Biodegradable Polyurethanes: Design, Synthesis, Properties and Potential Applications

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Abstract. This chapter reviews recent developments in biodegradable polyurethanes for applications in regenerative medicine and biomedical implants. A brief introduction to the chemistry, synthesis and structure property relationships in biodegradable polyurethanes developed for biomedical applications is provided. Numerous formulation strategies to address the mechanical property and biodegradability requirements for applications in cardiovascular, orthopaedic and nerve regeneration are reviewed to illustrate the structure-property-function relationships of biodegradable polyurethanes. Fabrication of scaffolds using processing techniques such as electrospinning and temperature induced phase separation is discussed. The compatibility, growth and proliferation of osteoblasts, chondrocytes, fibroblasts, endothelial cells, smooth muscle cells, and stem cells are summarised to demonstrate the suitability of polyurethane scaffolds for tissue engineering applications. Long-term *in-vivo* studies to demonstrate the functional performance, safety and biodegradation of polyurethane implants are summarized to illustrate the potential advantages of this class of polymers for emerging applications in tissue engineering and the next generation of biomedical implants.

Keywords: Biodegradable polyurethanes; regenerative medicine; medical implants; mechanical properties; biocompatibility; biodegradation; tissue engineering; polyester polyols; aliphatic diisocyanates; cardiovascular; orthopaedic; nerve regeneration

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1.0 Introduction

Polyurethanes are an important class of synthetic polymers with many industrial applications. The major applications include flexible and rigid foams, thermoplastic elastomers, adhesives and surface coatings [1-2]. Although the polyurethanes were introduced in the 1930s for industrial applications, their potential for biomedical applications was not realized until 1960s. Biomer® was the first polyurethane introduced for cardiovascular applications due to its excellent mechanical properties and good biocompatibility. Pellethane® was another polyurethane elastomer introduced as a lead insulator in cardiac pacemakers. In the 1980s it was revealed that these polyurethanes in long-term implants tend to degrade resulting in surface micro cracking causing, in some cases, device failure [3]. The underlying mechanism was considered to involve oxidative degradation of the polyether soft segment which is one of the major segments forming the polyurethane chemical structure. The oxidative degradation is triggered by several biological events initiated by the recruitment of monocytes to the surface of the implant, where they can differentiate into macrophages and foreign body giant cells. The release of biologically active molecules such as superoxides by activated macrophages, initiates the oxidative degradation of the methylene-ether linkages in the polyether segment of the polyurethane [4]. Further details on the biodegradation of polyurethanes can be found

in several excellent reviews published recently [5-9]. Research efforts during the 1980s and the 90s have seen the development of several families of polyurethanes with improved oxidative stability and broad range of mechanical properties to suit the needs of medical devices for a wide range of biomedical applications, in particular cardiovascular devices. The improvement in oxidative stability was achieved by replacing the polyether soft segment with those having chemical functional groups less susceptible to oxidative and hydrolytic degradation. The major chemical structure variations investigated included the reduction of susceptible ether linkages [10-12], and incorporation of carbonate [13], hydrocarbon [7] and siloxane functionalities in the soft segment [14-17]. Polyurethanes incorporating siloxane-based soft segments are arguably the most biostable polyurethanes available today for long-term medical implant applications [18].

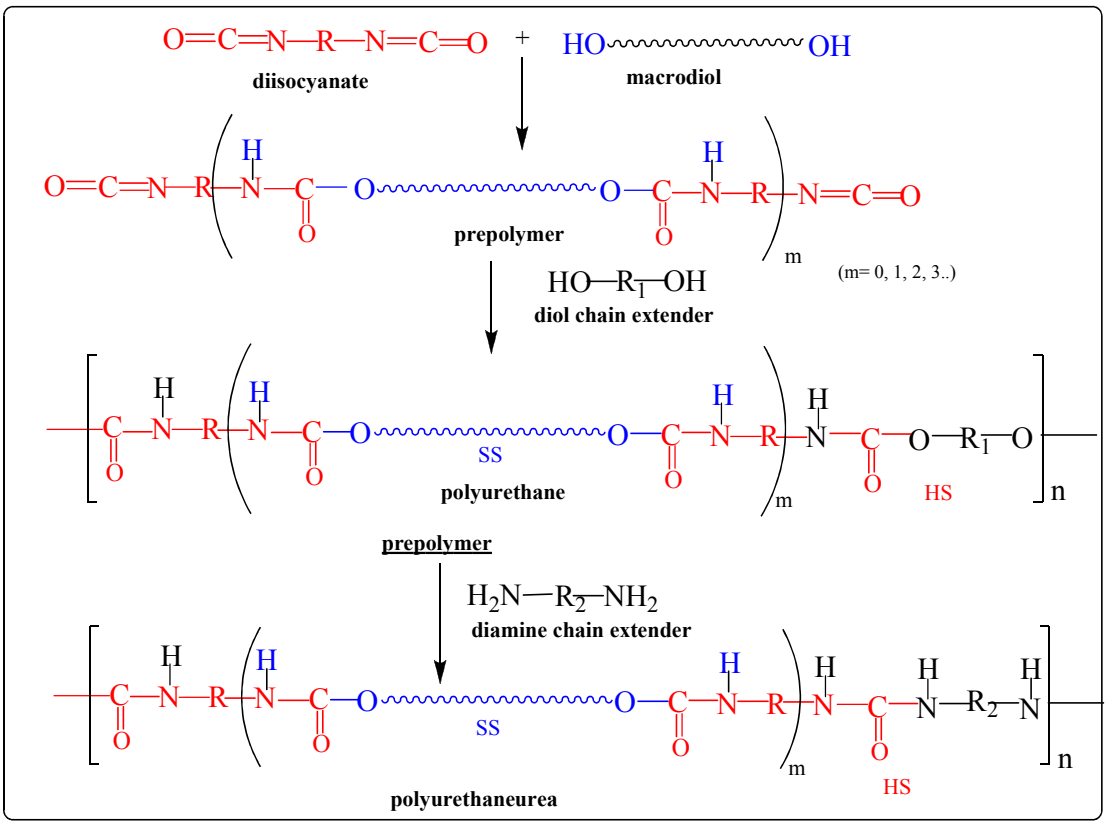
The emergence of tissue engineering as a potential technique to help repair and regenerate damaged and diseased biological tissues in the 1990s, saw the need for novel biodegradable materials to enable the advancement of this technology toward clinically useful products and therapies. In most of the early investigations biodegradable polymers such as poly(glycolide)s, poly(lactide)s and their copolymers with a long history of clinical use were employed, despite those being not optimal for most of the tissue engineering applications. Materials that are not only biocompatible and degradable but also with surface characteristics conducive to cell growth and proliferation were in demand for these applications. Ideal scaffolds for tissue engineering should also have mechanical properties compliant with biological tissues, suitable degradation kinetics as well as the ability to be fabricated into porous scaffolds with appropriate pore sizes and geometry. Among synthetic polymers, polyurethanes offer many advantages in designing materials to fulfil these requirements. The availability of a variety of precursor molecules, the relative ease of polyurethane synthesis and formulation options to tailor mechanical property and degradation requirements are among the key advantages. In addition, polyurethanes can be processed using a variety of techniques and formulated as *in-situ* curable liquid prepolymer systems.

Over the last 20 years, many research groups have investigated structure/property effects, biocompatibility and biodegradation of a range of polyurethane materials to

explore their potential in tissue engineering applications and other biodegradable medical implants. This chapter provides a brief introduction to the synthesis of biodegradable polyurethanes and the current understanding of their structure/property relationships, processability, biocompatibility and biodegradation along with available *in-vivo* data on safety and potential applications in biodegradable medical implants and as scaffolds for tissue engineered products and therapies.

2.0 Polyurethane Chemistry

The chemical reaction between an isocyanate group and a hydroxyl or amine group generates urethane and urea groups, respectively. This reaction has been employed to synthesise a range of thermoplastic polyurethanes (TPUs) and thermoset polyurethanes (TSPs). TPUs are prepared by reacting three compounds; a diisocyanate, a difunctional polyol (macrodiol) and a dihydroxy or diamine chain extender [1]. These monomers react to form linear, segmented copolymers consisting of alternating 'hard' and 'soft' segment blocks, which are characteristic structural features of TPUs. The hard segment (HS) is derived from the reaction of a diisocyanate with a chain extender, whereas the soft segment (SS) is derived from the long chain linear diol (macrodiol or polyol). The general chemical structure of a TPU is illustrated in Scheme 1. Due to thermodynamic incompatibility of soft and hard segments, polyurethanes exhibit two-phase morphology, and the respective segments aggregate to form microdomains. HS domains form ordered structures while the SS domains, with some exceptions are generally amorphous. The relative compatibility of the two segments dictates the morphology and thus the properties of polyurethanes; a highly phase separated TPU is generally poor in mechanical properties [1, 3].



Scheme 1. Reaction scheme for preparation of polyurethane and polyurethane urea

The use of one or more of tri or higher functional polyols, isocyanates or chain extender in a polyurethane formulation generates cross linked TSPs, and this strategy has been mostly employed in industrial PU foam manufacture [2]. The choice of appropriate monomer combinations and by controlling their relative proportions, flexible and rigid polyurethane foams can be prepared.

The reaction between isocyanate and hydroxyl group is exothermic, and catalysts such as organo-metallic compounds and tertiary amines increase reaction rate. On the other hand, the reaction of isocyanate group with a primary amine group is extremely fast, typically 1000 times faster than that with hydroxyl, and often the reaction is carried out at low temperature or in solvents to control the reaction exotherm. The polymerisation proceeds via a step-growth polymerisation mechanism and many excellent text books and review articles provide detailed information on steps to follow in order to synthesize high molecular weight polyurethanes [1, 3]. The general reaction scheme involved in polyurethane synthesis is illustrated in Scheme I.

