



**Biodegradable
Polymers:**
Recent Developments
and New Perspectives

Edited by
Geraldine Rohman



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Geraldine Rohman

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EDITORIAL FOREWORD

Due to their various qualities, such as lightness, chemical and microbial stability, non-degradable polymeric materials are routinely used in a wide range of applications in everyday life. However, due to the growing concern for environmental and waste management issues, bio-based and biodegradable polymers have recently raised great interest. Produced from renewable or petroleum resources, these polymers are hydrolytically or enzymatically degraded. As a consequence, they have numerous advantages, so that they find applications in packaging and biomedical field, such as drug delivery, tissue engineering and as temporary implants. Nevertheless, their main drawbacks are a higher cost in comparison with commodity polymers, and inferior properties. Therefore, researches on bio-based and biodegradable polymers must be continued in order to improve their performances and penetrate new markets.

The aim of this book is to address advances in the field and proposes alternative ways for polymer degradation. Some chapters are dedicated to the synthesis of innovative biodegradable and bio-based polymers, while others focus on their properties improvement. Some examples of biopolymer expectations in biomedical or food applications are also discussed. Finally, biodegradability potential of vinyl polymers is approached.

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Géraldine Rohman received her Ph.D. in Chemistry and Materials Science in 2005 from University Paris 12 under the supervision of Pr. P. Guerin and Dr. D. Grande. Her work concerned “Mesoporous polymeric materials: a new elaboration process from semi-interpenetrating and interpenetrating polymer networks partially hydrolysable”. Then she did her post-doctoral training with Pr. N. Cameron at Durham University where she developed scaffolds for tissue engineering. In 2008, she worked as laboratory engineer at INRA on the modification of polymer films for food packaging applications. Since 2009, she is associate professor in chemistry and polymer materials at University Paris 13. Her research topics are currently the grafting of bioactive polymers in order to improve the biological response of biomaterials, and the elaboration of porous scaffolds from biodegradable or non biodegradable polymers.

**SYNTHESIS AND STRUCTURE-PROPERTY
RELATIONSHIPS OF BIODEGRADABLE
POLYURETHANES**

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5.1. INTRODUCTION

This chapter deals with a commercially very important part of the polyurethane (PU) polymer family, biodegradable polyurethanes (BioPUs). PUs are multiblock copolymers composed of a high molecular weight macrodiol, called a soft segment, and a hard segment composed of a diisocyanate and a low molecular weight diol. As a result of the thermodynamic incompatibility of the hard and soft segments in PU copolymers the phenomenon of microphase separation occurs. Nowadays, it is generally accepted that the overall properties, as well as the biocompatibility, of segmented PU and poly(urethane urea) (PUU) copolymers are correlated to the degree of microphase separation [1,2]. The thermoplastic and elastic behaviour of these copolymers can be explained by their multiphase structure. The elastomeric properties of these copolymers are generally attributed to the phase separation of the hard and soft segments; the hard domains serve as crosslinks and reinforcing fillers in the matrix of the soft segment. It is generally assumed that the soft phase is responsible for the reversible elasticity of the polymeric material, whereas the hard phase is responsible for the mechanical strength properties.

As expected, the properties of the final PU product and, consequently, its application, depend on the chemical structure and composition of the copolymer [3,4]. This means that the nature and properties of the soft and hard segments, which can differ greatly in their chemical structure and polarity, have a crucial role in determining the nature and properties of PUs but, on the other hand, also provide opportunities for the design of polymers with the desired properties [2]. Due to their good mechanical properties and biocompatibility, PUs have been widely used in the biomedical area, mainly as biostable materials such as heart valves, *intra*-aortic balloons, aortic grafts, catheters, pacing lead insulation, *etc.* [5-9]. Boretos and Pierce [10] first suggested the use of PUs for biomedical applications such as the elastomeric components of a cardiac assist pump and its arterial cannulas in 1967. Avco-Everett Research Laboratory (Everett, U.S.) and Ethicon Corp. (Somerville, U.S.) commercialized the first official PUs for biomedical application, Avcothane™ (1971) and Biomer™ (1972), respectively [11]. Avcothane™ was a PU/siloxane hybrid, while Biomer™ was a version of Lycra® T-126. Both of them were synthesized in solution and fabricated from solution, *e.g.* by dipping, spraying or casting, and were not extrudable or mouldable. Avcothane™ was used as an *intra*-aortic balloon pump and today is on the market under the trademark Cardiothane-51® (Arrow International, Reading, U.S.). Biomer™ was used in the Jarvik Heart and, as the first artificial heart, it was implanted in 1982. Avcothane™ and Biomer™ are characterized by many desirable properties, including good thromboresistance, biostability and flex life, needed to make cardiac assist devices safe and efficacious. The first medical grade thermoplastic polyether-urethane was commercialized in 1977 (Upjohn

Chemical, North Haven, U.S.) under the trademark Pellethane™, and it was used as the catheter for the Avco™ *intra*-aortic balloon pump [12]. Furthermore, due to their good flex life in flowing blood, thermoplastic PUs based on poly(tetramethylene oxide) (PTMO) are used as soft segments in long-term implantation of blood pumps and prostheses.

In the 1990s the interest of scientists shifted from biostability towards the development of biodegradable PUs; biodegradability has become a key issue for novel biomedical applications, ranging from medical device coatings to drug delivery and even tissue engineering. For example, biodegradable elastomeric scaffolds enable the construction or modelling of several soft tissues that include blood vessels, cartilage, smooth muscle cells and cardiovascular tissue [13,14]. Besides that, different implantable devices such as stents, sutures and biosensors can contain biodegradable elastomer parts integrated within their design [15-17]. Actifit™ is a segmented aliphatic PU based on poly(ϵ -caprolactone) (PCL), and 1,4-butane diisocyanate (BDI), which has recently arrived on the market. This arthroscopically implanted PU scaffold provides a temporary structure that supports the ingrowth of new tissue to replace the surgically removed damaged meniscal tissue. Here it should be noted that several reactants commonly used in PU formulations such as, for example, 4,4'-diisocyanatodiphenylmethane (MDI) or 3,3'-dichloro-4,4'-diaminodiphenylmethane (MOCA or MBOCA), degrade to toxic products and therefore have to be excluded from the synthesis of BioPUs. The choice of reactants in order to obtain polymers with non-toxic degradation products, which will give a medical implant with good mechanical properties, is the main challenge of the production of novel BioPUs [18-20]. The development of properly biodegradable PU materials with appropriate mechanical and target functional properties (*e.g.* non-toxicity, good biocompatibility, tailored degradation rate from weeks to years) is a focal point of biomedical science, especially in the last decade. In this chapter, recent developments in the synthesis, properties and applications of BioPUs, porous BioPUs and their nanocomposites are presented. Future trends in BioPU development are also addressed.

5.2. SYNTHESIS OF BioPUs

Biodegradability as the key feature of novel biomedical PUs can be achieved by incorporating labile and hydrolysable moieties into the polymer backbones [21-23], usually in macrodiol soft segments such as hydroxyl-terminated oligomers of PCL and polylactides [24-26]. Besides that, it is possible to create BioPUs from biodegradable hard segments by using non-toxic chain extenders and aliphatic diisocyanates [27]. However, regardless of specific requirements in the choice of starting material, the chemistry of BioPU preparation is very similar to that of other PU copolymers.

The basic chemical reaction for the synthesis of PUs is the reaction between a diisocyanate and a difunctional alcohol in which a urethane group is formed. This reaction is a so-called polyaddition reaction which does not generate by-products. The reaction is extremely exothermic ($170\text{--}190\text{ kJ mol}^{-1}$) [28], and it is affected by the structure of both reactants. The third component of PU formulation, the low molecular weight diol, is a so-called chain extender. Besides that, when diamines are used as the chain extender in the chain extension step rather than diols, a urea bond is formed, and the resulting PUU copolymers contain both urethane and urea bonds.

Depending on the order of addition of reactants to the reaction mixture, polyaddition can be performed in one or in two stages. In single-stage synthesis, all reactants are added simultaneously at the start of the reaction and then the reaction mixture is heated. The single-stage preparation of PUs, as the conventional industrial process, is quick and easy to perform, but this method does not allow control of the reaction in terms of obtaining a regular sequence of hard and soft segments. This disadvantage of the single-stage synthesis can be overcome by performing the two-stage procedure which involves the synthesis of a prepolymer with terminal NCO groups. The prepolymer is obtained in the form of a viscous liquid or solid with a low melting temperature, by reacting macrodiol with an excess of diisocyanate. In the second reaction step, the prepolymer reacts with a chain extender to form a sequence of hard segments, and the overall molecular weight of the polymer increases. The prepolymer molar mass depends on the molecular weight of the macrodiol and the molar ratio of the starting compounds, and is generally in the range of $1000\text{--}5000\text{ g mol}^{-1}$, and it can be easily stored, which is advantageous for industrial purposes [2].

In the synthesis of PUs, there are several important factors: the type of reactants, monomer concentration, reaction time and temperature, as well as the molar ratio of the reacting groups. Figure 1 shows the synthesis of PU and PUU by the two-stage polyaddition procedure.

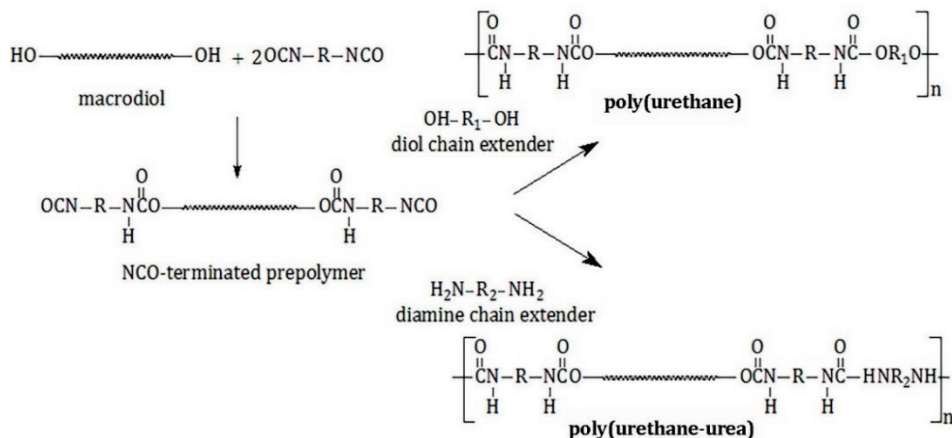


Figure 1. The synthesis of PU and PUU by the two-stage polyaddition reaction

The polyaddition reaction takes place in the presence of catalysts such as tertiary amines and organometallic compounds of tin, lead and iron; dibutyltin dilaurate (DBTDL), and tin(II) octoate [Sn(Oct)₂], are commonly used. These compounds act as Lewis acids which, according to the proposed mechanism, in the first stage of the reaction, form the complex intermediate of an isocyanate and a hydroxyl group [28]. The complex formation increases the acidity of the carbon atom of the NCO group, making it more reactive towards the hydroxyl oxygen of the macrodiol.

Methods for the synthesis of segmented PUs also differ in the type of reaction medium. The polyaddition reaction can be carried out in a melt, in a solution of organic solvent or in aqueous solution. Melt polymerization is the main industrial process for the preparation of various commercial PUs, as it reduces production costs and avoids the pollution of large amounts of organic solvents, while polymerization in solution is the most common method in laboratory synthesis of PUs. During polymerization in a melt, the incompatibility of the reactants leads to the formation of a heterogeneous reaction system relatively quickly after the start of the reaction. The composition of the final product is primarily controlled by the rate of diffusion of the reactants from one phase to another, and then by the rate constant for the reaction between the different functional groups. The problem of heterogeneity in the reaction mixture can be avoided by choosing an appropriate solvent, which is critical to promote solubilization and to prevent premature precipitation of the growing polymer chains, thus ensuring copolymers of high molecular weight. Generally, synthesis carried out in solution is accompanied by fewer side reactions than melt synthesis. Side reactions include, for example, the formation of allophanate and biuret linkages, which leads to branching of macromolecular chains and increased molecular weight of the product [2]. For the synthesis of segmented PUs, polar aprotic solvents such as *N,N*-dimethylacetamide (DMAc),

N,N-dimethylformamide (DMF) and *N*-methyl-2-pyrrolidone (NMP) are commonly used. In the case when the soft and hard segments have extremely different solubility parameters, it is necessary to use a mixture of solvents that have different polarity [29]. Recently, segmented poly(dimethylsiloxane)-based PUU copolymers have been synthesized by the two-step solution polymerization procedure in a tetrahydrofuran/NMP mixture with a large proportion of polar NMP solvent, which provides good solubility of the growing chains, thus ensuring copolymers of relatively high molecular weight [30]. Also, the use of isopropanol (IPA) as a solvent for the synthesis of polyurea copolymers with a high hard segment content has been reported [29,31].

