been widely used to prepare hydrogels [65], and recently also for the preparation of elastomers based on lactide, ε-caprolactone and TMC monomers [64,65]. To improve the processability, photocurable poly(glycerol sebacate) was developed [66]. These materials have found application as tissue adhesives [67] and in the engineering of cardiac muscle [68]. In the case of photo-induced crosslinking, the biocompatibility of the initiators is a concern as well, but some photo-initiators have been shown to be well-tolerated by a range of mammalian cells [69].

Some biodegradable polymers can be chemically crosslinked by e-beam irradiation [70]. As discussed below, γ-irradiation of PTMC results in crosslinked, flexible and elastic networks [71].

TMC-based elastomers
The first synthesis of PTMC by Carothers and van Natta dates back to 1930. PTMC is synthesized by ring-opening polymerization of the cyclic TMC monomer [72], as shown in Figure 6. This aliphatic polycarbonate with a glass transition temperature of approximately -17°C, is amorphous and flexible at physiological temperatures. Currently, TMC-based polymers are used for the preparation of biodegradable sutures (MaxonTM, BiosynTM, CaprosynTM; all Covidien), tissue-fixation devices (SuretacTM, EndostitchTM; both Smith & Nephew, MA, USA), meshes to repair hernia (Gore Bio-A®; WL Gore & Associates, AR, USA) and to prevent tissue adhesion (FlexiSurge®; Medisse, Ede, The Netherlands).

In vitro, the nonenzymatic hydrolysis of PTMC is very slow [76]. Even after 8 weeks of incubation in highly acidic (pH = 1) or highly basic (pH = 13) buffers, the molecular weight of PTMC remained unchanged and less than 2% mass loss was reported [73]. PTMC degrades in vivo at a much faster rate than that observed in vitro. The surface erosion rates of films and rods implanted subcutaneously in rats or in femur and tibia bones of rabbits were 11.0 and 7.7 μm/day, respectively [73,79]. The more rapid erosion in vivo, suggests that enzymes or other active species released by cells can be involved in the degradation of this polymer. We have shown that lipase from Thermomyces lanuginosus, as well as cholesterol esterase, effectively catalyze the hydrolysis of PTMC [73,74]. Upon degradation of PTMC, water soluble and nonacidic products such as 1,3-propanediol, TMC monomer, and oligomers with an average degree of polymerization of 2.9 were formed. It should be noted that PTMC oligomers with an average degree of polymerization lower than 3.7 are water soluble [73].

Initially, the mechanical strength of PTMC was considered to be too low for biomedical applications, and the TMC monomer was only used for copolymerization with lactides [50], glycolide [75] and ε-caprolactone [76]. PTMC was also used for blending with rigid PLA or PGA to tune their properties. However, our research group has shown that high-molecular-weight PTMC (Mn > 200 kg/mol) is a tough, flexible and elastomeric polymer with an elastic modulus of approximately 6 MPa [71].

The degradability of PTMC into nonacidic products by surface erosion and its flexible and elastomeric nature make TMC-based (co)polymers interesting for drug delivery and soft tissue-engineering applications [77,78]. Moreover, in vivo studies showed that PTMC and copolymers of TMC with DLLA or ε-caprolactone are biocompatible materials, inducing a mild tissue response upon subcutaneous implantation in rats [79,80]. These TMC-based polymers also allow adhesion and proliferation of mammalian cells including human Schwann cells, human umbilical vein endothelial cells and rat cardiomyocytes [78].

Linear PTMC and its amorphous copolymers with ε-caprolactone or DLLA of low glass transition temperatures are flexible materials. However, due to the lack of chemical crosslinks, even high-molecular-weight TMC (co)polymers have low form–stability and flow irreversibly as can be seen in Figure 7. It was observed that porous scaffolds prepared from these polymers shrink upon incubation in physiological buffers at 37°C [78]. This is undesirable, as it would decrease the size of the pores and reduce the porosity of the scaffolds. In addition, in drug delivery, changes in the surface area might lead to changes

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**Figure 5. Trimethylene carbonate–lactide block copolymer.**

PTMC: Trimethylene carbonate.

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**Figure 6. Ring-opening polymerization of trimethylene carbonate.**

PTMC: Poly(trimethylene carbonate); TMC: Trimethylene carbonate.
in drug-release rates, as these polymers show surface erosion behavior.

It was found that γ-irradiation under vacuum leads to crosslinking of high-molecular-weight PTMC and improves its creep resistance \[71\]. By means of a dip coating and salt leaching technique, porous tubular scaffolds for vascular tissue engineering were developed. After γ-irradiation, compliant and creep-resistant scaffolds were obtained, which were seeded with human smooth muscle cells. Subsequent culturing in a pulsatile flow bioreactor yielded constructs representing the medial layer of small-diameter arteries \[81\]. Creep-resistant TMC-based networks have also been prepared by photocrosslinking of methacrylate- or fumarate-end capped oligomers \[64\]. By means of the rapid prototyping technique stereolithography, designed tissue-engineering scaffolds can be built at high resolutions using methacrylate-functionalized PTMC macromers \[82\], as shown in Figure 8. These biocompatible, flexible and elastic scaffolds have well-defined pore architectures and porosities, and can be used for a wide variety of regenerative medicine applications including the preparation of vascular, cartilage and bone tissue.

### Effects of molecular weight & crosslink density on degradation/erosion of elastomers

The erosion rates of specimens prepared from linear PTMC increase with increasing PTMC molecular weight, both in vivo and in vitro in lipase solution (Thermomyces lanuginosus) \[73\]. This can be explained by an increase of hydrophobicity of the specimens.