In principle, polyurethanes can be prepared via one- or two-step batch procedures or by semi-continuous processes such as reactive extrusion [1-2]. One-step batch synthesis of TPUs involves the reaction of a mixture of the pre-dried macrodiol and the chain extender with the diisocyanate in the presence of a catalyst. The reaction is generally catalysed with dibutyltin dilaurate, stannous octoate or amine catalysts and is exothermic. The mixing of reagents is typically carried out between 70 and 80^{o}C. This "one-step" reaction can also be carried out in special continuous mixing machines, reactive extruders, or in continuous injection moulding machines.

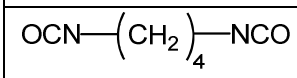
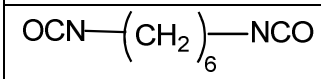
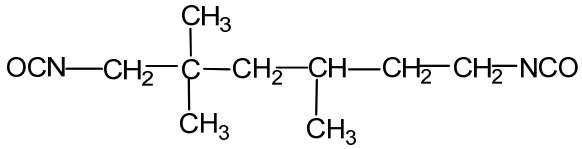
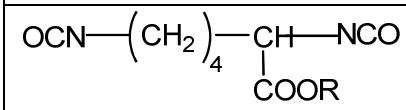
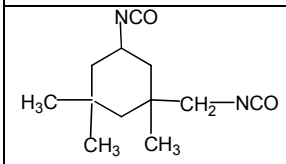
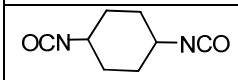
The two-step procedure gives good control of polymer architecture and can be carried out in bulk or in solvents, such as rigorously dried N,N-dimethylformamide or N,N-dimethylacetamide [19]. Polymerisations carried out in solvent are commercially less attractive and generally reserved for the preparation of solvent-castable polyurethanes or for laboratory investigations. The two-step batch procedure involves end-capping the macrodiol with diisocyanate and subsequently chain extending the resulting prepolymer with a low molecular weight diol or diamine (see Scheme 1). Both bulk and solution two-step processes are useful methods for preparing polyurethanes from non-polar macrodiols, which are less compatible with the generally more polar HS forming components (i.e., the diisocyanate and chain extender). The end-capping in the first step changes the solubility parameter of the macrodiol making it more compatible with other components, preventing the formation of compositionally heterogeneous polymers.

2.1 Precursors

2.11 Diisocyanates

In formulating polyurethanes for most industrial applications, the widely used diisocyanates are 4,4’-diphenylmethane diisocyanate (MDI) and toluene

Table 1. Aliphatic diisocyanates commonly used in formulating biodegradable polyurethanes and polyurethaneureas

ISOCYANATE	**Chemical Name**
	1,4-Butanediisocyanate (BDI)
	1,6-Hexamethylene diisocyanate (HDI)
	2,2,4-Trimethyl hexamethylene diisocyanate (TMDI)
	Ethyl 2,6-diisocyanatohexanoate (R= Ethyl, ELDI) and Methyl 2,6-diisocyanatohexanoate (R= methyl, MLDI)
	Isophorone diisocyanate (IPDI)
	1,4-Cyclohexane diisocyanate (CHDI)

diisocyanate (TDI). However, for biomedical applications aliphatic diisocyanates are preferred to avoid potential toxicity issues associated with aromatic diamines formed as one of the degradation products [20-21]. Table 1 lists the diisocyanates commonly used in formulating biodegradable polyurethanes. Among these Ethyl 2,6-diisocyanatohexanoate (ELDI) and Methyl 2,6-diisocyanatohexanoate (MLDI) are preferred due to the release of non toxic lysine, upon degradation of the corresponding urethane or urea linkages.

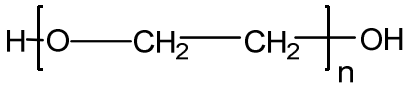
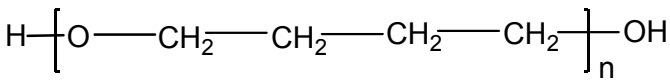
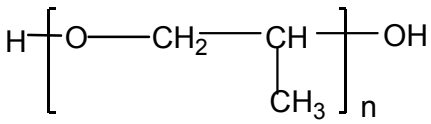
Until recently both MLDI and ELDI were commercially available form Kyowa Hakko Kogyo (Tokyo, Japan) or can be synthesized according to the literature

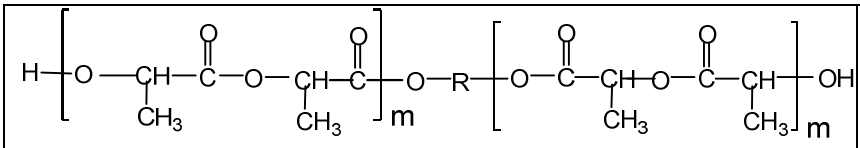
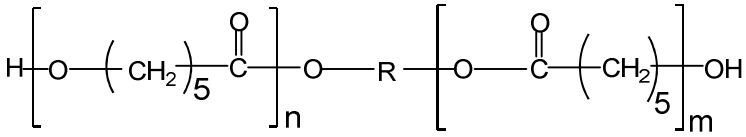
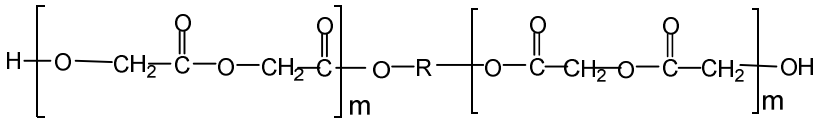
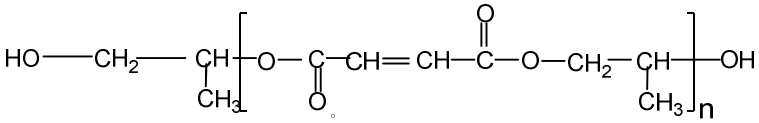
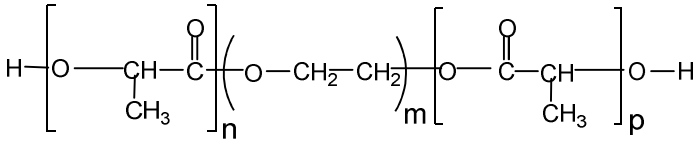
reported method [22-23]. Except 1,4-butanediisocyanate, the other diisocyanates in Table 1 are commercially available from various sources.

2.12 Polyols

The polyols used in biodegradable polyurethanes are oligomers with hydroxyl end functional groups (2 or higher functionality). The most widely used molecular weight range is from 500 to 2000 Da, but higher molecular weights up to 5000 Da have also been used in some PU formulations. The term macrodiol is also used to describe these oligomers in the literature when the polyol is difunctional. Table 2 illustrates polyols commonly used in formulating biodegradable polyurethanes. The chemical structure of the polyol has a significant influence on the degradation of polyurethanes as well as on hydrolytic and hydrophobic characteristics. The hydrolytic degradation is the main mechanism of degradation, although certain enzymes also initiate soft segment degradation [24]. Oligomers with amine end-functional groups are also used in PUU formulations, but to a lesser extent.

Table 2. Polyols used in formulating biodegradable polyurethanes and polyurethaneureas [R = $(CH_2)_n$]

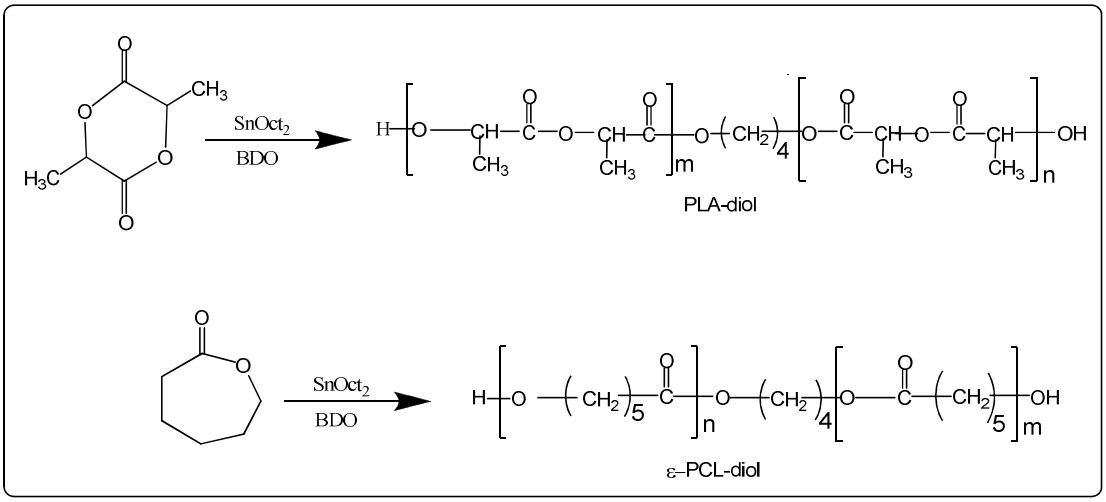
POLYOL STRUCTURE	**CHEMICAL NAME (Abbreviation)**
	Poly(ethylene oxide) (PEO-diol) or PEG-diol
	Poly(tetramethylene oxide) (PTMO-diol)
	Poly(propylene oxide) (PPO-diol)
	Poly(D,L-lactide)

	(PLA-diol)
	Poly(ε-caprolactone) (ε-PCL-diol)
	Poly(glycolide) (PGA-diol)
	Poly(propylene fumarate diol (PPF-diol
	Poly(lactic acid-ethyleneglycol-co-lactic acid) diol (PCL-co-PEG-co-PCL)

Most polyether polyols are prepared by ring-opening polymerisation of the corresponding cyclic ether monomers. For example, Poly(propylene glycol) is prepared by ring-opening polymerisation of propylene oxide with an initiator (alcohols or amines) and a catalyst. Three groups of catalysts are generally used to catalyse the polymerisation; base catalysts, acid catalysts and coordination catalysts [2].