5.3. STRUCTURE–PROPERTY RELATIONSHIPS IN BioPUs

5.3.1. Soft segments

BioPUs are generally built of biodegradable polyester or polyether soft segments, such as PCL, poly(D,L-lactide), polyglycolide, poly(ethylene oxide) (PEO) and PTMO. The ester-containing polymers and, in particular aliphatic polyesters, appear the most attractive because of their variable biodegradability and versatile physical, chemical and biological properties. Besides that, PU and PUU copolymers with poly(dimethylsiloxane) (PDMS) as the soft segment play a very important role in special technical and medical applications because of the many unique properties of PDMS, including a low glass transition temperature, low surface energy, high permeability to many gases, biocompatibility and thermal stability [32]. A large number of studied BioPUs contain PDMS mainly in mixtures with aliphatic polyethers or polyesters as co-soft segments [33].

5.3.1.1. Polyester soft segments

5.3.1.1.1. Polylactide- and glycolide-based BioPUs

Among the aliphatic polyester family, polymers derived from lactic acid enantiomers and glycolic acid have been widely investigated for biomedical applications. Poly(lactide-*co*-glycolide) matrices are often used as construct materials and tissue scaffolds. They can be custom-synthesized to meet the absorption time requirement, and they are also clinically familiar. There are several methods of processing these porous, synthetic matrices. The most common method is solution casting or particle leaching as developed by Mikos *et al.* [34] which will be discussed later in detail. High weight polylactide (PLA) and polyglycolide (PGA) are obtained by ring-opening polymerization (ROP) of cyclic diesters, *i.e.* L-lactide, D-lactide, D,L-lactide and glycolide [35]. In the case of lactide-containing polymer chains, the chirality of the polymer units

provides a worthwhile means of adjusting bioresorption rates as well as physical and mechanical characteristics [36].

The standard catalyst utilized for BioPUs based on lactide polymerization is $\text{Sn}(\text{Oct})_2$ [37-40] with lauryl alcohol (1-dodecanol) which is usually added as a real initiator. The most important characteristic of $\text{Sn}(\text{Oct})_2$ is that this catalyst is considered to be biologically safe [41]. $\text{Sn}(\text{Oct})_2$ has many advantages over other catalysts in that it is highly soluble in organic solvents and molten lactide in the bulk state and very stable in storage. With these characteristics, $\text{Sn}(\text{Oct})_2$ has been used as the catalyst in the industrial production of PLA. It also shows excellent catalytic activity to give high molecular weight poly(L-lactide) (PLLA) [42]. The mechanism of this tin-catalysed polymerization of lactide has been the subject of discussion for a long time. In the so-called 'insertion-coordination mechanism', a hydroxyl compound (alcohol) is added as the real initiator. The alcohol initiator first reacts with $\text{Sn}(\text{Oct})_2$ to generate a tin alkoxide bond by ligand exchange and then one of the exocyclic carbonyl oxygen atoms of the lactide temporarily coordinates with the tin atom of the catalyst having the alkoxide form. This coordination enhances the nucleophilicity of the alkoxide part of the initiator as well as the electrophilicity of the lactide carbonyl group. In the next step, the acyl-oxygen bond (between the carbonyl group and the endocyclic oxygen) of the lactide is broken, making the lactide chain open to insert into the tin-oxygen bond (alkoxide) of the catalyst. The following propagation is induced by an identical mechanism and continues as additional lactide molecules are inserted into the tin-oxygen bond [43-46]. The insertion-coordination mechanism of lactide polymerization is supported by a Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) mass spectrum showing molecular peaks that correspond to the oligomeric PLLA chains connecting with tin residues, which are propagating species formed with the $\text{Sn}(\text{Oct})_2$ /lauryl alcohol system [39,47].

PLLA has high mechanical strength, easy processability and a high melting temperature, with an equilibrium melting point of 207 °C and a glass transition temperature of about 60 °C [48-50]. A stereocomplex with a higher melting point comprised of a 1 : 1 mixture of PLLA and poly(D-lactide) is also known [51-54]. Introducing stereochemical defects into PLLA (*e.g.* by incorporating controlled amounts of *meso*-lactide or D-lactide) reduces the melting point, the rate of crystallization and the extent of crystallization with minimal effect on the glass transition temperature [55]. PLA resins containing more than 93 % L-lactic acid are semi-crystalline while PLA with 50–93 % L-lactic acid is amorphous [55]. The presence of either *meso*- or D-lactide units in PLLA leads to imperfections in the crystalline structure, thus reducing the crystallinity percentage. Solubility experiments on P(L,D)LA copolymers with different D to L ratios indicate that copolymers with a close to 50/50 L/D structure show improved solubility. Also, it has been shown that the phase separation of this

P(L,D)LA stereocopolymer is generated most easily from an *n*-hexane solution [56].

Recently, binary and ternary segmented PUs based on low molar mass homopolymers – PEO, PLLA, poly(trimethylene carbonate) (PTMC) and 2,4-toluene diisocyanate (TDI) – have been synthesized using 1,4-butanediol (1,4-BD) and DBTDL as the chain extender and catalyst, respectively. The blocks were randomly distributed in the polymer chains, which resulted in suppression of the crystallization of the blocks in most of the PUs. The intrinsic properties of each block, such as the hydrophilicity of PEO, stiffness of PLLA and elasticity of PTMC, are combined and modulated in the PUs. PTMC confers unique properties to ternary PUs owing to its partial miscibility with both PEO and PLLA [57].

Also, crosslinked PU networks have been prepared by reacting hydroxy-telechelic prepolymers with tolylene diisocyanate. Several trifunctional, hydroxy-telechelic polyester and poly(ester carbonate) homopolymers and copolymers were synthesized by the triol-initiated, bulk ROP of D,L-lactide, glycolide, ϵ -caprolactone, and/or trimethylene carbonate. The poly(D,L-lactide) and poly(D,L-lactide-*co*-trimethylene carbonate) (PLTMC) networks had the highest tensile strengths of 49.60 and 41.27 MPa, respectively, and glass transition temperatures of 51.3 and 21.3 °C, respectively. All other networks were highly flexible with tensile strengths of 12 MPa or less. Tensile properties, monitored as a function of degradation time, indicated that the poly(ϵ -caprolactone-*co*-D,L-lactide) and PLTMC networks displayed a linear loss of strength with respect to weight during the first 30 days of degradation, while the other networks degraded either too slowly or too quickly to establish such a linear relationship [58].

A series of biodegradable polylactide-based polyurethanes (PLAUs) was synthesized using PLA diol ($M_n=3200$) as the soft segment, MDI, TDI and isophorone diisocyanate (IPDI) as the hard segment and 1,4-BD as the chain extender. Among them, the MDI-based PLAUs has the highest glass transition temperature, T_g , maximum tensile strength and restoration force, the TDI-based PLAUs has the lowest T_g and the IPDI-based PLAUs has the highest tensile modulus and elongation at break. They are all amorphous polymers. The shape recovery of the three PLAUs is almost complete in a tensile elongation of 150 % or a two-fold compression. They can keep their temporary shape easily at room temperature (20 °C). More importantly, they can deform and recover at a temperature below their T_g values, which means that they can meet different practical demands for shape-memory medical devices by selecting the appropriate hard segment and adjusting the ratio of hard to soft segments [59].

Recently, Fabbri *et al.* [60] synthesized novel, fully bio-based PLA triblock copoly(ester urethane)s with a controlled molecular architecture by a new solvent-free process which involves coupling ROP with a chain extension reaction. A series of A-B-A triblock copolymers were produced, where the hard

block A is PLA and the soft block B is an *ad hoc*-designed random aliphatic copolyester, poly(butylene succinate/azelate), with high flexibility in the presence of hexamethylene diisocyanate (HDI) as a chain extender. The synthetic approach used to prepare the polymers under investigation allows the typical problems of copolymerization, including a substantial decrease of the melting temperature when significant amounts of comonomeric units are introduced along the homopolymer backbone, to be overcome.

Hsu and Chen [61] prepared lactide-grafted PUs by exposing the PU films to argon plasma discharge, then grafting L-lactide onto the treated surface. The water contact angle of these PUs was decreased by L-lactide grafting, indicating the hydrophilicity of the modified surface. Grafting also increased the O/C atomic ratio and $C_{C=O}/C_{total}$ percentage on the surfaces as detected by electron spectroscopy for chemical analysis (ESCA). The grafted surfaces showed enhanced attachment and growth in both 3T3 fibroblast and human umbilical vein endothelial cell culture tests.

PLLA is a truly bio-based polymer derived from annually renewable resources and due to this, together with the excellent properties noted above, PLLA is regarded as one of the most promising biodegradable polymers [62]. However, the further application of PLLA as a substitute for commodity plastics such as polyethylene or polypropylene is significantly restricted by its inherent brittleness, as evidenced by the limited elongation at break and low impact strength. Considerable efforts have been made to improve the fracture toughness of PLLA, such as the addition of plasticizers, nanoparticles or flexible polymers into the PLLA matrix, or increasing the degree of crystallinity of PLLA [63].

The excellent properties do not change since the chemical structure of PLLA is kept during physical blending. A lot of flexible polymers, both biodegradable and non-biodegradable, have been blended with PLLA to improve its toughness. A novel way of tailoring the physical properties of super-tough PLLA/crosslinked polyurethane (CPU) blends is through adjusting the crosslinking density of *in situ*-formed CPU. The crosslinking density of CPU can be controlled by the feeding content of the trifunctional monomer glycerol, which in turn affects the phase morphology of PLLA/CPU blends, and thus the physical properties, especially the impact toughness, can be well tuned. PLLA/CPU blends with a CPU phase dispersed in the PLLA matrix were prepared by reactive blending of PLLA with PEO, glycerol and MDI. The gel fraction increased while the swelling ratio decreased with increasing glycerol content. Fourier transform infrared (FTIR) analysis suggests that interfacial compatibilization between PLLA and CPU occurs *via* reaction between the hydroxyl group of PLLA and the isocyanate group of MDI. The elongation at break and notched impact strength of PLLA/CPU blends were increased by up to 38 and 21 times those of neat PLLA [64].

Also, introducing flexible polymers into PLLA is considered as the most efficient way to enhance the fracture toughness of PLLA [65]. Many studies have been carried out to improve the compatibility between PLLA and a flexible polymer. Recently, Shi *et al.* [66] reported on the structure and morphology of ternary nanocomposites composed of a poly(L-lactide)/thermoplastic polyurethane (PLLA/TPU) blend and carbon nanotubes (CNTs). The results showed that CNTs selectively localize in the TPU phase, leading to a morphological change from sea-island morphology to quasi-cocontinuous morphology. The high CNT content induces the formation of a percolated network structure. Consequently, super-toughened PLLA/TPU/CNT nanocomposites were prepared successfully. More apparent cavitation of the TPU phase and intensified local plastic deformation of the PLLA matrix under the impact load were observed on the impact-fractured surface of the ternary nanocomposites. These are believed to be the main toughening mechanisms for the ternary nanocomposites. After being annealed, besides the morphological change of the nanocomposites, the PLLA matrix also exhibited a large number of crystalline structures. Furthermore, the impact toughness of the ternary nanocomposites was enhanced further. The same group of authors reported the introduction of dicumyl peroxide (DCP) into commercial TPU-toughened PLLA blends. The results showed that the presence of DCP at a relatively high concentration (0.2–0.5 wt. %) not only results in the homogeneous distribution of TPU particles with largely decreased particle size but also improves the interfacial interaction between PLLA and TPU components. Consequently, super-toughened PLLA/TPU blends with greatly enhanced impact strength have been obtained successfully [67].

Recently, biodegradable CPU has been synthesized using PEO, L-lactide and HDI, with iron acetylacetonate as the catalyst and PEO as the extender. The synthesized CPU possesses good flexibility with a quite low glass transition temperature ($T_g = -22^\circ\text{C}$) and good wettability. Water uptake has been measured as high as $229.7 \pm 18.7\%$. These properties make CPU a good candidate material for engineering soft tissues such as the hypopharynx. *In vitro* and *in vivo* tests show that CPU has the ability to support the growth of human hypopharyngeal fibroblasts, and angiogenesis has been observed around CPU after subcutaneous implantation in Sprague Dawley (SD) male rats [68].

5.3.1.1.2. Poly(ϵ -caprolactone)-based BioPUs

PCL is another biodegradable polyester that has been extensively investigated with great potential in biomedical applications, having an estimated life-time of more than two years. Hydrolysis of the ester bonds in PCL occurs at low rates, particularly in pH values around neutral [69]. For PCL polymers with relatively low molar mass, higher rates of hydrolysis are observed, under both basic and acidic conditions [70]. PCL was first synthesized by Carothers by ROP of ϵ -caprolactone. The high molecular weight polymer is a strong, ductile

polymer with excellent mechanical characteristics. It is a hydrophobic and semi-crystalline polymer with a melting point of 59–64 °C and glass transition temperature of –60 °C. At room temperature, PCL is in a rubbery state and has a relatively low tensile strength (23 MPa) but very high ultimate elongation (> 700 %). PCL has the unique characteristic of being miscible with almost all other polymers (polyethylene, polypropylene, polystyrene, poly(methyl methacrylate), polycarbonates, polysulfone, poly(vinyl acetate), *etc.*). High molecular weight PCL is usually used as an additive to other polymers to obtain special effects, but it is also used as the major ingredient in many formulations.