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**Figure 7.** Effect of crosslinking on the form-stability of high-molecular-weight poly(trimethylene carbonate).
Specimens prepared from the linear polymer (left) and poly(trimethylene carbonate) specimens crosslinked by γ-irradiation (right), which initially were disk-shaped with a diameter of 10 mm, were incubated in phosphate-buffered saline (pH = 7.4) for 1 week.

**Figure 8.** Poly(trimethylene carbonate) scaffold with a gyroid pore architecture built by stereolithography. (A) Photographic image and (B) scanning electron microscopic image.
Reproduced with permission from \[82\].
with increasing PTMC molecular weight, resulting in an increase of activity of enzyme molecules adsorbed onto the surface of the samples.

Crosslinking of PTMC specimens by $\gamma$-irradiation results in a decrease of mass loss, both in vivo and in vitro in lipase solution. The rate of mass loss decreases with increasing crosslink density [83,84]. This can be explained in terms of a (more) hindered chain mobility due to (denser) network formation. The same effect of crosslink density on the rate of mass loss has been reported for poly(diol citrate) samples in vitro in phosphate-buffered saline solution [55] and for poly(glycerol sebacate) specimens in vivo, although the latter effect was limited [56]. The decrease of in vivo mass loss by $\gamma$-irradiation of PTMC is also limited, which can be overcome by adding pentaerythritol triacrylate as a crosslinking aid [85,86].

Textile-based & electrospun structures

Using textile-based technologies, nonwoven, woven and knitted structures have been prepared for biomedical applications [87–90]. These structures show elastic behavior since they are composed of networks, not at the molecular level but at the scale of fibers. As these textile-based structures are porous, they allow the seeding of cells for tissue-engineering applications. Electrospinning is an alternative technique to prepare nonwoven fiber structures [91,92]. As compared with the textile-based structures, fabrics prepared by electrospinning contain fibers with a smaller diameter (in the micron to submicron range) allowing better mimicking of the ECM. Polymers used to prepare textile-based and electrospun structures can either be nonelastomeric, elastomeric or of biological origin. A novel way of electrospinning is cell electrospinning, in which the polymer solution to spin the fibers contains living cells, enabling scaffold preparation and cell seeding in a single step [93,94]. This technique facilitates homogeneous cell seeding and reduces the preparation time of a construct.

Shape-memory properties of biodegradable elastomeric networks

In addition to excellent biocompatibility and mechanical properties comparable with those of soft tissues, biodegradable elastomers may have shape-memory properties, which are also very useful for biomedical applications. Shape-memory polymers can be fixed in a temporary shape and return to their permanent shape after application of an appropriate stimulus, which is in most cases heat. In addition, light has been reported as a stimulus, as well as indirect

Figure 9. Spiral-shaped device with shape-memory properties prepared from a copolymer network of 60% $\alpha\beta$-lactide and 40% trimethylene carbonate. (A) Permanent shape, (B) temporary shape at 0°C, (C) transient shape at 37°C and (D) final permanent shape at 37°C. Reproduced with permission from [97].
Various methods can be used to prepare porous scaffolds from biodegradable elastomers for the engineering of soft tissues, such as polymer casting/salt leaching, stereolithography and electrospinning, as well as textile-based technologies. A novel application of biodegradable elastomers is the preparation of devices with shape-memory properties, such as closure devices and stents.

Biodegradable elastomers are suitable polymers for the preparation of scaffolds for soft tissue engineering. Degrading of these polymers can take place by bulk or surface erosion, of which the latter mechanism has a number of advantages such as better preservation of the structural integrity and mechanical properties of the scaffolds after implantation. Moreover, the predictability of the surface erosion process is advantageous for drug-delivery applications, allowing sequential and zero-order release of bioactive compounds.

Elastomers are either physically or chemically cross-linked systems, of which the latter have the advantage that degradation is homogeneous. Photo-initiated crosslinking of functionalized macromers is a suitable technique to prepare elastomeric networks, since relatively rapid crosslinking takes place at low temperatures. In this way, networks have been prepared based on lactic acid, sebacic acid, ε-caprolactone and TMC monomers. A special form of photo-crosslinking is stereolithography, allowing the preparation of designed scaffolds at high resolutions with full control of the pore architecture. By tuning of the pore architecture, mechanical properties and degradation rates, scaffolds can be prepared for various tissue-engineering applications. In the near future, stereolithography will also allow the incorporation of biologically active functional groups or compounds in the structures (e.g., cell adhesion sequences, adhesive proteins or growth factors).

Conclusion & future perspective

Biodegradable elastomers are suitable polymers for the preparation of scaffolds for soft tissue engineering. Degradation of these polymers can take place by bulk or surface erosion, of which the latter mechanism has a number of advantages such as better preservation of the structural integrity and mechanical properties of the scaffolds after implantation. Moreover, the predictability of the surface erosion process is advantageous for drug-delivery applications, allowing sequential and zero-order release of bioactive compounds.

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which will further enhance or direct regeneration of a specific tissue. Moreover, the development of novel biomedical devices with shape-memory properties will be an important future application of biodegradable elastomers.

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References
Papers of special note have been highlighted as:
• of interest; •• of considerable interest

•• Provides a good overview of degradable polymers for tissue-engineering applications.
•• Excellently describes the foreign body reaction to biomaterials implanted in the body.
• Describes the importance of the extracellular matrix in tissue engineering.
• Provides an overview of techniques to fabricate polymer scaffolds for tissue engineering.
Review

Bat, Zhang, Feijen, Grijpma & Poot

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Features the applications of biodegradable elastomers in regenerative medicine.

** Features the applications of biodegradable elastomers in regenerative medicine.
Biodegradable elastomers for biomedical applications & regenerative medicine


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