Polyester polyols based on caprolactone, glycolide and lactides can be prepared by using either the ring-opening polymerisation [25] or by acid-catalysed condensation polymerisation of the corresponding hydroxyl acids [26-27]. Scheme 2 illustrates the preparation of ε-PCL diol and PLA-diol via the ring –opening polymerisation route. Stannous octoate is the most widely used catalyst and the polymerisation is generally

conducted at 160°C under a nitrogen atmosphere. The use of a polyhydroxy initiator such as pentaerythritol leads to polyols with star or hyper-branched structures.



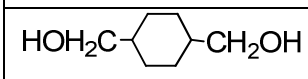
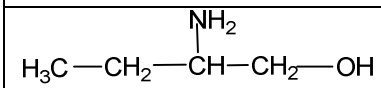
Scheme 2. Ring-opening polymerisation of D,L-lactide and caprolactone

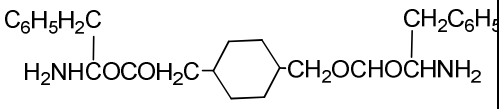
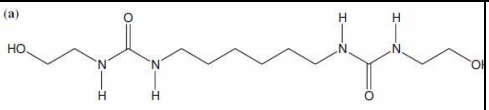
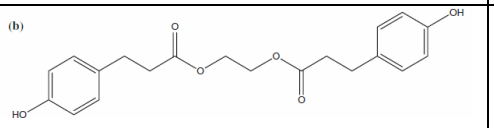
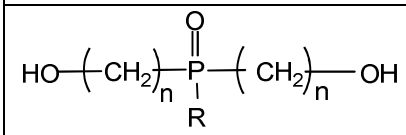
The condensation polymerisation of hydroxy acids (catalysed by stannous octoate) is also used to prepare polyester polyols [27].

2.13 Chain Extenders

Table 3 lists some of the most commonly used chain extenders in biodegradable polyurethane formulations as well as some of the novel chains extenders developed, primarily to enhance the degradation rate of the hard segment.

Table 3. Conventional and novel chain extenders useful in formulating biodegradable polyurethanes and polyurethaneureas

Structure	Chemical Name
$HO\text{-}CH_2\text{-}CH_2\text{-}OH$	Ethylene glycol (EG)
$HO\text{-}(CH_2)_4\text{-}OH$	1,4-Butanediol (BDO)
	1,4-Cyclohexanedimethanol (CHDM)
$H_2N\text{-}CH_2\text{-}CH_2\text{-}NH_2$	1,2-Ethanediamine (ED)
$H_2N\text{-}(CH_2)_4\text{-}NH_2$	1,4-Butanediamine (BDA)
	2-Amino-1-butanol (ABDO)

Chain extenders with degradable linkages	
$HOCH_2CH_2OCOCH(CH_3)OH$	2-Hydroxyethyl-2-hydroxypropanoate [28]
	4-((1-(1-Amino-2-phenylethoxy)ethoxy)methylcyclohexyl)methyl-2-amino-3-phenylpropanoate [24, 29-30]
	1,1-(Hexane-1,6-diyl)bis(3-(2-hydroxyethylurea [31-32]
	Ethane-1,2-diyl bis(3-(4-hydroxyphenyl)propanoate [31-32]
	R=H, n=2: Bis(2-hydroxyethyl)phosphate (BGP) R=H, n=2: Bis(2-hydroxyhexyl)phosphate(BHP) [33-35]

3.0 Polyurethane Structure Property Relationships

The chemical structure of the diisocyanate, polyol and chain extender as well as the relative proportions of these components in the polyurethane determine its mechanical properties, processability and biodegradation. Only a limited number of suitable diisocyanates are commercially available for formulation of biodegradable polyurethanes (see Table 1).

Many reviews articles and text books are available on the structure-property relationships of polyurethanes based on aromatic diisocyanates such as MDI and common polyether and polyester polyols [1, 3, 36-37]. The information from these studies has provided a good understanding of the relationship of chemical structures of monomers forming hard and soft segments in polyurethanes with mechanical properties and morphology. Many of the reported investigations related to biodegradable polyurethanes have used this knowledge in formulating polyurethanes, while focusing on precursors which are considered to produce non-toxic degradation products. Only a few studies could be cited where systematic investigations are

conducted to understand the structure property relationships of biodegradable polyurethanes [38-41]. In the following sections a summary of the studies that provide information to understand the influence of the hard segment and soft segment chemical structure on PU properties is provided.

3.1 Hard Segment

The chemical structure of the diisocyanate and the chain extender which form the HS of PU has a significant influence on PU morphology and mechanical properties. HDI is the most widely chosen diisocyanate in formulating biodegradable polyurethanes. The commercial availability and relative non-toxic nature [42] of the corresponding diamine 1,6-hexanediamine, which is the by-product upon polyurethane degradation may be the main reasons for its choice. BDI is also another aliphatic diisocyanate used in the synthesis of biodegradable polyurethanes. The symmetrical molecular structures of these two diisocyanates lead to better ordering of the hard segment through inter molecular hydrogen bonding, resulting in high strength elastomers. Elastomers with ultimate tensile strength up to 60 MPa and elongation up to 950% have been reported for HDI-based polyurethanes [39].

The morphology differences between aromatic (MDI) and aliphatic diisocyanate (HDI) was investigated by d'Arlas *et al*. [43] by preparing polyurethanes based on poly(hexamethylene carbonate-co-caprolactone) diol and 1,4-butanediol as SS, and chain extender, respectively. DSC and FTIR data demonstrated that MDI-based polyurethanes were less phase separated than those based on HDI.

De Groot *et al*. prepared PUUs based on ELDI, BDI and HDI with poly(ε-PCL-diol) (MW 2000) and 1,4-btanediamine as polyol and chain extender, respectively to compare mechanical properties [38]. HDI produced a PUU with a high ultimate tensile strength (UTS) of 38 MPa and high elongation (1168%) compared to BDI (29 MPa UTS and 1024% elongation). ELDI based PUUs exhibited poor mechanical properties (17 MPa UTS and 800% elongation) and the differences in properties are attributed to different degrees of ordering in the hard segment. This morphology

difference was further reflected in tear strength and permanent set values. BDI based materials exhibited the highest tear strength and lowest permanent set in the series.

Hassan *et al*. [44] reported preparation of high strength elastomers based on MLDI using a two-step solution polymerisation procedure. In a somewhat unconventional manner, the HS blocks containing ELDI and BDO were prepared first in toluene and reacted with ε-PCL-diol (MW 2000) to produce an elastomer with 33 MPa tensile strength and 1000% elongation at break. Using a similar synthesis procedure, Spaans *et al.* [45] prepared high modulus and high strength polyurethanes based on BDI, BDO and ε-PCL-diol (MW 2000). This procedure allowed the synthesis of PUs with uniform-size hard segment resulting in high modulus (105 MPa) and tensile strength (35 MPa).

Diisocyanates with non-linear structures such as CHDI and IPDI have also been used in synthesizing biodegradable polyurethanes, although to a much lesser extent. Due to less flexible backbone structure, resulting from cyclohexane rings, these diisocyanates generally produce stiffer materials compared to their linear analogues. Polyurethanes based on aliphatic diisocyanates 1,3 and 1,4-bis(isocyanato methyl) cyclohexane exhibit excellent mechanical properties and dynamic viscoelastic properties compared to those based on other aliphatic diisocyanates such as IPDI and HMDI as reported by Xie *et al*. [46]. The tensile strength of polyurethanes prepared from 1,3 and 1,4-bis(isocyanato methyl) cyclohexane, ε-PCL-diol and BDO was 50 MPa at 35% hard segment. The corresponding polyurethane prepared from H_{12}MDI showed only 16.8 MPa tensile strength. 1,3 and 1,4-Bis(isocyanato methyl) cyclohexane-based PUs also demonstrated higher elongation, compression set and Shore hardness compared to those based on H_{12}MDI. In addition, 1,3 and 1,4-bis(isocyanato methyl) cyclohexane elastomers displayed superior dynamic performance supported by constant modulus values over a wider working temperature window, lower tan δ values, high softening temperature, and higher critical point temperature. The property difference was less significant for polyurethaneureas prepared from 1,3 and 1,4-bis(isocyanato methyl) cyclohexane, H_{12}MDI and IPDI with caprolactone and Ethacure 100 chain extender. At 20% hard segment, the tensile strength of PUU from all three diisocyanates was in the range 36-37 MPa [46].

Hettrich et al. [47] reported the synthesis of novel diisocyanates based on amino acids containing ester linkages. PUs based on these diisocyanates contain HS with ester linkages, making them more susceptible to hydrolytic degradation. Recently Bezwada [48-49] reported the synthesis of diisocyanates with hydrolytically degradable ester linkages bridging the aromatic rings with the isocyanate functional groups.

Conventional chain extenders such as BDO, 1,2-ethanediol, 1,2-ethanediamine are used in preparing most biodegradable polyurethane formulations. 1,4-Butanediamine (putrescine) is a naturally occurring compound and is used as a chain extender in biodegradable polyurethanes due its relatively low toxicity [50]. The major influence of chain extender structure on polyurethanes properties is attributed to its effect on hard segment ordering which in turn affects the polyurethane crystallinity and mechanical properties. Generally short-chain compact and symmetrical molecules favour better ordering of the hard segment.