PUs that contain PCL as soft segments commonly present low rates of hydrolysis at neutral pH. These rates are affected by the degree of crystallinity, the molar mass of the PCL segment and the presence of enzymes [71,72]. Linear triblock copolymers, PLLA-*b*-PCL-*b*-PLLA, have been synthesized *via* ROP of L-lactide with three different PCL diols, varying the molecular weight of the blocks as well as the relative content of each block. Poly(ester urethane)s have been synthesized by chain extension of these triblock copolymers using HDI. Differential scanning calorimetry (DSC) and small-angle X-ray scattering (SAXS) experiments have shown that in triblock copolymers the crystallinity of the PCL is strongly influenced by the presence and nature of PLLA. In particular, the presence of PLLA crystals is related to a reduction of the crystal size as well as the degree of crystallinity of the PCL blocks. Poly(ester urethane)s show a lower degree of crystallinity of both blocks than the initial triblock precursors due to the restrictions imposed by the multiblock segmented structure of the final poly(ester urethane). Moreover, the shift in the T_m values of both crystalline blocks towards closer values in the poly(ester urethane)s can be attributed to the higher miscibility of the blocks in the PU with respect to the triblock copolymer [73]. BioPUs and PUUs based on PCL and BDI have proved to be biocompatible *in vivo* and to have appropriate mechanical properties [74]. Skarja and Woodhouse [18,75,76] have developed biodegradable segmented PUs based on PCL or PEO macrodiol as the soft segment, with hard segments based on a phenylalanine diester chain extender and L-lysine diisocyanate (LDI). The results of the characterization show that the degradation rate and mechanical properties of these materials can be optimized by blending PCL- and PEO-based PUs. The overall properties of PCL-based PUs are affected by the crystallinity of the soft segment, where the soft segment crystal structure may act as reinforcing filler, which results in increased ultimate tensile strength, initial modulus and strain at break.

Kultys *et al.* [77] synthesized three series of thermoplastic PUs with hard segment content ranging from 20–60 wt. %, using PTMO, PCL or polycarbonate (PC) macrodiols ($M_n = 2000 \text{ g mol}^{-1}$) as the soft segments. The copolymers based on PTMO and PCL exhibited higher tensile strength (20.9–42.6 MPa) compared to the analogous copolymers of the PC series (5.6–29.9 MPa) at similar elongation at break (350–750 %). The copolymers of the PC series

showed generally higher hardness and modulus of elasticity. Moreover, for the PTMO and PCL series, decreasing the soft segment content caused a slight deterioration in thermal stability. In each series of copolymers, decreased soft segment content resulted in increased glass transition temperature, tensile strength, modulus of elasticity and hardness, as well as in decreased elongation at break. The PTMO- and PCL-based copolymers showed tensile strength similar to commercial PTMO-MDI-*s*-BD PUs, *i.e.* Pellethane™ 2103-70A and 85A.

However, PC-based copolymers show poorer tensile strength in comparison with commercial MDI-1,4-BD-based PUs containing poly(hexane-1,6-diethylene carbonate) diol as the soft segment, *i.e.* Bionate® and ChronoFlex®.

Biodegradable and cell-compatible PUU elastomers with variable mechanical properties and great potential for soft tissue scaffold development have been synthesized by choosing soft segments (SS) of different chemical structure and molecular weight (M_n). Three different macrodiols (PCL, PTMC or poly(δ -valerolactone-*co*- ϵ -caprolactone), PVLCL) were reacted with BDI using putrescine as the chain extender by a two-step method, with a macrodiol/BDI/putrescine molar ratio of 1 : 2 : 1. PUUs with non-crystalline PTMC or PVLCL macrodiols showed improved elasticity and resilience compared to PUUs with crystalline PCL SS. Figure 2 shows representative stress–strain curves of the PUUs where it can be seen that the polymer tensile strengths range from 30 to 60 MPa and elongations at break from 800 % to 1300 %. Varying the PUU SS impacted the mechanical properties in terms of initial modulus and permanent deformation. PUUs with crystalline PCL SS had much higher permanent deformation than those with non-crystalline SS of PTMC or PVLCL. Initial moduli were mainly dependent on SS molecular weight, with higher SS associated with a lower initial modulus [78]. PUUs with non-crystalline SS all showed improved elasticity and resilience relative to crystalline PCL-based PUUs, especially for PUUs with high molecular weight SS (PTMC, $M_n = 5400 \text{ g mol}^{-1}$ and PVLCL, $M_n = 6000 \text{ g mol}^{-1}$), of which the permanent deformation after tensile failure was only $12 \pm 7 \%$ and $39 \pm 4 \%$, respectively. The SS molecular weight also influenced the tensile modulus in an inverse fashion.

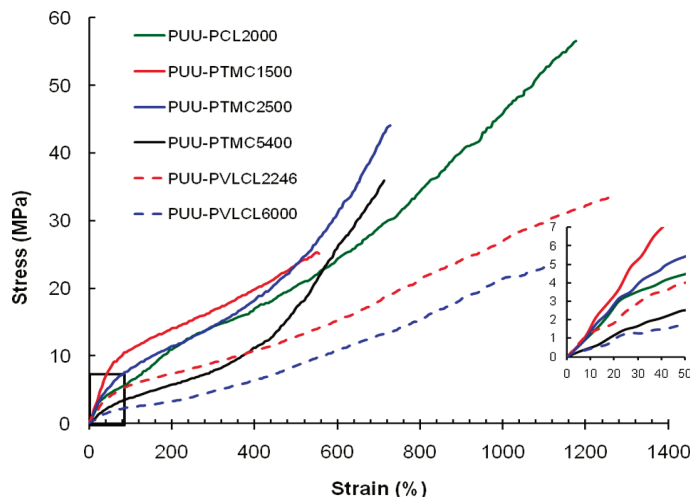


Figure 2. Tensile response curves of BioPUUs based on PCL, PTMC or PVLCL macrodiols, BDI and putrescine chain extender at a molar ratio of 1 : 2 : 1, respectively [78]

PCL has a melting temperature, T_m , of $\sim 55^\circ\text{C}$. However, PUs and PUUs based on PCL segments have T_m values that are lower by $30\text{--}40^\circ\text{C}$ due to the hindrance effects of the physical crosslinking in the hard domain on the crystallization of PCL SS [79,80]. Figure 3 shows DSC thermograms of PUUs based on PCL, PTMC or PVLCL macrodiols. DSC analysis showed that the T_m value of PUU-PCL2000 was 31°C , which means that this sample still exhibited semi-crystalline behaviour at body temperature (37°C). The crystallinity and T_m of PUU-PCL2000 was greatly affected by the deformation history of the sample (Figure 3b). For the sample stretched with a permanent set of 677%, the stretching gave rise to higher crystallinity and a sharper T_m peak (50°C) than the original sample, whereas after the crystals were melted and the sample was cooled under no stress, the T_m returned to 31°C . Because the PUU with crystalline PCL SS is susceptible to stretch-induced crystallization under large strain, non-crystalline and biodegradable PTMC or PVLCL were used as the SS to obtain more resilient PUUs. PTMC is an amorphous biodegradable elastomer of a relatively soft nature with a tensile modulus of 2.9 MPa and a T_g of 17°C . The DSC spectra of PUU-PVLCL2500 and PUU-PVLCL6000 showed much lower T_m values (-5 and 8°C , respectively, Figure 3a) than those of PCL.

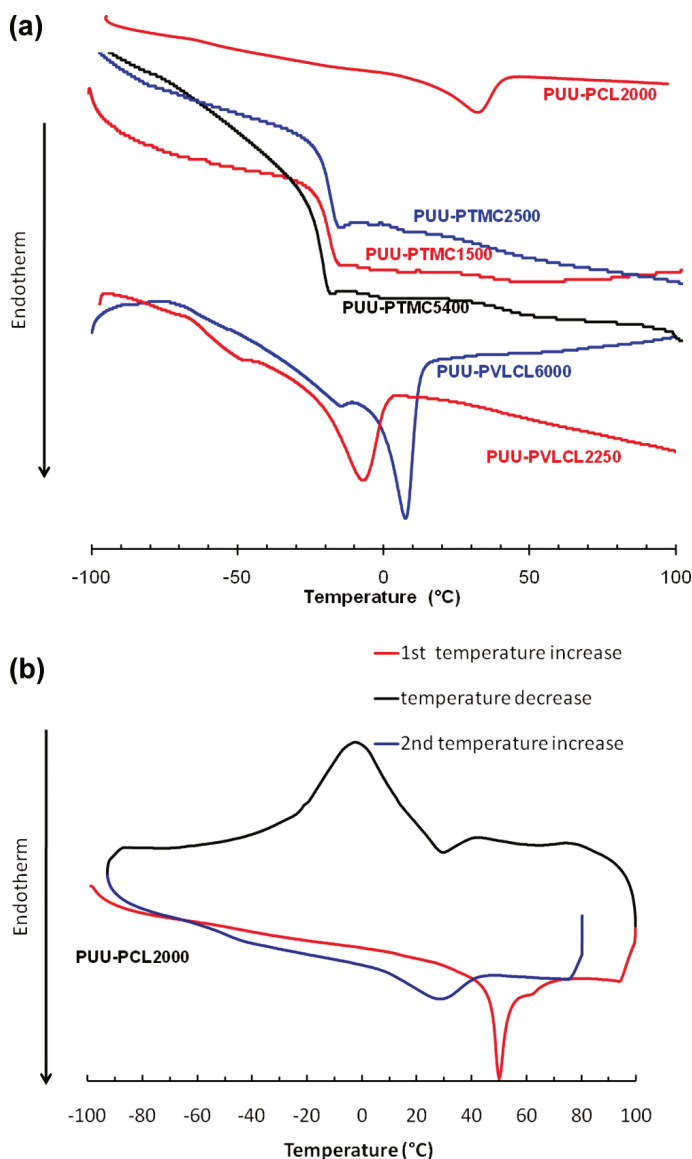


Figure 3. DSC analysis of (a) PUUs and (b) stretched PUU-PCL2000 (permanent deformation of 677%) with temperature change [78]

Recently, biodegradable PCL/PU has been synthesized by curing with water. To prepare a prepolymer, MDI, PCL diol and PTMO were used. The prepolymer was then cured using H₂O to form a new type of PU, PCL/H₂O-PU, whose synthesis was confirmed by FTIR analysis. The thermal resistance and glass transition temperature of PCL/H₂O-PU increased with the H₂O and hard segment content. Stress–strain curves for the PCL/H₂O-PU samples showed that, with increasing H₂O content, the tensile strength and Young’s modulus

increased, but the elongation at break decreased. Wide-angle X-ray scattering (WAXS) patterns indicated that, with a higher H₂O content, the arrangement of polymer chains was more ordered, although the morphology was still amorphous. The degree of swelling in an aqueous ethanol solution and the hydrolytic degradation rate increased with the PCL content. Scanning electron microscopic (SEM) images showed that, during the degradation period, the original wrinkled surface of PCL/H₂O-PU became smooth, and then some cracks were formed. The cracks became more severe when the degradation was conducted at a higher temperature [81].

5.3.1.1.3. Poly(dimethylsiloxane)-based BioPUs

Although PDMS-based PUs and PUUs (PUSs and PUUSs, respectively) are recognized as the most stable PUs for long-term medical implant applications, many of them, especially those with polyester or polyether soft co-segments, have been investigated and used as BioPUs. Due to the specific behaviour and many unique properties of PDMS segments, including low glass transition temperature ($-123\text{ }^{\circ}\text{C}$), low surface energy, good biocompatibility and thermal and thermo-oxidative stability, as well as ultraviolet resistance and high permeability to many gases, PDMS-based PUs are suitable for applications such as elastomers, coatings and biological implants [32,33] and represent a permanent scientific interest of our research group. The first PDMS-based segmented PUs were prepared from hydroxypropyl- and hydroxybutyl-terminated PDMS. However, these initial attempts resulted in copolymers with rather low molecular weight and poor mechanical properties, mainly due to solubility problems during synthesis [82]. A key feature of PUS and PUUS copolymers is almost complete phase separation between the hard and soft segments in copolymers due to the extremely large differences in the solubility parameters of PDMS and urethane and urea groups (15.6 , 37.2 and $45.6\text{ J}^{1/2}\text{ cm}^{-3/2}$, respectively) [82]. In some studies, the synthesis of PU and polyurea copolymers based on hydroxyhexyl-, aminopropyl- or methylaminopropyl-terminated PDMS with relatively high molecular weight and good mechanical properties was reported [29,82]. Considering the large difference in polarity between the urethane/urea hard segments and the siloxane soft segments, there are now two general approaches to the synthesis of PUS and PUUS copolymers. The first involves the presence of polyether or polyester segments as co-soft segments, in order to improve the miscibility of PDMS with the urethane or/and urea units [83-85]. Gunatillake *et al.* [86,87] reported that thermoplastic PUs based on mixed PDMS and poly(hexamethylene oxide) (PHMO) as the soft segments exhibit excellent tensile strength ($\sim 28\text{ MPa}$), elongation at break ($\sim 580\%$) and Young's modulus ($\sim 33\text{ MPa}$).