The design of chain extenders bearing specific functional groups as part of its main chain has been one of the approaches employed by researchers to enhance hard segment degradation, which otherwise is the slowest segment to degrade in polyurethanes. Some of these novel chain extenders are listed in Table 3. Functional groups include ester [28] phosphate ester [33-34] and diurea [51]. Chain extenders based on amino acids have also been developed to enhance enzyme mediated degradation of polyurethanes [24, 29-30, 52]. The influence of these novel chain extenders on polyurethane properties and biodegradability will be discussed in the section on 'designing biodegradable polyurethanes for biomedical applications'.

3.2 Soft Segment

The chemical structure of the polyol (macrodiol) which forms the SS influences the properties of polyurethanes and in particular the degradation rate. In many of the studies reported in the literature this aspect has been exploited in designing polyurethanes for specific applications. The common polyols employed in formulating biodegradable polyurethanes include poly(ε-caprolactone), poly(ethylene

glycol), poly(propylene glycol), polyols based on hydroxy acids such as glycolic acid, lactic acid and their copolymers and poly(3-hydroxybutyrate)diols (see Table 2). Poly(caprolactone) diol is arguably the most widely investigated polyol in biodegradable polyurethanes, and generally produces polyurethanes with good elastomeric properties due to its low glass transition temperature Tg (-60°C).

The effect of ε-PCL-diol molecular weight on polyurethane properties was investigated by Heijkants *et al.* [53] by preparing a series of polyurethanes with uniform-size hard segment length based on BDI and BDO. The ε-PCL-diol molecular weights were in the range 750 to 2800 Da and polyurethanes were synthesized using a two-step procedure without the use of a catalyst. The tensile strength gradually increased from 38.7 MPa for PCL-750 to 55 MPa for PCL-1900, while the elongation at break increased from 870% to 1173%. Polyurethanes based on PCL molecular weight 1600 Da and lower, exhibited crystalline urethane and amorphous PCL phases with some dispersed hard segments. In polyurethane with PCL molecular weights higher than 1600 Da, an additional SS crystalline phase was observed. This study illustrates that polyurethane with good mechanical properties can be prepared from ε-PCL-diol and choice of its molecular weight has an influence on the morphology [53-54]. Gorna *et al*. also investigated the effect of ε-PCL-diol molecular weight (530, 1250 and 2000 Da), catalyst and chain extender on molecular and physical characteristics [55]. Diisocyanates HDI and IPDI along with chain extenders BDO, 2-amino-1-butanol, thiodiethylene glycol and mercapto ethyl ether were used in preparing polyurethanes according to the two-step procedure. The isocyanate structure did not show a significant influence on mechanical properties. Among the catalysts investigated Fe, dibutyltin dilaurate, and Zn are reported to be more effective than stannous octoate. Polyurethanes with good mechanical properties have also been prepared with other diisocyanates, MLDI [44] and TDI [54].

In conventional PU elastomer formulations, a short chain diol or diamine is used as a chain extender. However, researchers have reported the preparation of polyurethanes without using a conventional chain extender; instead the polyol was directly reacted with a stoichiometric amount of the diisocyanate, where it is employed as a chain linker [41]. For example, Saad *et al*. [56] synthesized a series of polyurethanes using

a mixture of ε-PCL and poly(R-3-hydroxybutyrate)diol (PHB) by linking with HDI using a one-step solution (1,2-dichloroethane) polymerisation procedure. The molecular weights of PHB were 2100, 3000 and 44000 Da, where as those for ε-PCL-diol were 1080, 2200, 3700 and 5800. The polyurethane with ε-PCL-diol alone as the soft segment exhibited higher UTS (30.5 MPa) compared to those based on ε-PCL-diol and PHB mixed soft segments, the tensile properties of these polyurethanes were dependent on the relative amounts of ε-PCL-diol and PHB as well as the polyol molecular weight; the UTS ranged from 11 to 27 MPa in the series. The polyurethanes with higher molecular weight polyols exhibited greater phase separation than those based on low molecular weight polyols as demonstrated by DSC and WAXD results.

Similarly, many researchers have used this approach where a mixture of polyols or copolymers of different monomers is used to alter mechanical properties, vary hydrophilic/hydrophobic balance, improve biocompatibility, and more importantly to alter degradation kinetics [57-62]. Gorna *et al*. [57-59] investigated the effect of incorporating the hydrophilic polyols poly(ethylene oxide) (PEO-diol), poly(ethylene-propylene-ethylene oxide) (PEO-PPO-PEO) diols and hydrophobic a ε-PCL-diol on the properties of biodegradable polyurethanes. The HS in these polyurethanes was based on HDI and BDO or 2-amino-1-butanol. Increasing the PEO content resulted in higher water absorption; polyurethane based on 50/50 mixture of PEO-diol (2000 Da) and ε-PCL-diol (530 Da) absorbed 212% water, compared with 2% for ε-PCL-diol based polyurethane. The amount of PEO-diol, and its molecular weight significantly affected the mechanical properties, water absorption, and rate of hydrolytic degradation.

In another study, Gong *et al*. [62] synthesized copolymer polyols with PEG and ε-caprolactone and investigated the properties of polyurethanes prepared using IPDI and BDO. The water absorption and the degradation rate were influenced by the relative hard segment weight percentage and the relative amounts of PEG and PCL in the soft segment. Polyurethanes with higher PCL content absorbed less water and exhibited slow hydrolytic degradation.

Linear diols of triblock copolymers based on lactic acid (LA) and ethylene glycol, chain extended with HDI produced poly(ether-ester) urethanes with different degradation rates [60]. Polyurethane based on a copolymer diol with a higher percentage of LA was more hydrophobic and degraded slowly under *in-vitro* conditions, compared to the copolymer with a high PEG content. Kylmä *et al*. [61] employed a melt-processing method to prepare polyester urethane blends to investigate the effect of blending poly(lactic acid-co-ε-caprolactone urethane) [(P(LA-co-CL)] on the properties and morphology of lactic acid-based amorphous poly(ester urethane)s. The copolymer polyols with different ratios of LA and CL were used as the rubbery component (low Tg) to modify the properties of more rigid and brittle PLA based polyurethanes. These polyurethanes were prepared with HDI as the chain linker. The incorporation of the rubbery polyurethane, resulted in toughening of the more brittle PLA-based polyurethane and the LA:CL ratio influenced the phase mixing of the two polyurethanes. Polyol based on LA:CL (70/30) with 20% loading in the blend produced phased mixed materials with elongations of ~100%, however the strength of the materials was compromised.

De Groot *et al*. [63] prepared polyurethanes based on BDI and copoly(L-lactide/ ε-caprolactone) using the prepolymer method. Chain extension with BDO produced polyurethanes with poor mechanical properties, presumably due to trans-esterification. This problem was avoided by chain extending the copolymer diol with an isocyanate-terminated hard block, and a polyurethane with tensile strength of 45 MPa was achieved.

In summary, these studies clearly illustrate the various formulation options available to design polyurethanes with mechanical properties ranging from high strength elastomers to soft materials as well as to vary hydrophobic and hydrophilic characteristics.

4.0 Processing and Fabrication

A key advantage of polyurethanes over other synthetic polymers is their ability to be processed using a range of thermal and solvent based techniques to give various

structural forms and to enable the fabrication of scaffolds with varying pore geometry and architecture. Thermal processing of polyurethanes using extrusion, reaction extrusion, injection and compression moulding are described in excellent review articles and text books [1-3] and will not be discussed in this chapter.

Many of the papers on biodegradable polyurethanes reported in the literature have described different techniques to fabricate porous scaffolds for implantation and evaluation for tissue engineering applications. These techniques include salt leaching/polymer coagulation [64], thermally induced phase separation (TIPS) [65-68], electrospinning [65-66, 69-76], freeze drying [65, 77], reactive compression moulding [78], dip coating, solvent–casting particulate-leaching [79] as well as printing techniques such as ink-jet fabrication [80-81], drop on demand printing [82], and bioplotting/3D printing [83].

The TIPS method involves, the dissolution of the polymer in a suitable solvent, placing it in a mould and quenching to very low temperatures to phase separate and freeze the solvent. Typically, liquid nitrogen or dry ice/acetone may be required for quenching depending on the freezing point of the solvent. After removing the mould, the solid is placed in absolute alcohol at -20°C for an extended period of time to extract the solvent. The type of solvent, the polymer concentration and rate of cooling influence porosity, pore size and geometry. Figure 1 shows electron micrographs of scaffolds prepared by TIPS method under different conditions. The PEUU in this case was prepared from BDI, PEG-*b*-PCL-*b*-PEG polyol and BDA [68]. Freeze drying of polyurethane solutions is another method used to fabricate porous scaffolds.