However, in PUUS copolymers, the presence of the second soft segment, which has the ability to form hydrogen bonds with the hard segments, can lead to extensive phase mixing of the hard and soft segments and to a deterioration in

mechanical properties due to the decrease of phase separation in the copolymers [88,89]. The second approach to the synthesis of PUS and PUUS copolymers is based on using end-functionalized PDMS as a single soft segment, whereby the terminal units attached to the ends of the siloxane oligomers act as a 'compatibilizer' between the highly polar urethane/urea hard segments and the non-polar siloxane soft segments [85]. Figure 4 shows the structures of some PDMS end-functionalized prepolymers for synthesis of segmented PUs.

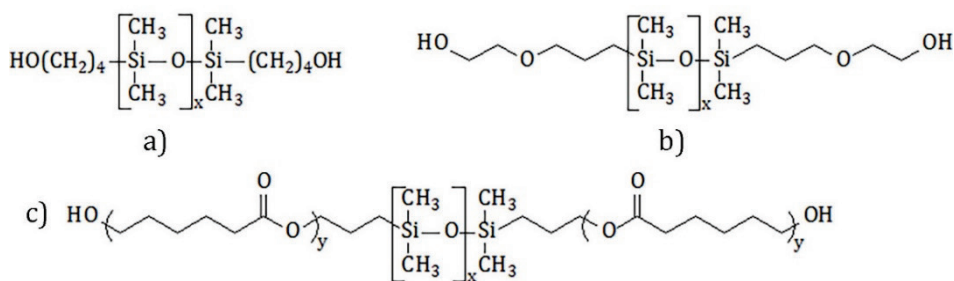


Figure 4. Chemical structures of siloxane-containing prepolymers: (a) α,ω -dihydroxybutyl-PDMS, (b) α,ω -bis(6-hydroxyethoxypropyl)-PDMS, (c) α,ω -dihydroxy-PCL-*b*-PDMS-*b*-PCL

The synthesis of PU copolymers using siloxane-containing prepolymers with PCL and ethylene oxide terminal units has been described [90-98]; these terminal units of siloxane-containing prepolymers were used in order to increase the miscibility of polar and non-polar reactants. Thermoplastic PU elastomers based on PDMS were synthesized by a two-step polyaddition procedure in solution, from MDI, 1,4-BD and α,ω -dihydroxy-PCL-*b*-PDMS-*b*-PCL [94]. The combination of the properties of PCL and PDMS makes these block copolymers good candidates for surface modifying additives, drug encapsulation and biomaterial applications. With increasing hard segment content (from 9 to 63 wt. %), the storage moduli, microphase separation and hydrophilicity of these copolymers increased. DSC of these samples showed that, depending on their composition, these PUs display the melting temperature of the soft and hard segments or only of the soft segment. PUs with a hard segment content above 20 wt. % had various high temperature transitions which correspond to the melting temperature of the hard segments. The value of the degree of crystallinity of PCL segments (14-42 %) tended to decrease with increasing hard segment content, from which it can be concluded that the presence of the hard segments probably disturbs the crystal growth of the PCL segments. The degree of crystallinity of the hard segments ranged from 3 % to 15 % and increased with increasing hard segment content. Atomic force microscopy (AFM) results showed that formation of the

spherulite superstructure increases with increasing hard segment content. With a change of hard segment content from 9 to 63 wt.%, the properties of the thermoplastic PUs changed from those of softer to tougher polymeric material.

Thermoplastic PUs based on α,ω -bis(6-hydroxyethoxypropyl)-PDMS (EO-PDMS-EO), with PDMS block and hydrophilic terminal ethoxy units, containing 20–60 wt.% hard segment have been synthesized and characterized [91,93]. FTIR, AFM and dynamic mechanic analysis (DMA) confirmed the phase-separated structure in these copolymers. Three phase transitions were detected by DSC and DMA. The first phase transition (at temperatures from -110 to -102 °C) corresponds to the glass transition of PDMS in the soft segment. The second transition was detected in the temperature range from 65 to 75 °C and is a result of the glass transition of the hard segments. The third transition, in the range from 157 to 193 °C, is due to melting of the highly organized (crystalline) hard segments. The degrees of crystallinity of the copolymers were in the range 8.7% to 23.5%, depending on the hard segment content. These thermoplastic PUs showed a spherulite-like structure that is believed to arise from the crystallization of the hard segments. The surfaces of those thermoplastic PUs with higher PDMS content were more hydrophobic, which is attributed to the low surface tension of the PDMS segments and their ability to migrate to the surface.

Potentially biocompatible thermoplastic PUS and PUUS copolymers based on α,ω -dihydroxypropyl-PDMS with different soft segment content have been prepared and characterized [30,97,99]. In these copolymers, the crystallinity, moduli, hydrophilicity, surface free energy and surface roughness increased with decreasing PDMS content. SAXS analysis of PUUS revealed a phase-separated structure, in which the high initial elastic modulus and high tensile strength values of the PUUS copolymers result from the presence of very strong urea bidentate hydrogen bonding in the hard segments.

Recently, preparation and characterization of segmented PUs from α,ω -dihydroxypoly(propylene oxide)-*b*-poly(dimethylsiloxane)-*b*-poly(propylene oxide) (PPO-*b*-PDMS-*b*-PPO) triblock copolymer as the soft segment and MDI and 1,4-BD as the hard segment have been reported. Incorporation of PPO-*b*-PDMS-*b*-PPO leads to improvements in thermal stability. SAXS and WAXS experiments indicate that PUs synthesized with a higher hard segment content have more developed and distinct phase-separated morphology. The water contact angle increases while water absorption decreases with increasing hydrophobic PPO-*b*-PDMS-*b*-PPO segment content. SEM and AFM analysis revealed that copolymers with a lower content of PPO-*b*-PDMS-*b*-PPO segments have higher microphase separation between segments, demonstrating proper surface and morphological properties with great potential for a variety of applications such as hydrophobic coatings in biomedicine [100,101].

PDMS-based BioPU copolymers often contain PLA segments. Ho *et al.* [102] have prepared an (AB)_n-type multiblock PU containing alternating PLLA and PDMS segments by chain extension of hydroxy-telechelic PLLA-*b*-PDMS-*b*-PLLA triblock copolymers. These triblock copolymers were synthesized by the ROP of L-lactide initiated by α,ω -hydroxyl-functionalized PDMS, using HDI as the chain extender. From the results of thermal analysis, two glass transition temperatures, measured by DSC, showed the occurrence of phase separation phenomena in both the triblock and multiblock copolymers because of the difference of solubility parameters between the PLLA and PDMS segments. The order of the chain extension reaction depended on the weight-average molar mass (M_w) of the triblock copolymer: a second-order reaction was transformed into a third-order reaction as the M_w of the triblock copolymer increased from 7000 to 25,000 g mol⁻¹, perhaps because of inhibition of the formation of an active complex involved in the catalysed urethane reaction by polymer chain aggregation. As expected, the mechanical properties of the multiblock PU copolymers demonstrated that the introduction of the extremely flexible PDMS segment substantially improved the elongation at breakage, and the tensile strength and tensile modulus declined due to the intrinsic elasticity of such segments.

Block copolymers of PLA and PDMS can be simply obtained by transesterification reactions with PDMS containing amine ends at moderate temperatures for short reaction times. Hazer *et al.* [103] prepared PLA-*b*-PDMS linear block copolymers which were obtained by the transesterification reaction in chloroform solution between PDMS bis-(2-aminopropyl ether) ($M_n = 2000$ g mol⁻¹) with PLA in the presence of stannous octoate. Blends of pure PLA with PLA-*b*-PDMS block copolymers displayed improved elastic properties (elongation up to 140 %) compared to pure PLA (elongation ~ 9 %).

5.3.1.2. Polyether soft segments

Polyether-based PUs for biomedical applications usually consist of PTMO or PEO soft segments and hard segments based on MDI and 1,4-BD. However, PEO is considered a better starting material in BioPU formulation for specific applications such as drug delivery, cell encapsulation and tissue engineering due to a large increase in water swelling and decrease in oil swelling in comparison to those based on hydrophobic PTMO soft segments.

It is considered that PU copolymers with PEO soft segments show low non-specific protein adsorption and are resistant to bacterial and animal cell adhesion due to the intrinsic hydrophilicity of PEO [104,105]. The mechanical properties and degradation rate of PEO-based thermoplastic PUs can be tailored by changing the content and molecular weight of PEO soft segments. The role of soft segment ordering in PU mechanical properties and morphology in semi-crystalline segmented PUs containing either PEO ($M_n = 1000$ and 4600 g mol⁻¹) or PEO-*b*-poly(propylene oxide)-*b*-PEO (PEO-PPO-PEO,

$M_n = 1900 \text{ g mol}^{-1}$) soft segments and HDI-1,4-BD hard segments (33 wt. %) has been studied [106]. The presence of dispersed semi-crystalline regions within the continuous soft domain has been shown to provide a reinforcing effect when compared to that of a non-crystalline soft segment PU. Incorporating a semi-crystalline soft segment (PEO, 1000 g mol^{-1}) has been shown to improve overall sample toughness. However, if higher molecular weight PEO soft segments are employed (4600 g mol^{-1}), extensibility and, consequently, toughness are adversely affected due to an increased continuous domain modulus. Interdomain hydrogen bonding is suppressed by the presence of a PPO block in the soft segment, leading to hard domains that possess a longer persistence length due to more regular hard segment packing and strong phase separation in PUs based on PEO-PPO-PEO soft segments.

Fromstein and Woodhouse [107] compared BioPU blends made from segmented PUs containing an amino acid-based chain extender and diisocyanate groups and soft segments based on PEO or PCL diols. The highly hydrophilic PEO was incorporated to increase the blends' susceptibility to degradation, while the PCL PU was selected to provide higher moduli and percentage elongations (strains) than the PEO parent materials can achieve. All four blends were determined to be semi-crystalline, elastomeric materials that possess similarly shaped stress-strain curves to that of the PCL-based parent PU. As the percentage composition of PEO PU within the blend increased, the material became weaker and less extensible. The blends demonstrated rapid initial degradation in buffer followed by significantly slower, prolonged degradation, likely corresponding to an initial loss of primarily PEO-containing polymer, followed by slower degradation of the PCL PU. All four blends were successfully formed into three-dimensional porous scaffolds utilizing solvent casting/particulate leaching methods.

5.3.2. Hard segments

For most commercial PUs, aromatic diisocyanates are used because they are much more reactive than aliphatic ones and provide materials with good mechanical properties. However, for BioPU formulations, aliphatic diisocyanates are mostly employed because their ultimate degradation products are more likely to be non-toxic [12,108,109]. Aliphatic or cyclic diisocyanates (HDI, 4,4'-methylenebis(cyclohexyl isocyanate), HMDI, IPDI) are used instead of aromatic diisocyanates, for example MDI and TDI, which are considered to degrade into carcinogenic and mutagenic aromatic amines [110].

The influence of diisocyanates on the properties of PUs is reflected most through the high-temperature properties and crystallinity of these materials; these are mainly studied using DSC and DMA. Barikani and Hepburn [111] were among the first to study the effect of the structure of different diisocyanates on the thermal properties of a series of PUs obtained by two-

stage polymerization from PLC, 1,4-BD and various diisocyanates: CHDI, *p*-phenylene diisocyanate (*p*PDI), MDI, HDI and an 80/20 mixture of 2,4- and 2,6-TDI. The molar ratio of PCL/diisocyanate/1,4-BD in all examined samples was 1/2.6/1. However, only in later research [112] was the effect of the spatial structure and symmetry of the diisocyanate molecules on the properties of PUs fully recognized. The results showed that the symmetry of the diisocyanate molecule has a major role in determining the morphology of the segmented PU and polyurea copolymers. PUs and polyureas prepared by the reaction of symmetrical diisocyanates have a significantly higher degree of microphase separation than copolymers synthesized from less symmetrical or sterically restricted diisocyanates. In particular, copolymers with symmetrical hard segments showed significantly higher moduli and a wider, temperature-insensitive rubbery plateau. In addition, compared to thermoplastic PUs, the presence of bidentate hydrogen bonds in polyurea results in substantially more cohesive hard phase formation, which further results in an increase of the moduli and in the expansion of the rubbery plateau in these materials [113].

PUU copolymers with hard segments derived only from diisocyanates linked *via* urea linkages have been synthesized using two-armed PLC as the soft segment and methyl 2,6-diisocyanatohexanoate (LDI) as the hard segment. The length of the hard segment varied from 4.8 to 11.6 LDI units. Stress–strain measurements showed an increase in elastic modulus, from 146 to 235 MPa, with an increase in hard segment length, while the elongation at break decreased from 980 % to 548 %. FTIR spectroscopy showed an increase in hydrogen bonding as the hard segment length increased [114]. Some authors have reported that aliphatic BDI and LDI can degrade in the body to the diamine putrescine and amino acid lysine, respectively, which play an important role in cell growth and differentiation [115, 116]. Guan *et al.* [74] reported the synthesis of biodegradable PU and PUU copolymers based on PCL, BDI and a putrescine chain extender. Degradation products from these copolymers demonstrated no toxic effects on human endothelial cells cultured *in vitro*. However, the use of putrescine can be controversial, as some papers describe it as a toxic substance [117].