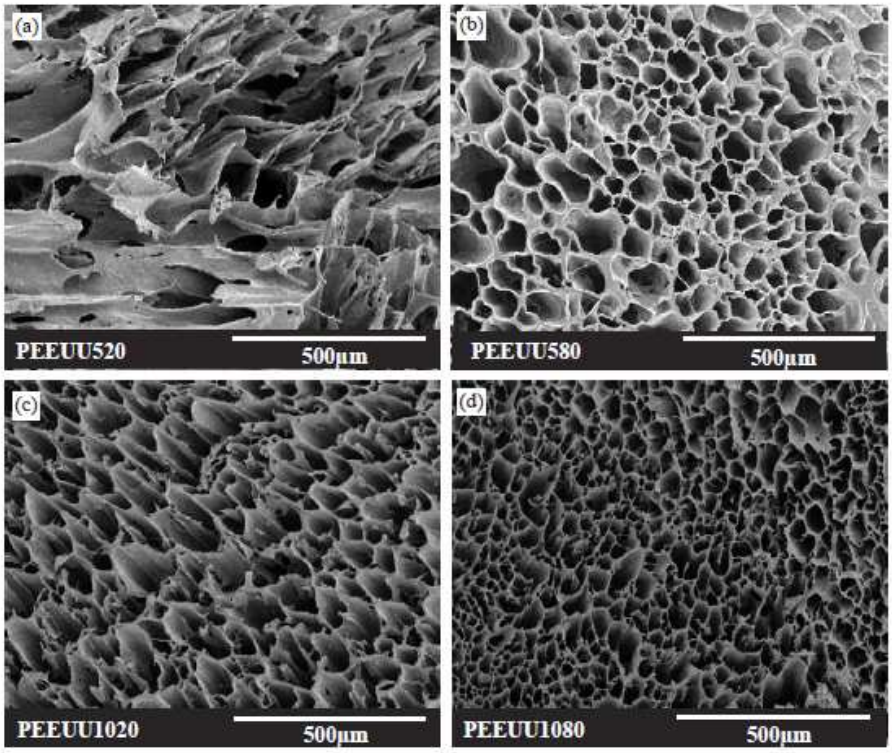


Fig. 1. Electron micrographs of PEUU scaffolds (longitudinal cross sections) prepared from different PEUU solution concentrations and quenching temperatures (a) 5%, -20°C (b) 5%, -80°C (c) 10%, -20°C (d) 10%, -80°C. (Reprinted from Biomaterials 2005, 26, 3961-3971; Guan, J.; Fujimoto, K. L.; Sacks, M. S.; Wagner, W. R.;. with permission from Elsevier)

Electospinning is a well established process to prepare fibres with diameters in the nanoscale or submicron scale. This process has been employed for the fabrication of nanofibre scaffolds from numerous synthetic polymers including poly(lactic acid), poly(glycolic acid), poly(ε-caprolactone), poly(hydroxybutyrate), as well as their blends [84]. However, this technique has been employed to a relatively lesser extent in fabricating scaffolds from biodegradable polyurethanes.

The process utilizes the electrostatic attraction between a charged polymer and a grounded or oppositely charged collection plate within an electric field. The polymer droplets in the electric field will extend into a cone before elongating into a fine jet. In a typical laboratory process (Figure 2), the polymer, dissolved in a solvent or in melt form is pumped through a thin nozzle with an inner diameter on the order of 100 µm. The nozzle serves as an electrode and a high electric filed of 100- 500kVm^{-1} is

applied to it with a counter electrode placed at a distance 10 to 25 cm distance from the nozzle. Electrospun fibres are collected on a substrate to which the counter electrode is in contact. The shape and size of fibres formed in this process are governed by many parameters. The polymer molecular weight, polydispersity, glass transition temperature, solution viscosity and concentrations are few of those parameters. The vapour pressure of the solvent and the relative humidity of the surroundings can also have significant effect. In addition, the properties of the substrate used to collect fibres, the feed rate, field strength and geometry of the electrode also play a major role in fibre formation.

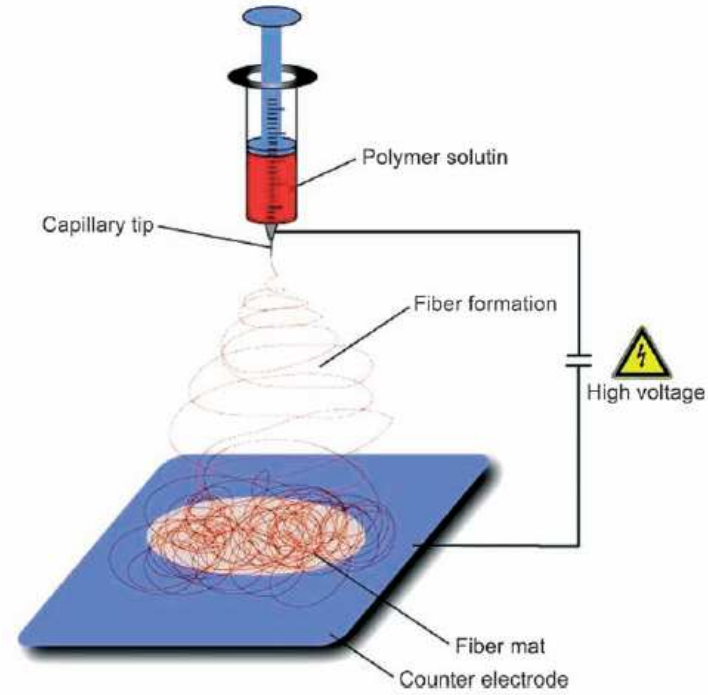


***Fig*. 2.** A laboratory set up for an electrospinning experiment with a perpendicular arrangement of electrodes. (Greiner, A. and Wendorff, J. H. Electrospinning: A Fascinating method for the preparation of ultrathin fibres. Angew. Chem. Int. Ed. 2007, 46, 5670-5703. Copyright Wiley-VCH Verlag & Co KGaA. Reprinted with permission)

Biodegradable polyurethanes have been successfully electrospun into nano and micron size fibres and fibre mats with varying porosity (Fig. 3) as scaffolds for tissue engineering [32, 71-76, 85-86].

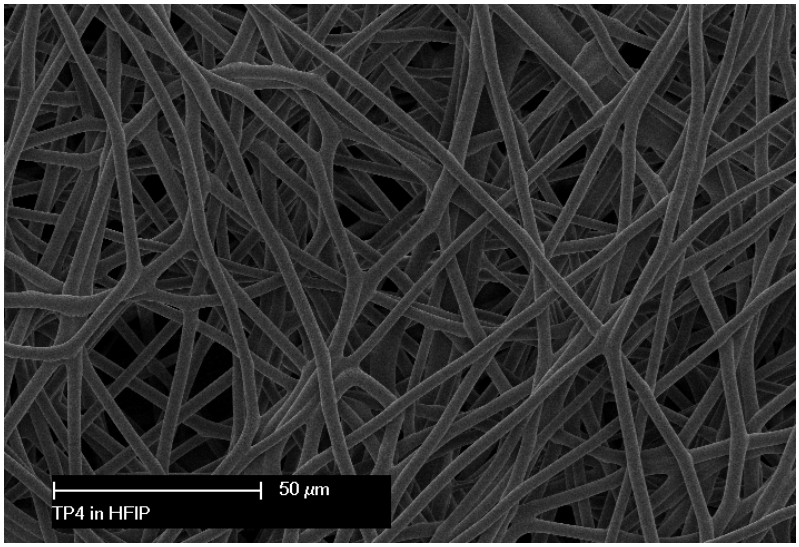


Fig. 3. Electrospun fibres of biodegradable polyurethane NovoSorb™[87]

Caracciolo *et al*. have successfully electrospun biodegradable polyester polyurethanes based on HDI, ε-PCL diol and novel diester-diphenol or diurea-diol chain extenders [31]. Bead free PU fibres with diameters of ~700 nm were prepared by optimising the processing parameters. This process has also been utilized to fabricate nanofibres as delivery systems for drugs [88], anti-bacterials agents such as silver nanoparticles [73], antibiotics [74]. An interesting study where smooth muscle cells were electrosprayed on to electrospun fibres without loosing cell viability illustrates the potential of this technique in fabricating scaffolds with cells [76]. The PUU used in this study was based on BDI, ε-PCL-diol and BDA and was electrospun using a hexafluoroisopropanol (HFIP) solution with concentrations in the range 5-12%. To incorporate cells a microintegration technique was used where cells were electrosprayed simultaneously with electrospinning of PEUU solutions 23 cm from the target. The micro integrated scaffolds fabricated this way exhibited good tensile properties, 2.0 to 6.5 MPa tensile strength and elongation 850 to 1700%. The viability of cells under perfusion culture conditions were 131% and 98% better than static culture, respectively after 4 and 7 days.

These studies not only illustrate the application of electrospinning to fabricate scaffolds with nanoscale fibres with varying pore size and porosity from biodegradable polyurethanes, but also demonstrate techniques to incorporate various bioactive additives during fabrication.

5.0 Designing Biodegradable Polyurethanes for Biomedical Applications

The major drive in the development of biodegradable polyurethanes is the need for better materials for next generation medical implants requiring improved biocompatibility and controlled biodegradation to address the materials need in tissue engineered products and therapies. The ability to tailor mechanical, biological and physiochemical properties of polyurethanes make this class of synthetic polymers particularly attractive materials to fabricate scaffolds for tissue engineering applications. Understanding the relationship of the molecular structure of polyurethanes on mechanical properties, biocompatibility, and degradation in *in-vivo* environments plays a pivotal role in designing biodegradable polyurethanes for these applications. Biodegradable polyurethanes have been evaluated extensively for cardiovascular [6, 29-30, 50, 52, 66-68, 76, 89-103], musculoskeletal [38, 45, 51, 58, 104-128] and to a lesser extent nerve tissue [129-131] regeneration.