The most important chain extenders are linear diols such as ethanediol, 1,4-BD, 1,6-hexanediol and hydroquinone-bis-(2-hydroxyethyl)ether. Compared to diols, diamines react with isocyanate groups more quickly, forming hard segments with a higher concentration of hydrogen bonds, which leads to higher glass temperature values of the hard segments and higher thermal stability of the synthesized copolymers. However, for the same reason, polyureas show poor solubility in common organic solvents and it can be more difficult to melt these copolymers. Generally, PUs based on aliphatic diols are softer and more flexible than copolymers based on aromatic diols. PUs which are synthesized without a chain extender, by direct reaction of diisocyanate or macrodiol, generally have very poor physical properties and often do not show

microphase separation. The introduction of a chain extender can increase the length of the hard segments, allowing their segregation. This further leads to an improvement in mechanical properties such as the modulus and increased glass transition temperature of the hard segment in the copolymer. Changing the molar ratios of macrodiol and the chain extender can change the properties of PUs from hard and solid materials to the elastomer form, as a result of changes of the weight fraction of the hard segments in the copolymer [28].

The structure of the chain extender has a great influence on the properties of segmented PUs. Copolymers derived from diols with an even number of CH_2 groups can achieve a fully extended conformation that allows hydrogen bonding in both directions perpendicular to the axis of the polymer chain. Such hydrogen bonding is not favourable when diols with an odd number of CH_2 groups are used. Likewise, molecules lower in the series, *i.e.* ethanediol and 1,3-propanediol, are too short, which prevents packing of the MDI residues into the hard segments [118].

Wang and Kenney [119] reported the influence of various chain extenders on the morphology and properties of PUs based on a PTMO soft segment. The tensile strength and modulus of the synthesized copolymers were increased, while the elongation at break was decreased by changing the extender in the order: 1,3-butanediol, 1,5-pentanediol, 1,4-BD. Also, study of the effects of chain extender structure and hard segment content has shown that PUs synthesized from symmetrical and rigid difunctional extenders have superior mechanical and physical properties compared to PUs obtained from asymmetric polyfunctional chain extenders.

Also, the use of chain extenders based on amino acids in BioPUs in order to improve biodegradability mediated by enzymes has been reported [18,75,76]. Caracciolo *et al.* [20] reported the preparation of two series of biomedical segmented polyurethanes (SPU) based on PCL, HDI or LDI and three different chain extenders. Chain extenders containing urea groups or an aromatic amino-acid derivative were incorporated in the SPU formulation to strengthen the hard segment interactions through either bidentate hydrogen bonding or π -stacking interactions, respectively. The structure–property relationships of SPU were investigated by varying the composition of the hard segment (diisocyanate and the chain extender). The different chemical composition and symmetry of the hard segment modulated the phase separation of the soft and hard domains, as demonstrated by the thermal behaviour. The hard segment association was enhanced to a greater extent by using a combination of symmetric diisocyanate and urea–diol chain extenders. The hard segment cohesion had an important effect on the observed mechanical behaviour. PUs synthesized using HDI (Series H) were stronger than those obtained using LDI (Series L). The latter SPU exhibited no tendency to undergo cold-drawing and the lowest ultimate properties. Incorporation of an aromatic chain extender produced the opposite effect, resulting in PUs with the highest elongation and tearing energy (Series H)

and the lowest strain at break (Series L). Since the synthesized BioPUs possess a range of thermal and mechanical properties, these materials may hold potential for use in soft tissue engineering scaffold applications.

Baez *et al.* [120] have reported the synthesis and characterization of segmented poly(ester–urethane–amide)s (PEUAs) based on PCL and diamide–diol chain extenders (DCEs) of different length ($n = 2, 4, 6$). PEUAs based on HDI or 1,4-diisocyanatobutane were highly crystalline with high melting points. When the hard segment was derived from LDI, prepared PEUAs showed lower melting points with a much lower crystallinity. PEUAs derived from PCL diols of molecular weight 539, 1243, or 1923 g mol⁻¹, HDI and these DCEs presented a phase-separated morphology as proved by DSC and SAXS, even at a hard segment content as low as 17 %. The hard segment melting point in the PEUAs was lower than for the corresponding hard segment models due to the shorter length of the segments and it increased when the hard segment content increased. For PEUAs of the same hard segment content and the same PCL length, the hard segment melting point decreased when the length of the DCE increased, due to the lower concentration of hydrogen bonds. For PEUAs of the same hard segment content and the same DCE, the hard segment melting point decreased when the length of the PCL decreased because the length of the hard segment increased. The hard segment was thermally less stable than the PCL soft segment, with a slight dependence on chain extender length. SAXS analysis demonstrated that, at temperatures above the melting point of the hard segment, the PEUAs became a homogeneous material that separated again in phases on cooling. The length scale of the phase-separated structure was fairly constant and decreased when the hard segment content was above 54 %, probably due to a change in morphology. Mechanical properties were good and mainly affected by the hard segment content. Water uptake was negligible for PEUAs with longer PCL diols and very small for PEUAs with the shortest PCL diol, due to the crystallinity of the hard segment, while the degradation rate was very slow. The degradation mechanism was proven to be surface erosion.

A variety of poly(ether urethane) networks have been synthesized from epoxidized methyl oleate (EMO)-based polyether polyols, 1,3-propanediol and LDI as a non-toxic coupling agent, with a hard segment content between 31.4 % and 52.3 %. WAXS and DSC results showed that the use of non-symmetric and methyl ester side chain-containing LDI inhibits any hard segment crystallinity. However, the significant hydrogen bonding of the urethane groups, noted by FTIR, as well as T_g values obtained by DSC and DMA, indicate that the PUs were phase-segregated to varying degrees. Degradation behaviour was found to depend strongly on the hard segment content, as hydrophilicity promotes susceptibility to hydrolysis and leads to a higher degradation rate. The wide range of material properties that have been achieved as well as the use of a potentially non-toxic diisocyanate make these degradable polymers useful for a variety of biomaterial applications [121].

5.4. APPLICATIONS OF BioPUs

5.4.1. Biodegradation and biocompatibility

The term 'biodegradable polymer' has been widely used for polymers that undergo *in vivo* degradation, where biodegradation implies a biological breakdown of material. Some authors extended these definitions to denote materials which form soluble products that can be easily removed from the implantation site and excreted from the body. The definitions of the terms that are now generally accepted were agreed at the Second International Scientific Workshop on Biodegradable Polymers and Plastics (Montpellier, France). Accordingly, polymer degradation is a deleterious change in the properties of a polymer due to a change in the chemical structure, while a biodegradable polymer is a polymer in which the degradation is mediated, at least partially, by a biological system. A bioabsorbable polymer is a polymer that can be assimilated by a biological system and erosion reflects the process of dissolution or wearing away of the polymer from the surface. In the case of biodegradable polymers, the prefix 'bio' is usually considered as reflecting phenomena resulting from contact with living elements such as tissues, cells, bodily fluids or microorganisms. Both natural and synthetic biodegradable polymers can be the subject of controlled degradation under the inherent environmental stress in biological systems with or without enzyme-assisted mechanisms. Besides enzymes, water and oxygen are regarded as biological elements, although a lot of authors still tend to limit discussions of biodegradation to enzymatic attack only. Medical applications of these materials cover a wide spectrum of activities including the controlled release of drugs, fertilizers and pesticides, absorbable surgical implants, skin grafts and bone plates. In addition to medical applications, another important motive for the development of new biodegradable polymers is connected to waste management of polymer packaging materials [122].

Biodegradation of various PU elastomers is mainly a consequence of cleavage of hydrolytically sensitive bonds present in their soft segments, although oxidative degradation of urethane bonds of the hard segments into amines has also been reported. The key factors that determine the kinetics of the hydrolytic degradation of BioPUs are their chemical structure and composition [58]. Guan *et al.* [25] showed that the *in vitro* degradation rate of BioPUs based on mixed triblock PCL-PEO-PCL soft segments (PEEUU) depends on their soft segment structure. Increasing PEO length or decreasing PCL length in the triblock segment increased PEEUU water absorption and the biodegradation rate. Also, poly(ester urea urethane) (PEUUR) foams, based on mixed PCL, glycolide and poly(D,L-lactide) soft segments, LDI and glycerol, degraded *in vitro* to non-cytotoxic decomposition products. Differences in the half-life of these polyester triol components translated to differences in the degradation rate of the BioPU foams [123]. The tensile properties of crosslinked PU networks, prepared by bulk ROP of D,L-lactide, glycolide, ϵ -caprolactone

and/or trimethylene carbonate, were monitored as a function of degradation time. The results of these experiments indicated that the poly(ϵ -caprolactone-co-D,L-lactide) and PLTMC networks displayed a linear loss of strength with respect to weight during the first 30 days of degradation, while the other networks degraded either too slowly or too quickly to establish such a linear relationship [58].

Ma *et al.* [78] studied hydrolytic degradation of biodegradable PUU elastomers based on three different macrodiols with molecular weights ranging from 2000 to 2500 g mol⁻¹ (PCL, PTMC or PVLCL, BDI and putrescine as the chain extender). Accelerated degradation experiments were conducted in phosphate buffered saline (PBS) containing 100 U mL⁻¹ lipase and they showed significantly greater mass loss for the two polyester-based PUUs versus the PC-based PUU and for PVLCL versus PCL polyester PUUs (Figure 5). Basic cytocompatibility was demonstrated with primary vascular smooth muscle cell culture. The synthesized families of PUUs showed variable elastomeric behaviour that can be explained in terms of the underlying molecular design and crystalline behaviour.

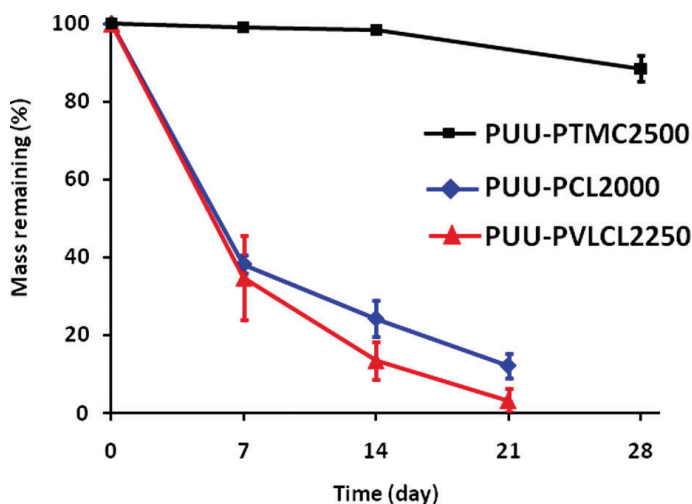


Figure 5. Degradation curves of PUUs in PBS solution containing 100 U mL⁻¹ lipase at 37 °C [78]

Besides that, urethane, urea and ester bonds are also susceptible to enzymatic degradation to free amines and α -amino alcohols, respectively, which means that the process of biodegradation can occur in BioPU hard segments [124,125].

On the other hand, biocompatibility, in the broadest sense, implies the ability of the polymer to be in contact with a living system without producing an adverse effect [126]. The ideal biomaterial is, thus, non-toxic, non-

immunogenic and accepted by the human body [127]. However, the concept of biocompatibility gets a specific meaning only in terms of the final use of the material. For example, it is important that biomaterials for vascular graft have low thrombogenic potential and allow proper spread of endothelial cells; materials used as scaffolds in regenerative medicine must support extracellular matrix deposition, cell attachment and proliferation; drug delivery systems must avoid interactions with blood, proteins, cells and the coagulation system, and avoid accumulation in organs of the reticuloendothelial system and alterations of the immune system.

Therefore, systematic investigation of the biocompatibility of a polymer or other material includes a battery of tests which proves its safety for biomedical application. The full battery of tests recommended by the Food and Drug Administration for the specific material and device can be found in the ISO 10993 guidelines. For example, initial tests for an implant device in prolonged or permanent contact with blood include evaluation of cytotoxicity, sensitization, irritation or intracutaneous reactivity, systemic toxicity (acute), subchronic toxicity (subacute toxicity), genotoxicity, haemocompatibility and effects after implantation. Elastomeric BioPUs have been proposed for use in orthopaedic applications (bone tissue substitutes, cartilage repair) [128,129], for abdominal wall repair, as a temporary support for transplanted human retinal pigment epithelium cells, as a tracheal prosthesis and in soft tissue engineering [130]. Keeping in mind the broad spectrum of PU biomedical applications, this section will focus only on the issues related to biocompatibility, degradation behaviour and overall properties of BioPU-based porous tissue scaffolds and drug delivery systems, as well as nanocomposites, but not on other numerous biostable PUs, the detailed discussion of which is given elsewhere [113].

5.4.2. Porous BioPUs–tissue scaffolds

Scaffolds play a crucial role in tissue engineering, which represents the fabrication of functional replacements for damaged tissues or organs [131]. The function of tissue scaffolds is to provide an appropriate base for tissue growth and cell proliferation, while simultaneously undergoing controlled degradation to non-cytotoxic decomposition products *in vivo* and supporting the growth and proliferation of the required cell types [132]. Artificial scaffolds utilized in regenerative medicine and in tissue engineering should have mechanical properties resembling those of the healthy target tissue in order to avoid inflammatory reactions. Elastic moduli of natural tissue vary over several orders of magnitude, from units of kPa (*e.g.* in brain) to units of MPa (in bone tissue). PUs and PUUs have been identified as two of the most promising kinds of biomaterials with the above-mentioned properties. From a biocompatibility point of view, the most important issues regarding tissue scaffolds are the cytotoxicity of the original structure and the degradation products as well as the degradation rate of the polymer. Cytotoxicity is

assessed through different *in vitro* methods, *e.g.* cell integrity and mitochondrial activity, LDH (lactate dehydrogenase) and MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide) assays or following *in vivo* implantation of the investigated biomaterial through various histological techniques. Biodegradation is estimated after real-time (at $37 \pm 1^\circ\text{C}$) or accelerated (at $70 \pm 1^\circ\text{C}$) degradation through evaluation of mass reduction, molecular weight, FTIR, UV analysis of leaching and the morphology of the surface and cross section of polymers [130]. In addition to non-toxicity and a satisfactory degradation rate, tissue scaffolds should be characterized by a suitable, porous structure with uniformly distributed interconnected pores to allow cell and tissue ingrowth. Depending on the specific application, scaffolds are designed to have great porosity (above 90 %) and proper pore dimension (from ten to hundreds of μm). According to the literature, the proper pore diameter in scaffolds for skin regeneration is in the range from 20 to 150 μm , while for bone, the best pore size is from 200 to 400 μm . Also, scaffolds designed for liver regeneration should have a pore diameter of 20 μm to allow the growth of hepatocytes [133].

5.4.2.1. Fabrication of porous BioPUs

A great advantage of BioPU polymers compared to other biodegradable materials is the ability to be processed in a wide range of conditions to fabricate porous tissue scaffolds. Techniques for the fabrication of three-dimensional porous structures are based on transforming polymers from the solid to liquid state, mostly by melting or dissolving [131].

The most common method is solvent casting/particle leaching (SCPL) [134–139] as developed by Mikos [34], which involves leaching out solid particles from the polymer solution. In this technique, particles with a specified diameter are added to the polymer solution, with a concentration in the range from 5 % to 20 % [131]. After solvent evaporation by air-drying, vacuum-drying or freeze-drying, salt particles remain embedded throughout the polymer matrix. After immersion in water, salt particles are leached out, leaving a porous structure. By this technique, highly porous scaffolds with porosity up to 93 % and average pore sizes of up to 500 μm can be obtained [140]. Sin *et al.* [141] reported the fabrication of highly porous three-dimensional scaffolds with a well-interconnected porous structure at a polymer solution concentration of up to 20 % by air- or vacuum-drying to remove the solvent. When salt particle sizes of 212–295, 295–425 or 425–531 μm and a 15 % w/v polymer solution concentration were used, the porosity of the scaffolds was between 83 % and 92 % and the compression moduli of the scaffolds were between 13 and 28 kPa. Type I collagen acidic solution was introduced into the pores of a PU scaffold to coat collagen onto the pore walls throughout the whole PU scaffold. SEM analysis confirmed that the human aortic endothelial cells (HAECs) were cultured in the collagen-coated PU scaffold for 2 weeks. This enhanced SCPL method which involved

the combination of the conventional method, a centrifugation step and collagen coating resulted in a spatially uniform distribution of cells throughout the collagen-coated PU scaffold. In this case, the centrifugation step resulted in improved pore uniformity and pore interconnectivity of scaffolds.

In a combined salt leaching–phase inverse technique, PU is dissolved in a good solvent and then a non-solvent is dropped into the polymer solution. When the good solvent in the polymer solution is exchanged for a non-solvent, the polymer precipitates to form a polymer paste. A solid porogen with different particle sizes is added to the paste upon vigorous stirring. Finally, the solvent/non-solvent and the porogen are removed using water, and a porous scaffold forms [142]. BioPUs based on HDI, PCL and a biologically active isosorbide diol as the chain extender, have been processed into 3D porous scaffolds by applying the combined salt leaching–phase inverse process. The critical parameters controlling pore size and geometry are the choice of solvent and non-solvent used for scaffold preparation and the size of the solid porogen crystals. Scaffolds prepared from a polymer solution in solvents such as dimethyl sulfoxide (DMSO) or NMP do not have a homogenous pore structure which means that numerous pores are closed. The scaffolds fabricated in DMF show the best pore structure [134].

Gas foaming is a well-known process in PU technology used for the production of flexible and rigid polyurethane foams (PUR) [143]. In the gas foaming method, chain extension with water can be used to obtain PU copolymers. During this type of chain extension reaction, carbon dioxide is generated and it can be used to produce a pore structure. This method of fabrication of porous BioPUs has a huge advantage because the use of potentially toxic solvents and porogenic components, used often in some other techniques, can be avoided. However, using this method it is very difficult to obtain porous structures with pores of controlled size and interconnectivity. During gas foaming, large, closed pores can be created inside the polymer scaffold, which makes adequate cell proliferation improbable [144-147]. Scaffolds made by gas foaming are usually used for reconstruction of bone defects resulting from the treatment of bone fractures or tumours or for the reconstruction of bone tissues. Kim *et al.* [144] applied PU foaming fabrication to manufacture a bone scaffold satisfying various functional requirements. As a result, bone scaffolds having a pore size ranging from 300 to 800 μm and a porosity ranging from 75 % to 85 % can be manufactured using this process. In *in vitro* and *in vivo* animal tests, it has been confirmed that the scaffold manufactured in this study can be effectively used as a bone scaffold which is biocompatible and has the ability to induce bone differentiation and regeneration. Gorna and Gogolewski [148] reported the synthesis of crosslinked 3D BioPU (foam) scaffolds with controlled hydrophilicity for bone graft substitutes. These scaffolds had hydrophilic-to-hydrophobic content ratios of 70 : 30, 50 : 50 and 30 : 70 and they were prepared from HDI and a PEO diol as a hydrophilic component, and PCL diol, amine-based polyol or

sucrose-based polyol as a hydrophobic component, water as the chain extender and a foaming agent in the presence of different catalysts. The scaffolds had an open-pore structure with pores whose size and geometry depended on the material's chemical composition. The compressive strengths of these open pore-structured scaffolds were in the range of 4–340 kPa and the compressive moduli in the range of 9–1960 kPa, the values of which increased with increasing PLC content. Of the two materials with the same amount of PLC, the compressive strengths and moduli were higher for the one containing inorganic fillers.

Thermally-induced phase separation (TIPS) is a technique that includes quenching of the polymer solution below the freezing point of the solvent and the formation of two phases with different polymer content. The solid formed in the polymer-rich phase is imbued with crystals formed in the polymer-poor phase. These crystals are removed, leaving a highly porous structure (more than 90 %) [149-151]. A composite scaffold is fabricated using the TIPS process from chemically very different poly(lactic-co-glycolic) (PLGA) and BioPU copolymers. This processing method has been tuned to allow molecular mixing of these two polymers and controlled phase separation behaviour. Pure PLGA scaffolds possess a smooth, directional fibrous sheet-like structure with pore sizes of 0.1–200 μm , a porous Young's modulus of 93.5 kPa and are relatively brittle to touch. Pure PU scaffolds have an isotropic emulsion-like structure, a porous Young's modulus of 15.7 kPa and are much more elastic than PLGA scaffolds. On the other hand, the composite PLGA / PU scaffold exhibits advantageous morphological, mechanical, cell adhesion and growth-supporting properties [149].

Melt moulding is another conventional method for porous scaffold fabrication which is considered as the most convenient and economical, since it allows the rapid production of polymer scaffolds of various shapes and sizes. A biodegradable polymer, in the form of granules or powder, is placed in a mould together with the porogen compounds and this mixture is heated above the polymer's glass transition temperature (T_g) at elevated pressure [131]. After the formation of a scaffold, the porogen is leached out, in a way similar to the SCPL method, leaving a porous structure. This procedure does not require use of organic solvents, but may include the presence of a non-porous layer on the surface of the scaffold and incomplete leaching out of the porogen compound.

The use of a combination of these conventional methods is also reported. Thus, porous scaffolds have been made from two PUs based on the TIPS of a polymer dissolved in a DMSO / water mixture in combination with salt leaching. In this way, it is possible to obtain very porous foams with very high interconnectivity [152]. Also, a PUU-based porous scaffold designed for bone tissue engineering is prepared by using a mixture of inorganic (sodium chloride) and polymeric PEO porogen and the compression moulding process under optimum conditions. Leaching out the impregnated porogen particles by soaking in water (as a safe solvent) leads to a final scaffold with the desired morphology.

An increase in the pore interconnectivity is observed as the NaCl / PEO ratio is increased while the scaffold with an NaCl / PEO ratio of 60 : 25 exhibits suitable morphology for osteoblast cell attachment and growth [153].

Some advanced techniques such as electrospinning [154,155], rapid prototyping [156,157] including different methods of 3D printing and 3D plotting have also been developed [158-162].

Electrospinning is a method that produces fibrous scaffolds where electric force is used to draw charged threads from polymer solutions or melts. The diameters of the obtained fibres are in the range from tens of microns to tens of nanometres. Although either synthetic or natural materials can be used without concerns regarding unfavourable immune responses or disease transmission, synthetic polymers, including PUs, allow a greater ability to tailor the mechanical properties and degradation rate of scaffolds [163]. Electrospinning can be altered to influence either the surface topography of the fibres themselves or the larger topography of the 'web' of spun fibres. Improved deposition efficiencies are a necessary advance needed to maintain the attractiveness of this technique. While the role of residual solvent in the electrospun polymer remains unclear, high pressure CO₂ can be used to enhance chemical functionality while maintaining polymer morphology. Electrospun pore sizes, as spun, are typically too small for cells to pass through. These scaffolds usually need to be subjected to additional processing to improve internal proliferation [164].

Recently, a composite scaffold consisting of an electrospun biodegradable poly(ether ester urethane)urea (BPUR) and PEO hydrogel has been investigated for aortic valve tissue engineering. This multilayered approach permitted the fabrication of a scaffold that met the desired mechanical requirements while enabling the 3D culture of cells. The scaffold was tuned to mimic the tensile strength, anisotropy and extensibility of the natural aortic valve through design of the electrospun PU mesh layer. Valve interstitial cells were encapsulated inside the hydrogel portion of the scaffold around the electrospun mesh, creating a composite scaffold approximately 200 µm thick. Figure 6 shows SEM images which were analysed to determine the fibre diameter and degree of alignment for the electrospun meshes of the BPUR / PEO composite scaffolds. The fibres were smooth with homogeneous morphology (a) and average fibre diameters of 0.50 ± 0.07 µm. Fibre alignment analysis indicated that fibres were predominately aligned in one direction (b). Measurements taken from both stereomicroscopic images and cryosections were used to determine the average thickness of the BPUR. The electrospun BPUR meshes were measured as 95.5 ± 3.8 µm thick using the stereomicroscope and 91.7 ± 4.79 µm using cryosections. Combined, these measurements yield an average thickness of 94.2 ± 5.2 µm [165].

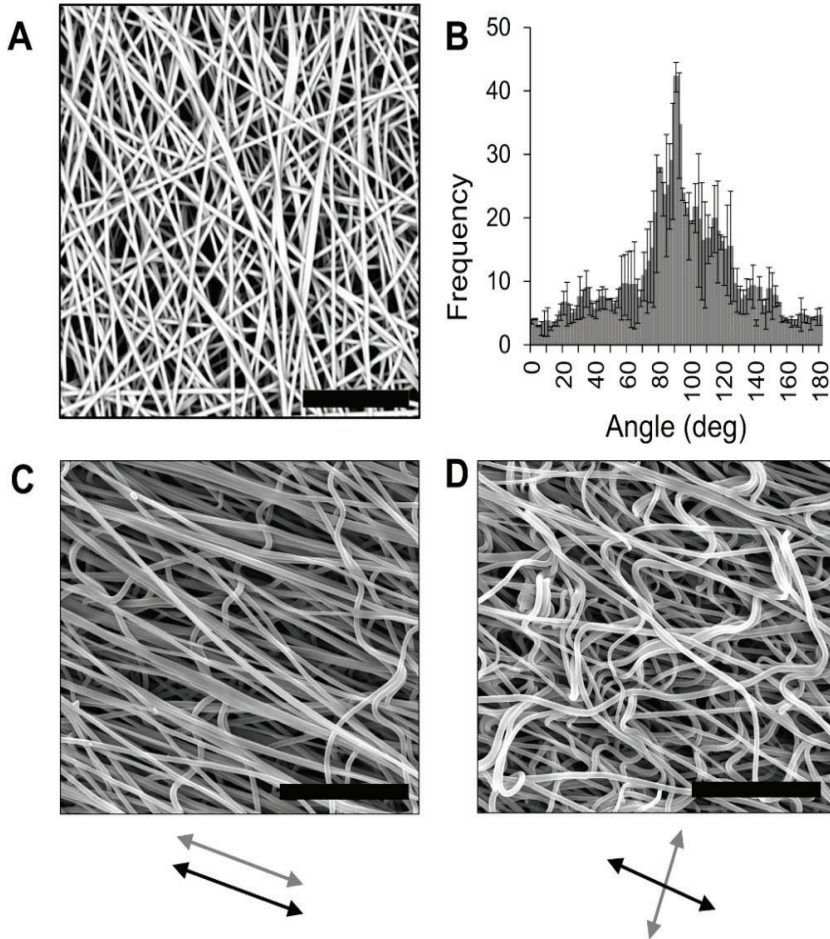


Figure 6. (A) SEM of electrospun BPUR; scale = 10 μm ; (B) histogram of fibre angle showing the alignment of fibres; (C, D) SEM images of electrospun BPUR under tension applied either (C) parallel or (D) perpendicular to the fibre alignment; grey = direction of primary alignment of electrospun fibres; black = direction of applied force; scale = 10 μm [165].