5.1 Cardiovascular applications

Biodegradable materials with good biocompatibility, elasticity and high tensile strength are required to fabricate scaffolds for cardiovascular tissue engineering. Biodegradable polyurethanes with these properties have been formulated using polyols such as poly(caprolactone), PEG and their copolymers along with diisocyanates ELDI, HDI and BDI and chain extenders BDO, 1,4-BDA, and 1,3 BDA [59, 68, 117, 126, 132-137]. The low T_g of PCL (-60°C) imparts elastomeric properties to the PUU and incorporation of PEG makes it more hydrophilic and influences the degradation rate. Gorna *et al*. [59] reported on synthesis and properties of a series of polyurethanes based on PCL/PEG, HDI/IPDI and chain extenders BDO and 2-amino-1-butanol to vary the hydrophilic-hydrophobic ratio. The tensile strength of the PU varied in the range of 4 to 60 MPa whereas the elongation at break varied from 100 to 950%. Protein absorption was highest with PUs based on PCL and there was no protein absorption observed with those based on PCL/PEG combination, irrespective of the PEG molecular weight. Guan *et al*. [97] prepared a series of PUU elastomers based on PCL-PEG-PCL, BDI and 1,4-butanediamine to investigate mechanical properties, cytocompatibility and degradation. PUUs with tensile

strengths ranging from 8 to 20 MPa and breaking strains from 325% to 560% were produced and the endothelial cell adhesion on these PUUs was 60% of tissue culture polystyrene and was inversely related to its hydrophilicity. Immobilisation of cell adhesion peptide Arg-Gly-Asp improved the endothelial cell adhesion to levels comparable to TCP.

In other studies, Guan *et al*. [68] prepared PUUs based on PCL or PCL-PEG-PCL, BDI and BDA, and investigated properties of porous scaffolds prepared from these materials for soft tissue applications. Scaffolds with porosity in the range 80 to 97% were fabricated by applying a thermally induced phase separation approach with DMSO as the solvent. PUUs based on PCL produced scaffolds with tensile strength of 1 MPa and break elongation > 214%, and those based on PCL-PEG-PCL were weaker and degraded faster. Both PUUs supported smooth muscle cell adhesion and growth while the cell growth on PCL-PEG-PCL based PUUs was significantly higher.

An elastomeric, biodegradable porous (85%) cardiac patch was fabricated from a biodegradable PUU prepared from BDI, BDA and ε-PCL-diol 2000 by using thermally induced phase separation technique [99]. Surgical defects in the right ventricular outflow tract of adult rats were implanted with PUU patch along with poly(tetrafluoroethylene) (PTFE) patches (control) and explanted after 4, 8 and 12 weeks. At 4 weeks, fibroblast in-growth into PUU patch was observed and cellular infiltration of the implant increased with time. The control PTFE patch exhibited no cellular in-growth, and elicited a foreign body reaction. At 12 weeks, the PUU patch was completely degraded. The same authors investigated PUU cardiac patch for its effectiveness to promote vascular remodelling and improve function by implanting the patch onto subacute infarcts in Lewis rats [100]. After 8 weeks, the patch was largely remodelled and the left ventricular wall was thicker than the infraction control. The patch promoted the formation of new contractile phenotype smooth muscle tissue and improved contractile function

Polyurethane scaffolds fabricated from MDI, 1,3-diaminopropane and ε-PCL-diol, (530 Da) seeded with myoblasts was also investigated as an alternative to direct intramyocardial cell transplantation [92, 101]. The most favourable cell attachment *in-*

vivo was observed for laminin-coated scaffolds. However, there was no evidence of seeded cells penetrating the myocardium from the scaffolds and no signs of polymer degradation. In a related study [101] using a patch based on BDI/putrescine/PCL2000, there was no improvement in preservation of LV function relative to direct injection of myoblasts.

The modification of chain extender structure is one of the strategies used by researchers to enhance hard segment degradation rate in formulating polyurethanes for cardio vascular tissue engineering applications. The incorporation of chain extenders based on amino acids has been explored by several groups [66, 137-139] to develop PUUs for soft tissue engineering. Rechichi *et al*. [138] synthesized chain extenders by reacting phenylalanine with 1,4-cyclohexanedimethanol and prepared a series of PUUs using MLDI, PCL or PCL-PEG-PCL as the other components. *In-vitro* biological assays (cytotoxicity, fibroblast adhesion and proliferation) confirmed that these polyurethanes were non-toxic, and promoted adhesion and proliferation of fibroblasts. Fromstein *et al*. [66, 137] investigated the effect of blending amino-acid based PUUs prepared from MLDI/PCL2000 or MLDI/PEG (PEG 600 or 1000) on properties and degradation rate to assess their suitability for soft tissue engineering. The mechanical properties of the blends varied from 6 to 20MPa while elongation at break varied in the range 512% to 690%. The *in-vitro* degradation rate was dependent on the PEG content in the blend with PUUs based on PEG1000 exhibited the fastest rate in the series. The dipeptide Gly-Leu has also been introduced as part of chain extender by reacting with cyclohexanedimethanol [139].

The incorporation of growth factors to improve cell growth has also been explored with biodegradable polyurethanes [67, 91]. PUs based on BDI, ε-PCL-diol 2000 and amino acid based chain extender with H-Ala-Ala-Lys-OH and was electrospun to form fibrous scaffold with good mechanical strength (up top 11.1 MPa UTS) and elasticity (up to 88%). Insulin-like growth factor (IGF-1) encapsulated in PLGA micorspheres were electrosprayed on to the scaffold. The cell (mesenchymal stem cell) growth was significantly higher on scaffolds with IGF-1 [91]. In another study, the basic fibroblast growth factors (bFGF) was incorporated into scaffolds prepared from polyurethanes based on BDI/PCL200/BDA [67]. Scaffolds were prepared by the

thermally induced phase separation method and exhibited high porosity (90%) with good elasticity and mechanical strength. The growth factor was incorporated as part of the scaffold fabrication process with bovine serum albumin and in some cases, heparin was added which helped to increase bFGF release rates. The activity of bFGF was retained for up to 21 days and its biological activity was indicated by the higher densities of smooth muscle cells after 7 days compared to scaffolds without the growth factor.

In summary, the ability to formulate biodegradable polyurethanes with mechanical properties compliant with cardio vascular tissues, fabrication into porous scaffolds with good mechanical properties and high porosity as well as incorporation of biological agents to enhance cell growth and proliferation make this class of biodegradable polymers attractive for cardio vascular tissue engineering applications.

5.2 Musculoskeletal applications

Biodegradable polyurethanes are also an attractive class of synthetic polymers used in the fabrication of scaffolds to help regenerate cartilage and bone. Numerous studies on design synthesis and evaluation of polyurethanes for these applications have been reported in the literature. Grad *et al.* [128] investigated porous polyurethane scaffolds fabricated from HDI, ε-PCL, and isosorbide diol (1,4:3,6-dianhydro-D-sorbitol)[59] to assess their suitability for attachment and proliferation of primary chondrocytes under *in-vitro* conditions. This study demonstrated that the scaffolds supported chondrocyte attachment and the production of extracellular matrix proteins, though one of the limitations was the diffusion of large amounts of matrix molecules to the culture medium. The favourable mechanical properties of the scaffold may help provide mechanical stimulation to develop a functional cartilage-like extracellular matrix. Field et al. [140] reported on preliminary studies to evaluate the potential of an in-situ curable biodegradable polyurethane adhesives based on ELDI and dl-LA/ GA polyol to repair meniscal cartilage tissue. The adhesive was injected into a surgically created defect in sheep meniscus and the examination of histology sections of tissue explanted after one month saw evidence of cell migration to the defect site without any adverse tissue reactions.

Polyurethane based on MDI, ε-PCL-diol (530 Da) and 1,3-PDA has been evaluated for use in fabricating yarns for anterior cruciate ligament (ACL) reconstruction [109-110]. The fibres prepared using a wet-spinning process were of high strength and stiffness and retained 50% of its original tensile strength for more than 9 months at body temperature. This material trade named Artelon® is commercialized by Artimplant® AB, Goteborg, Sweden and has received CE Mark and FDA approval [110]. Artelon® films were observed to have equal or lower ability to activate human mononuclear cells *in-vitro* compared to titanium or polystyrene. *In-vivo* studies with rabbits and mini pigs to test biocompatibility and safety have been reported [109]. Artelon has also been developed as a spacer for the trapeziometacarpal joint (TMC) for the treatment of TMC osteoarthritis [141].

Biodegradable scaffolds fabricated from polyurethanes have been evaluated for the knee-joint meniscus. In some early studies MDI-based polyurethanes were evaluated for healing of meniscal lesions [113, 115, 142]. The use of MDI in formulating biodegradable polyurethanes may have the problem of toxicity associated with the degradation product MDA [20-21, 143]. To overcome this potential toxicity issue, polyurethanes based on aliphatic diisocyanate BDI, poly(ε-caprolactone-co-l-lactic acid) diol and 1,4-BDA or 1,4-BDO have been developed for cartilage tissue regeneration. A salt leaching/freeze-drying technique was used to prepare the scaffolds from these polyurethaneureas which have interconnected pores (150 to 300 microns) and have a modulus of 200 kPa, suitable for regeneration of fibrocartilage [108].

Micro-porous polyurethane amide and polyurethane-urea scaffolds have been evaluated by Spaans *et al.* [45, 116] for repair and replacement of knee-joint meniscus. The SS in these polyurethanes were based on 50/50 l-lactide/PCL polyol while the HS was based on BDI and adipic acid and water. The reaction of water with BDI releases carbon dioxide to generate the porous structure. The addition of surfactant and exposure to ultrasonic waves help regulate the pore size and structure [116] and scaffolds with 70 to 80% porosity were prepared by this technique. A

meniscal replica based on this polyurethane-urea was implanted in the lateral meniscus of dogs. Only fibro-cartilage was formed after 18 weeks, but the degeneration of the articular cartilage was decreased.

Kavlock *et al*. [118] have developed a family of biodegradable PUUs based on BDI, poly(ε-caprolactone) diol and tyramine-1,4-diisocyanatobutane-tyramine or its tyrosine analogue as chain extender. The phenyl groups in these chain extenders are expected to impart rigidity similar to PU with MDI-based hard segments. The new PUUs supported *in-vitro* attachment and proliferation of viable MG-63 human osteoblast-like cells. Bone marrow stromal cells cultured on rigid polymers films in osteogenic medium *in-vitro* up to 14 days exhibited comparable results to control poly(d,l-lactide-co-glycolide) with respect to cell number, alkaline phosphate activity, and osteopontin and osteocalcin expression.