Another method for tissue scaffold fabrication is 3D printing, an additive manufacturing technique that allows fabrication of modular and patient-specific scaffolds with high structural complexity and design flexibility. This technology enables the design and fabrication of constructs based on tissue images captured with commonly used medical imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) [166]. Common 3D printing methods involve the use of heat, toxic organic solvents or toxic photoinitiators for fabrication of synthetic scaffolds. Hsieh *et al.* [167] have recently reported the synthesis of two thermoresponsive BioPU dispersions. These water-based BioPUs were able to form a gel near 37 $^{\circ}\text{C}$

without any crosslinkers. They found that the newly developed 3D bioprinting technique involving neural stem cells (NSCs) embedded in thermoresponsive BioPU ink offers new possibilities for future applications of 3D bioprinting in neural tissue engineering. Their findings suggest that NSCs embedded in the appropriate PU hydrogels may have the potential to rescue the function of an impaired nervous system in neurodegenerative diseases [162,167].

Pfister *et al.* [168] compared the scaffolds fabricated by two different 3D processes from an aliphatic BioPU based on LDI and IPDI. Layer-by-layer construction of the scaffolds was performed by 3D printing, that is, by bonding together starch particles followed by infiltration and partial crosslinking of starch with LDI. Alternatively, the 3D bioplotting process permitted three-dimensional dispensing and reactive processing of poly(ether urethane)s derived from IPDI, PEO, and glycerol. They concluded that both 3D printing and 3D bioplotting are capable of producing BioPU scaffolds, but they also highlighted some differences between these two methods. In the 3D bioplotting process, PU prepolymers are used to form interconnected strands, similar to non-woven materials, composed of PU networks. In contrast, the 3D printing process requires a two-step fabrication involving the dextrose / water-mediated bonding of starch / cellulose powder mixtures followed by infiltration and crosslinking of the polysaccharides with lysine ethyl ester diisocyanates. Although the speed of 3D printing is higher than that of 3D bioplotting, the second post-treatment step required only for 3D printing is time-consuming. Dextrose / water-mediated powder particle bonding in 3D printing gives scaffolds with very rough surfaces and heterogeneous crosslinking, whereas the extrusion process typical for 3D bioplotting produces interconnected strands with very smooth surfaces and homogeneous crosslinking. However, this difference in surface roughness does not lead to improved cell adhesion and faster cell proliferation. Because of the limitations with respect to the average powder particle sizes (50–150 μm) in 3D printing and the preferred average nozzle diameters (150–250 μm) of the 3D bioplotter, the resulting accuracy is similar for both technologies. In contrast, stereolithography does not possess the extraordinary flexibility of the 3D bioplotting process with respect to the free choice of materials ranging from melts, solutions, reactive resins, pastes and cements to bioactive components such as proteins, hydrogels and even cells. However, the large dimensions of living cells make ultrahigh precision and resolution less prominent issues in scaffold fabrication for tissue engineering applications. The mechanical properties of these PU networks are primarily affected by the composition of the PU networks. For the 3D bioplotting process, the compositions can be varied over a very wide range, whereas the post-treatment step of the 3D printing process is much less flexible.

5.4.2.2. Properties and degradation behaviour of porous BioPUs

The use of PU scaffolds in orthopaedic applications is based on their mechanical properties, *i.e.* on the ability to maintain their shape and structure *in vivo*. The ability of PU to support cell–material interactions and calcium phosphate deposition (as a measure of new bone formation) can be enhanced by the incorporation of isoprenoid molecules into the PU chain [169] and by increasing the hydrophilicity of the scaffold [128]. The cytocompatibility of BioPUs evaluated for orthopaedic applications has been confirmed after successful cultivation of human bone-derived cells or bovine chondrocytes for as long as 14 days *in vitro* [170]. The PU scaffolds also kept their ability to produce a specific human bone extracellular matrix *in vivo* after implantation into immunodeficient mice for 4 and 13 weeks [170] and to promote healing of sheep iliac crest defects to varying extents after 6 months of implantation [128]. Another potential application of thermoplastic PUs for improving the visual results of patients with age-related macular degeneration was proposed by da Silva *et al.* [171]. They showed that PU aqueous dispersions based on PCL and /or PEO as the soft segments, and IPDI and hydrazine as the hard segments, are a suitable base support for the adhesion and growth of human retinal pigment epithelial cells. Implantation into the subretinal space of rats for 15 days did not produce any sign of acute or chronic inflammation or necrosis, and the architecture of the retina and other ocular tissues was preserved. In addition, the hydrolytic biodegradation process was favoured due to the ester bonds of the PCL and the degradation products were non-cytotoxic to retinal pigment epithelial cells. Furthermore, in order to enhance the bioactivity and biocompatibility of poly(ester urethane)urea (PEUU) used for abdominal wall repair, Hong *et al.* [172] created a biodegradable elastomeric scaffold by combining PEUU with varying porcine dermal extracellular matrix (dECM) digest content. dECM was used since it contains multiple growth factors and chemotactic agents which recruit progenitor cells *in situ* and promote tissue remodelling. No herniation, infection or tissue adhesion was observed after 8 weeks in a rat full-thickness abdominal wall replacement model. For soft tissue engineering applications, the biodegradability of thermoplastic PUs can be accelerated by enhancing susceptibility to collagenase and elastase, proteolytic enzymes involved in the degradation of the ECM. This can be achieved, for example, through the incorporation of type I collagen or an elastase-sensitive peptide sequence into the polymer scaffolds [130].

Chemically modified poly(3-hydroxybutyrate) is receiving increasing attention for use as a biomimetic copolymer for cell growth. Recently, Reyes *et al.* [173] reported preparation of a composite scaffold of grafted poly(3-hydroxybutyrate) PU with improved mechanical properties and a great potential for tissue engineering.

Three different PUUs with similar soft segment molecular weight from 2000 to 2500 g mol⁻¹ (PUU-PCL, PUU-PTMC and PUU-PVLCL) were subjected to accelerated degradation in lipase buffer. The mass loss over the measurement period from the two polyester-based PUUs, PUU-PCL2000 and PUU-PVLCL2250, was markedly higher ($p < 0.05$) than that for the PC-based PUU-PTMC2500. The two polyester-based PUUs also exhibited differences from one another in terms of mass loss, with PUU-PVLCL2250 losing greater mass than PUU-PCL2000 at day 21 ($p < 0.05$). The intrinsic viscosities of the three samples, PUU-PCL2000, PUU-PTMC2500 and PUU-PVLCL2250, significantly decreased after one week in lipase buffer (2.17 ± 0.01 to 0.48 ± 0.13 , 1.74 ± 0.02 to 0.66 ± 0.06 and 1.76 ± 0.01 to 0.40 ± 0.02 dL g⁻¹, respectively; $p < 0.01$). Although PUU-PTMC2500 experienced relatively less viscosity loss than the other two polymers, the viscosity loss was greater as a proportion than one might expect based on the measured mass loss.

To optimize tissue regeneration in different tissues, it is desirable that the degradation rate of scaffolds can be manipulated to comply with the various stages of tissue regeneration. Xu *et al.* [174] reported on a new family of reduction-sensitive BioPU elastomers containing various amounts of disulfide bonds (PU-SS) that were designed to achieve better control of the degradation process. Thus, degradation in PU-SS can be initiated and accelerated with the supplement of a biological product: the antioxidant glutathione (GSH). PUs can be processed into films and electrospun fibrous scaffolds. Synthesized materials exhibited robust mechanical properties and high elasticity. Accelerated degradation of materials was observed in the presence of GSH, and the rate of such degradation depends on the amount of disulfide present in the polymer backbone. The polymers and their degradation products exhibited no apparent cell toxicity while the electrospun scaffolds supported fibroblast growth *in vitro*. The *in vivo* subcutaneous implantation model showed that the polymers prompt minimal inflammatory responses and, as anticipated, polymers with a higher amount of disulfide bonds had faster degradation *in vivo*.

Tissue engineering implies the fabrication of scaffolds with high elasticity and strength combined with controllable biodegradable properties. New synthesis and fabrication strategies for BioPUs are often focused on tuning scaffold degradability without significantly affecting all morphological properties. Spagnuolo and Liu [175] prepared two similar L-tyrosine (DTH)-based PUs, blended them in the desired ratios, electrospun into morphologically acceptable fibrous scaffolds, characterized and subjected them to hydrolytic degradation testing. The scaffolds containing a higher percentage of the less resilient PEO₁₀₀₀-HDI-DTH degraded to a greater extent than those containing a lower percentage of the polymer (or a higher percentage of PCL₁₂₅₀-HDI-DTH) regardless of the composition of blends and configurations (electrospun scaffold and thin films). Degradation of the electrospun scaffolds was faster than that of thin films with the same polymer composition. However, while the

degradation results were notably different between blends, pore size and fibre diameter were not statistically distinct from one another across all blends.

Guan *et al.* [151] synthesized two kinds of biodegradable PUU, PEUU and poly(ether ester urethane)urea (PEEUU) from PCL, PCL-*b*-PEO-*b*-PCL, BDI and putrescine, for applications such as cell scaffolds in cardiovascular tissue engineering or other soft tissue applications. PEUU and PEEUU were further fabricated into scaffolds by the TIPS method using DMSO as a solvent. The PEUU scaffolds were flexible with breaking strains of 214 % and higher, and tensile strengths of approximately 1.0 MPa, whereas the PEEUU scaffolds generally had lower strengths and breaking strains. Scaffold degradation in aqueous buffer was related to the porosity and polymer hydrophilicity. Smooth muscle cells were filtration-seeded in the scaffolds and it was shown that both scaffolds supported cell adhesion and growth, with smooth muscle cells growing more extensively in the PEEUU scaffold.

5.4.3. BioPU-based drug delivery systems

Controlled drug delivery is one of the key topics of modern medicine. Substantial efforts have been made to improve bioavailability by preventing premature degradation and enhancing uptake, to maintain the drug concentration within the therapeutic window by controlling the drug release rate and to reduce side effects by targeting disease sites and target cells [176]. The release of drugs from polymeric systems refers to a process in which drugs migrate from their initial position inside a polymer matrix to the release medium. Alternatively, drug molecules which are initially adsorbed onto a material surface might be released once brought into contact with an external medium [177]. However, it should be noted that the incorporation of drugs into polymeric systems, especially at high drug concentrations, cannot only affect the polymer properties of the systems, but also influence the release mechanisms and therapeutic efficiency of the drug. The understanding of these small molecule–polymer systems contributes greatly to developing other polymeric systems with desired properties.

Delivery applications of BioPUs are based on the fact that PUs swell when exposed to solvents. Once a material is imbedded in a PU matrix, the matrix can deliver the solvent or active ingredient in a number of ways, including solubility and vapour pressure. Other polymer systems have this ability, but the versatility of the PU molecule (*e.g.* hydrophilicity or hydrophobicity) gives it special properties. Also, the ability to produce BioPUs as foams or elastomers grants additional degrees of freedom in the design of products with desired properties [178]. Drug delivery systems based on BioPUs can be in the form of nano- or microparticulate systems [179] such as micelles [180-182] nanoparticles [183,184], nanocapsules [185-187], microspheres [188,189] and pellets [190], as well as membrane systems [191-195].

Drugs can be covalently bound to PU segments, usually through interaction of suitable functional groups of the drug (*e.g.* hydroxyl or amine) with isocyanate, obtaining in that way drug incorporated into the polymer backbone [196] or dispersed in PU matrices [197]. Covalently bound drugs are released from the polymer *via* passive hydrolysis of urethane and urea bonds following their degradation rate [196], while the release of dispersed drugs depends on drug loading, the solubility of the drug in the matrix and intermolecular interactions between them, as well as on the swelling properties of the polymer [177]. PU-based systems have to date been evaluated for delivery of various pharmaceutical agents such as antibiotics [198], non-steroid anti-inflammatory drugs [199], anticancer drugs [200], growth factors, *etc.*

PU-based nano / microparticles are receiving much attention since their chemistry, size, shape and degree of porosity can be adjusted according to the end application. Amphiphilic PU copolymers self-arrange in a spherical form with a hydrophobic core, which serves as a reservoir of drug, and a hydrophilic shell, which stabilizes the structure in aqueous solution. This is particularly useful when a hydrophobic drug (*e.g.* most anticancer drugs) needs to be encapsulated, as well as when a long retention time in the circulation is desired. In addition, due to the flexibility of PU chemistry, the surface of PU-based microparticles can be functionalized with bioactive molecules in order to obtain targeted drug release. For example, the introduction of folic acid onto the outer micellar layer of PCL- and LDI-based PU nanomicelles results in enhanced cellular uptake and improved drug efficacy towards folic acid receptor-positive HeLa cancer cells *in vitro* [201]. In a similar manner, PCL-based PU microparticles derived from a tripeptide arginine-glycine-aspartic acid (RGD) are proposed to prefer endothelial cells of tumour neovasculature over mature endothelial cells of healthy blood vessels, since the former express higher levels of integrin receptors [200].