The effect of varying the chemical composition and hydrophilic to hydrophobic ratio on bone growth was evaluated by preparing a series of polyurethanes based on HDI, ε-PCl-diol and pluronics [58, 144]. Porous scaffolds fabricated from these polyurethanes were implanted in monocortical defects in the iliac crest of healthy sheep for 6 months and defect sites healed to varying extent with cancellous bone. The calcium to phosphate ratio was comparable to that of the healthy cancellous bone. The new bone in more hydrophilic implants exhibited a higher mineral content than the more hydrophobic implants. The cortex formation was not observed for any of the implants, instead a soft tissue layer grew over the surface of the defect. In another study [145], scaffolds incorporating a calcium-complexing agent (citric acid) implanted in estrogen-deficient sheep for 18-25 months, promoted the highest bone regeneration.

Incorporation of tricalcium phosphate, hydroxy apatite and calcium carbonate has been used to enhance the osteoconductivity of polyurethane scaffolds [89, 105, 144, 146]. Nanoparticle hydroxy apatite (up to 30%) was incorporated into a PU based on TDI, caster oil polyol and BDO and porous scaffolds were prepared by a foaming method. Both *in-vitro* and *in-vivo* data confirmed good cell adhesion, growth and proliferation [105]. In another study Liu *et al.* [146] incorporated HA into a

polyurethane based on H_{12}MDI, PCL and BDO during the synthesis. Scaffolds with porosity up to 83 % containing 50% HA and good compressive strength (554 kPa) were prepared by this approach.

5.3 Nerve regeneration

Scaffolds for nerve regeneration are tubular structures that guide the regenerating axions to the distal nerve stump. Nerve guides based on biodegradable polymers with built-in systems to deliver growth factors or growth factors producing cells are particularly attractive for peripheral nerve repair [131]. Biodegradable polyurethane can offer attractive properties and processing options in fabricating scaffolds for nerve regeneration.

Borkenhagen *et al*. [130] fabricated tubular structures based on polyurethanes prepared from poly[glycolide-co-(ε-caprolactone)]-diol and crystallizable blocks of poly[(R)-3-hydroxybutyric acid-co-(R)-3-hydroxyvaleric acid]-diol (PHB) with 2,2,4-trimethylhexamethylene diisocyanate (TMHDI) as the chain linker. The conduits (10 mm long) made from three different materials with varying PHB content (41, 17 or 8 wt% PHB) were implanted across an 8 mm gap in the sciatic nerve of rats for 4, 12 and 24 weeks. The regenerated tissue centrally located within the guide lumen was composed of numerous myelinated axons and Schwann cells; no significant difference in regeneration between different materials was observed. The inflammatory reaction associated with the polymer degradation had not interfered with the nerve regeneration process. At 24 weeks, the polymer with 8% PHB degraded the most.

Yin *et al*. [129] evaluated nerve guides fabricated from biodegradable elastomeric PU prepared from HDI, ε-PCL-diol and PEO-diol to repair a 12-mm femoral nerve gap in rabbits. Myelinated axon regeneration was observed from 4 weeks onward on the implantation, along with polymer degradation during the 12 week long study.

5.4 Injectable and *in-situ* cure polyurethane prepolymer systems

Two-component prepolymer systems formulated to react upon mixing under mild conditions have the advantage of delivering to the implant site, using minimally invasive procedures such as arthroscopic delivery. Such systems are particularly useful for applications in orthopaedic fracture fixation, as bone cements or bone void fillers, and have the potential to deliver growth factors or other promoters to enhance cell growth. Since the urethane forming reaction does not release any low molecular weight by-products, liquid two-part urethane systems can be formulated for these applications. Although two-part prepolymer systems are well known in PUR industry, their potential applications in such biomedical applications have been explored only recently.

The biodegradable polyurethanes discussed in previous sections were primarily linear thermoplastic elastomers and fabricated into scaffolds for direct implantation or seeded with cells and growth promoting agents to help tissue regeneration. The injectable prepolymer systems are formulated to form cross-linked polymer networks upon completion of the urethane/urea formation reaction once the components are mixed together. Gunatillake et al. [124, 147-150] have developed polyurethane prepolymers that can be cross linked to form both rigid and elastomeric materials (NovoSorb™, PolyNovo Biomaterials, Melbourne, Australia) useful for a range of biomedical applications including scaffolds for tissue engineering. The difference in reactivity of the two isocyanate functional groups in diisocyanates, such as ELDI or MLDI, is used to prepare prepolymers that are liquids at and above ambient temperature by reacting with multifunctional core molecules such as pentaerythritol. Under controlled reaction conditions, star/hyperbranched prepolymers with isocyanate end-functional groups are formed. For example, the reaction of a diisocyanate with a core molecule such as pentaerythritol, glucose or glycerol produces isocyanate end-functional prepolymers which are viscous liquids at ambient temperature. The second component (Prepolymer B) is usually a di-functional or multi-functional polyester polyol and suitable examples include polycaprolactone, poly(orthoester)s, poly(glycolic acid), poly(lactic acid) and their copolymer polyols. The reaction of the two prepolymers, along with other appropriate additives, produces a cross-linked polymer network. With appropriate choice of precursors, materials with compressive strength up to 260 MPa and compressive modulus over 2GPa have been produced [124]. Polyols with high glass transitions temperature [(ex. poly(glycolides)]

generated PU networks with high modulus. With the control of the cross-link density as well the appropriate choice of polyols and diisocyanates, polyurethanes network with a wide range of mechanical properties can be prepared. By the addition of an appropriate amount of water as a chain extender/cross linker, porous scaffolds are generated due to the carbon dioxide released during reaction. The polymer compositions can be formulated to cure with a low reaction exotherm and therefore designed to not exceed body temperature [124].

Polyurethane prepared by this approach have shown good compatibility with osteoblasts [149]. The contact angles of PUR films produced by this method were intermediate between the Thermonex (50°) and poly(D,L-lactic acid) (67°). The films supported the attachment of viable primary human osteoblasts, as evidenced by the healthy osteoblastic spindle-like morphology and >95% viability as assessed by live/dead staining. The metabolic activity of the cells increases from day 1 to 7, suggesting that the cells have proliferated on these materials [149].

The degradation, safety and suitability of injectable prepolymer system as a bone void filler were evaluated in a sheep implant study [124]. Prepolymer A was based on PE and ELDI, whereas prepolymer B was based on PE and DL-lactic acid (PEDLLA) or PE and glycolic acid (PEGA) with molecular weights 456 and 453, respectively. The cured polymers exhibited high compressive strength (100-190 MPa) and modulus (1600-2300 MPa). Precured cylindrical test specimens (porous and non-porous) were implanted in 10mm diameter implant sites drilled in sheep femurs. The prepolymer mixture in viscous liquid form was injected to fill the drill holes and allowed to set for 8 -10 min before closing the surgical site. Sheep implant study results demonstrated that the polymers in both injectable and precured forms did not cause any surgical difficulties or adverse tissue response. Evidence of new bone growth and the gradual degradation of the polymers were observed with increased implant time up to 6 months (Fig 3).

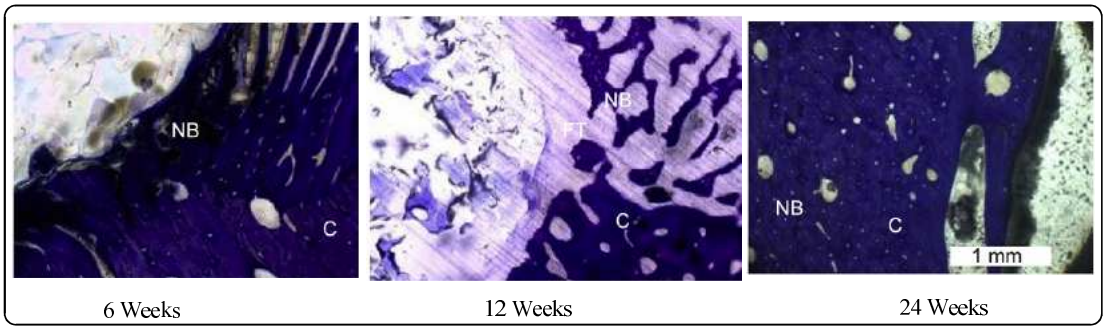


Fig. 3 Representative photomicrograps of histology sections of injectable porous polyurethane implants based on PE-ELDI (prepolymer A) and PEGA/PE-DLLA (Prepolymer B): Annotation: N= new bone, P = plug, FT or arrow = fibrous tissue, C = cortical bone [124]

Guelcher et al [151] have employed a quasi-prepolymer approach to eliminate the miscibility and viscosity issues associated with two-part prepolymer systems. In this process, a large excess of polyisocyanate is reacted with a polyol (e.g., NCO:OH equivalent ratio >5:1), to end-cap all the poloyol hydroxyls. The excess diisocyanate will keep the viscosity low of the quasi prepolymer. Biodegradable PUR networks were prepared by the reaction of the available isocyanate groups of the quasi prepolymer with a polyester polyol. The modulus of the cast polymers ranged from 1200 to 1430 MPa, while the compressive strength ranged from 82 to 111 MPa. The materials degraded to non toxic decomposition products and supported the attachment and proliferation of viable MC3T3 cells.

6.0 Biocompatibility and Biodegradation

Numerous *in-vitro* and *in-vi*vo studies have indicated that the biocompatibility of biodegradable polyurethanes is generally favourable in biological environments. Standard cytotoxicity assays and *in-vitro* cell attachment and proliferation studies have demonstrated that biodegradable polyurethanes with a broad range of chemical compositions have acceptable cytocompatibility.