Due to their customizable molecular structures, BioPU-based micelles with redox-responsive properties have been used as anticancer drug delivery systems. He *et al.* reported preparation of these BioPU-based micelles with redox-responsive properties using bis(2-hydroxyethyl) disulfide as the chain extender [202]. Disulfide bonds can be easily introduced into the hard segment of PUs by conventional two-step polymerization processes, which result in random distribution of the reduction-responsive disulfide linkages in PUs. Yao *et al.* [180] proposed that the disassembly and drug release profiles of PU micelles are related to the location of the disulfide linkages in the polymer main chain. In this study, BioPU copolymers were synthesized from the same amount of PEO, PCL and LDI and cystamine dihydrochloride (Cys) as the chain extender; two kinds of redox-responsive micelles with the same quantity of disulfide bonds, but at different locations, were prepared. In the first of them most of the disulfide bonds were located in the hydrophobic core of the PU micelles (PU-SS-C) while in the second, disulfide bonds were located primarily at the interface between the hydrophobic core and the hydrophilic shell (PU-

SS-I). Paclitaxel (PTX), as the model hydrophobic drug, was chosen to evaluate the loading and redox-triggered release of the PU micelles. It was demonstrated that the PU-SS-I micelles disassemble simultaneously in response to a 10 mM GSH stimulus and the payloads release more rapidly than those of PU-SS-C nanocarriers. These results showed that the release profiles of PU-based nanocarriers can be optimized by the location of the disulfide bond on the PU main chain.

Also, the use of BioPUs for chemical modification of natural polymers has become a very attractive field for improving their properties and making them suitable for controlled drug delivery applications [203,204]. Thus, BioPU-modified chitosan has been prepared by PU chain extension on a chitosan backbone through the reaction of an isocyanate-terminated PU prepolymer and the hydroxyl and amine linkages present in chitosan. The extent of solubility and the swelling characteristics of the modified chitosan decreased considerably with an increasing degree of substitution in graft copolymers as compared to pristine chitosan. Simultaneously, hydrophobic character, measured through contact angle, increased due to PU grafting. Chitosan graft copolymers are found to be bio- and haemocompatible in nature as observed through platelet aggregation, cell viability, cell adhesion and haemolysis studies. Further, graft copolymers do not supply any reactive oxygen in cell culture and the materials do not affect the biology of circulating blood cells [205].

The biocompatibility requirements for PUs as drug delivery systems are, to some extent, similar to those previously described for PU-based tissue scaffolds and are mostly related to the use of precursors which will degrade to harmless degradation products. The cytotoxicity of degradation products is estimated using different *in vitro* cell viability (*e.g.* MTT) assays. In addition, assessment of drug delivery system biocompatibility comprises evaluation of their interaction with the immune system and blood (*i.e.* blood cells, proteins and complement system) [206]. An immunocompatible drug delivery system is considered to induce minimal response from the host immune system, measured by macrophage activation, leukocyte adhesion, cytokine release [207] and T- and B-cell proliferation [208]. Interaction of drug delivery systems with blood to assess blood compatibility includes studies of haemolysis, platelet aggregation, coagulation time and complement activation [206]. A commonly accepted method for improvement of immuno- and blood compatibility is covalent binding of PEO to biomaterials including the PU surface. The presence of PEO in PU prevents protein adsorption, thus inhibiting uptake of the drug delivery system by the circulating blood cells and reducing the immunogenic response to a substance's surface [209].

5.4.4. BioPU-based nanocomposites

According to the most common definition, polymer-based nanocomposites are polymeric materials containing nanofillers, in which the polymer matrix is filled with a small amount of inorganic or organic nanoparticles. Nanocomposites are considered as materials which cover the area between inorganic glasses and organic polymers [210,211]. The two main types of filler for nanocomposite production are nanoparticles and nanoclays. In 2011 the Commission of the European Union defined nanoparticles as a natural, incidental or manufactured material containing particles, in an unbound state, as an aggregate or as an agglomerate, and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm [212]. The physical and chemical properties of nanoparticles are significantly different from their bulk materials due to their high surface area-to-volume ratios, i.e. high aspect ratios [213]. Commercially available nanoparticles such as a colloid solution of nanosilica in water or organic solvent and a fumed silica, or layered aluminosilicate clays (especially montmorillonite (MMT) or bentonite) are widely used in nanocomposites.

For the preparation of PU nanocomposites various methods can be used: distribution of a clay in macrodiol with a subsequent reaction with diisocyanate; interaction of PU with a clay in organic solvent with a subsequent evaporation of solvent; or reaction of diisocyanate with the hydroxyalkyl groups of an organic modifier in the clay with a subsequent reaction with macrodiol [214]. The addition of a small amount of nanofiller, which is capable of interacting, at the molecular level, with the polymer matrix, has considerable influence on the macroscopic properties of a polymer [215,216]. However, aggregation of nanoparticles and formation of agglomerates often occur during the preparation of nanocomposites, mostly due to the high interfacial reactivity and high surface tension energy of nanoparticles [217]. Compatibility of nanoparticles with the polymer matrix can be improved using various techniques such as the application of ultrasonic treatment, high-energy mechanical milling, chemical surface modification of nanoparticles using adequate modifiers, treatment with surfactants and encapsulation by polymers which act as a stabilizing agent [217,218].

Various BioPUs are unsuitable for the purpose of hard-tissue regeneration due to their weak mechanical properties [219,220]. As the polymer scaffold matrix gradually degrades and the resulting space is simultaneously filled with growing tissue, the scaffold structure should provide sufficient temporary mechanical support to withstand *in vitro* and *in vivo* stresses and loading in applications such as bone regeneration [221,222]. It is well documented that the properties of porous BioPUs can be improved by introducing nanoparticles or nanoclay into the PU matrix. The addition of nanoparticles into the PU matrix can slow down a steep reduction in mechanical properties during biodegradation [223,224]. Thus, the moduli of PU nanocomposites increase

from 3 to 7 MPa (133 %) and epoxy nanocomposites from 1.1 to 2.3 GPa (109 %) by the addition of 2–8 wt. % of layered silicate nanoparticles [225,226]. It has been reported that the storage modulus of PLA/layered silicate nanocomposites is increased from 1.63 to 2.32 GPa (42 %), and the biodegradation rate of the obtained nanocomposite is significantly accelerated in comparison to pristine polymer in terms of the weight loss and molecular weight [227]. Also, incorporation of small amounts of MMT into PLLA can increase the mechanical stiffness of PLLA porous scaffolds [224]. However, the possible toxicity of nanoparticles and other nanocomponents including carbon nanotubes and metal nanoparticles (such as Ag and Au nanoparticles) should be mentioned [228,229]. It seems that, compared to them, metal oxide nanoparticles (silica, alumina, titanium oxide and zinc oxide) show much less toxicity [230,231].

Dias *et al.* [232] prepared porous BioPUs, based on PCL oligomers and reinforced with nanometric clay, by reacting isocyanate-encapped PU chains with water to generate a porogenic and non-toxic CO₂ gas. The incorporation of nanoparticles allowed tailoring of the mechanical properties of the nanocomposites. SEM images showed that the porogenic procedure was able to produce materials containing large (pore sizes ranging from 184 to 327 μm) interconnected pores. *In vitro* assays performed with osteoblastic cells showed no cytotoxicity associated with the synthesized nanocomposite, while *in vivo* results after 29 days of implant showed that cells were able to penetrate through the porous structure to fully colonize the entire implant. Biocompatibility tests on the BioPU nanocomposites produced in this study revealed that this type of material can be potentially useful in engineering of many different tissues such as cartilage, bone, heart, valves, nerves, muscle, bladder and liver, among others.

BioPUs with shape-memory effects are attractive for use as minimally invasive medical devices. Wu *et al.* [233] prepared nanocomposites with shape-memory effects from biodegradable poly(glycerol sebacate urethane) (PGSU) and renewable cellulose nanocrystals (CNCs). Water-responsive mechanically adaptive properties and shape-memory performance of PGSU-CNC nanocomposites were observed, which are dependent on the CNC content. The PGSU-CNC nanocomposite containing 23.2 vol. % CNCs exhibited the best shape-memory effects among the nanocomposites investigated, with stable shape fixing and shape recovery ratios of 98 % and 99 %, respectively, attributable to the formation of a hydrophilic, yet strong, CNC network in the elastomeric matrix. The presence of CNCs improved the tensile strength of PGSU by up to 1040 % for the PGSU-CNC nanocomposite containing 18.6 vol. % CNCs, due to the strong interfacial interactions between CNCs and PGSU determined by FTIR. *In vitro* degradation profiles of these nanocomposites were assessed with and without the presence of an enzyme. The results showed that the PGSU6 nanocomposite (23 vol. % CNCs) experienced a weight loss of 17.5 % in 28 days in enzymatic PBS conditions. This value was lower

than that for neat PGSU, but confirms the hydrolytic degradability of the nanocomposite in the presence of an enzyme [233].

Da Silva *et al.* [234] prepared potential ocular implants to treat uveitis by incorporating dexamethasone acetate into BioPUs. PUs derived from PCL and having clay nanoparticles were obtained by producing an aqueous dispersion of the polymer. The incorporation of clay nanoparticles into the PU matrix has been demonstrated to be a useful tool to manipulate the mechanical properties in order to yield biomaterials that can display from very soft to stiff behaviour. High values of stiffness would be useful, for example, to produce ocular implants rigid enough to withstand a medical procedure that would insert the implant by forcing it to penetrate through ocular tissues without the need for a special incision. The presence of nanoparticles might be also useful to avoid an abrupt loss in stiffness during biodegradation of the implant. The incorporation of clay particles into the PU dispersion also leads to a reduction in both strain at failure and strength, an indication that the clay particles restrict the ability of the chains to flow under stress.

The introduction of reinforcing nanoparticles into a continuous polymer phase to form eco-friendly green nanocomposites has attracted a great deal of attention [235-237]. The use of chitin nanowhiskers (ChW) as a reinforcing nanofiller in the polymer matrix provides positive environmental benefits with respect to ultimate disposability and raw material use as well as strong mechanical properties. Recently, segmented biodegradable copoly(ether ester urethane)s were successfully synthesized through the chain extension of poly(3-hydroxybutyrate) (PHB) as hard segments and PCL-*b*-PEO-*b*-PCL macrodiols with different PEO block lengths as soft segments, with or without ChW, using HDI as a coupling agent in a one-step solution polymerization. These copolymers seem to combine the criterion of biodegradability with improved thermal stability and a wide processability window compared with high molecular weight PHB. The obtained copolymers are semi-crystalline thermoplastics whose crystalline domains stem from PHB and PCL-*b*-PEO-*b*-PCL segments. The T_m of PHB segments in the copolymers is decreased to ~ 130 °C, about 50 °C less than that of neat PHB, thus the copolymers are considered to be more processable than neat PHB. The ChW act as a nucleating agent, enhancing the crystallization rate of PCL-*b*-PEO-*b*-PCL soft segments from the glassy state. The incorporation of low ChW content enhances the crystallization rate of the PCL-*b*-PEO-*b*-PCL component from the molten state, while copolymers containing a relatively high ChW content retard the crystallization rate. The cold and melt crystallization of PHB enhances with increasing ChW content. TG analysis showed that the thermal stability of the copolymers is slightly enhanced with high ChW content [236].

5.5. CONCLUSION AND FUTURE TRENDS

Since the 1990s BioPUs have been widely studied from different aspects, among which the development of new materials for biomedical application is probably the most attractive topic. Biomedical applications include the controlled release of drugs, fertilizers and pesticides, absorbable surgical implants, skin grafts, bone plates and even tissue engineering. BioPUs are employed in tissue engineering and controlled release drug systems because of their suitable mechanical properties, good biocompatibility and biodegradability. The biodegradation rate of PUs depends on the chemical composition, sequence length, molecular weight, hydrophilic/hydrophobic balance, degree of crystallinity, morphology and surface topography. Many research groups worldwide have sought ways to improve the properties of BioPUs depending on the specific application. These efforts have often included optimization of the experimental conditions of PU synthesis, as well as chemical modification of the structure by choosing novel starting compounds and additives which can result in a broad range of mechanical, biological and physical properties.

In the tissue engineering field, the development of new technologies and advanced techniques for the fabrication of porous scaffolds is a permanent challenge for many research groups. The need for tissue scaffolds with high elasticity and strength combined with controllable biodegradation properties will bring new strategies for the synthesis and fabrication of BioPUs, still focusing on tuning the scaffold degradability without significantly affecting its mechanical properties. However, from a biocompatibility point of view, the most important issues regarding tissue scaffolds are the cytotoxicity of the original structure and the degradation products, as well as the polymers degradation rate. Therefore, many efforts will be directed to these topics, probably in a wide, multidisciplinary approach. Besides this, there is great potential for the development of new BioPU nanocomposites, and many opportunities both in terms of using novel nanoparticles and improving fabrication techniques. All areas of BioPU development will certainly increasingly involve the use of bio-resources, as well as the use of non-toxic starting materials.

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