6.1 Cell Compatibility

Attachment, growth and proliferation of chondrocytes [104, 107, 120, 125, 128, 132, 147, 152-153], osteoblasts [89, 126, 149, 154-157], fibroblasts [67, 138-139, 158-160], stem cells [66, 121, 161-163], and endothelial cells [94, 161, 164-166] on biodegradable polyurethanes with a wide variety of chemical compositions have been reported. These studies demonstrate the favourable cell adhesion and growth characteristics of biodegradable polyurethanes for different cell types.

Highly porous (pore size 100 to 300 nm) scaffolds fabricated from Degrapol®, biodegradable polyurethanes based on poly[(R)-3-hydroxybutyric acid-co-(R)-3-hydroxyvaleric acid]-diol, exhibited good cell attachment and growth of chondrocytes [153]. Chrondocytes maintained their phenotype including the expression of collagen type II and chondroitin sulphate. Only six days after cell seeding, a confluent cell multilayer was formed on the surface of the foam and histology sections confirmed massive cell in-growth into the pores. In comparison to alginate hydrogels, bovine chondrocyte viability on Degrapol® scaffolds was poor, presumably due to the difference in hydrophilicity [104, 152].

Biodegradable polyurethanes based on HDI, ε-PCL-diol and isosorbide diol also exhibited good compatibility with chondrocytes [128]. Bovine chondrocytes (isolated from young calves) were cultured on these PU scaffolds for 42 days *in-vitro* and a progressive increase in glucosaminoglycans and collagen was observed during the culture period. In another study [125], the effect of pore size on bovine chondrocyte growth and proliferation was investigated to assess porous PU scaffolds as a substitute for periosteal patches used in autologous cell implantation for articular cartilage regeneration. Thin membranes with varying pore sizes (5 to 60 µm range) along with P(l/dl-LA) control were included in the study. There was no observable pore size dependency on cell growth but the matrix production was higher in PU membranes during the first 10 days compared to P(l/dl-LA). Impregnation of membranes fabricated from isosorbide diol-based PUs with compounds such as isoprenoid (3,7,11-trimethyl-2,6,10-dodecratrien-1-diaminobutane amide) and plant polyprenols induce beneficial effects for cell growth [107, 132]. The incorporation of long-chain

plant polyprenols into these PU membranes enhanced extracellular matrix formation when tested *in-vitro* with chondrocytes harvested from LEW rats [132].

The compatibility, growth and proliferation of osteoblasts have also been evaluated on PU scaffolds with different chemical compositions [89, 127, 149, 154-157]. A prepolymer prepared from ELDI and glycerol was cross linked with water to form a porous spongy PU network. Under *in-vitro* conditions, rabbit bone marrow stromal cells attached to the polymer matrix and remained viable. Cells grown on PU surfaces did not differ from those that grew on tissue culture polystyrene. A similar polyurethane network prepared from ELDI, glycerol and ascorbic acid also supported adhesion and viability of osteoblastic precursor cells (OPC) *in-vitro*. Mouse OPCs produced multilayers confluent layers, characteristic of typical bone cells [127]. Ascorbic acid release due to PU degradation stimulated cell proliferation, type I collagen formation and alkaline phosphate synthesis. Wang et al. [155] investigated the influence of PU surface morphology on osteoblast growth by implanting (subcutaneous in Rat) three PU membranes with different surface morphologies. PUs based on MDI, poly(butylene adipate) diol and BDO were implanted as membranes with smooth, uneven (sunken) and particulate surface appearances. The cells on the particulate surfaces were well spread and flattened and had the highest cell adhesion.

Incorporation of hydroxy apatite nano-particles to PU scaffolds helps to improve bone formation as demonstrated by a subcutaneous study in rats [89]. After 5 weeks of implantation, histology examination of sections showed much of the PU is degraded and areas with rich woven bone and areas populated with cells. Polyurethane scaffolds with two different pore sizes (140-400 and 200-600 μm range), impregnated with platelet rich plasma or fibrin were evaluated for their suitability to grow bone marrow stormal cells *in-vitro*. Cells grew more efficiently in scaffolds with smaller pore size, while some calcification was observed in scaffolds with larger pore size. The effect on cell growth and proliferation was more pronounced in platelet impregnated scaffolds than those with fibrin [156].

Hafeman et al. [157] investigated the effect of triisocyanate composition on the biological and mechanical properties of biodegradable, injectable polyurethane scaffolds for bone and soft tissue engineering. Scaffolds were prepared by reactive

liquid moulding technique using HDI or ELDI triisocyanates and trifunctional polyols based on glycolide and d,l-Lactide. Scaffolds with hydrophilic properties were prepared by incorporating PEG as part of the polyol. Under *in-vitro* test conditions, embryonic mouse osteoblast precursor cells permeated and attached to porous scaffold interstices and the cell viability was 87.5-94.7% and 88.4-89.9%, respectively after 4-week and 8-week exposure to the degrading scaffold. Scaffolds implanted subcutaneously in rats exhibited progressive invasion of granulation tissue with little evidence of an overt inflammatory response or cytotoxicity.

Biodegradable polyurethane scaffolds have also been evaluated as substrates for growth and proliferation of stem cells [66, 80, 163, 167-168]. Nieponice et al. [163] incorporated muscle-derived stem cells (MDSCs) into the pores of tubular PEUU scaffolds using a rotational vacuum seeding device in order to understand the interaction and mechanical properties of the construct for vascular applications. After 3 days, the constructs appeared completely populated with cells that were spread within the polymer with cell populations increasing 2.1-fold. This study demonstrated that MDSCs can be rapidly seeded within porous biodegradable tubular scaffolds while maintaining cell viability and high proliferation rates without losing the stem cell phenotype for up to 7 days of *in-vitro* culture. In another study, Wang *et al*. [168] prepared PUs based on MDI, ε-PCL-diol and dimethylpropionic acid, and demonstrated that the PUs were non-toxic to human umbilical vein endothelial cells and mouse embryonic stem cells; both types of cells can effectively adhere to and spread on the PU surface.

The architecture of the PU scaffold has an influence on cell morphology. Fromstein *et al*. [66] evaluated the effect of the PU scaffold macro-architecture on adhesion, viability, and morphology of bioreactor-produced, embryonic, stem-cell-derived cardiomyocytes. Polyurethanes based on ELDI, poly(caprolactone) diol and phenylalanine chain extender [24, 29] were used to prepare two types of scaffolds using electrospinning and thermally induced phase separation (TIPS) techniques. Cells cultured on electrospun scaffolds were elongated in shape, whereas those fabricated using TIPS retained a rounded morphology. Despite these gross phenotypic and physiological differences, sarcoma myosin and connexion 43 expression was

evident, and contracting cells were observed on both types of scaffolds, suggesting that morphological changes induced by material macrostructure do not directly correlate with the functional differences [66]. The effect of implant architecture on cellular and antigenic response was demonstrated by investigating three different types of scaffold configurations [169]. PU prepared by chain linking poly((R)-3-hydroxybutyric acid)-diol and poly(epsilon-caprolactone-co-glycolide)-diol with 2,2,4-trimethyl hexamethylene diisocyanate was fabricated into three different configurations; non-porous film, porous mesh and porous membrane [158]. These samples were implanted subcutaneously into rabbits for 63 days. Histology analysis of explants after 21 and 63 days inferred that scaffolds with regular topography (compared to non-porous scaffolds) showed angiogenesis while the cellular infiltration increased with increasing porosity in the scaffold.

A novel biodegradable nanocomposite based on poly(hedraloligomeric silsesquioxane) nanocages with poly(hexanolactone/carbonates)urethane urea) (proprietary material UCL-NanoBio™) [170] showed good cytocompatibility to peripheral-blood mononuclear cells [80, 121]. Cells adhered on to composite scaffolds prepared using electrospray and electrospinning techniques and cell viability on composite surfaces was comparable with that of TCP. The cell viability on both types of scaffolds was similar, but there was significantly more cell infiltration into the electrospun scaffolds. Nanocomposites based on biodegradable PU and hydroxyapatite have also been shown to exhibit good cytocompatibility with bone marrow stromal stem cells. Similarly, fibrin-polyurethane composites provided good environment for culturing human bone marrow mesenchymal stem cells [167].

As part of evaluating biodegradable polyurethanes for dermal and vascular applications, the compatibility of skin cells, dermal fibroblasts and keratenocytes as well as microvascular endothelial cells has been investigated by Li *et al*. [161] with different polyurethanes. Three grades of scaffolds with varying degradation times based on a family of biodegradable polyurethanes (NovoSorb™) was assessed under both *in-vitro* and *in-vivo* environments for compatibility with keratinocytes, fibroblasts and microvascular endothelial cells [161]. All three scaffolds exhibited minimal cytotoxic effects to these three cell types and they grew normally in co-culture. Subcutaneous implantation of the polymers in rats demonstrated no systemic

toxic effects of the materials or their degradation products. The anticipated local foreign-body reaction compared favourably with commercially available medical sutures. Assessment of a three-dimensional polymer matrix *in-vivo* followed. The success of sequential culturing of dermal fibroblasts and keratinocytes within the matrix indicated that the generation of a cultured skin substitute is achievable. The polymeric matrix also provided a scaffold for the guided formation of a cultured microvasculature. When engrafted onto a surgically created full-thickness sheep wound, the non-cellular matrix integrated, healed with an epidermis supported by a basement membrane, and was capable of withstanding wound contraction. The resistance to contraction compared favourably with a commercially available collagen-based dermal matrix (Integra™).

Polyurethanes based on BDI and ε-PCL diol chain extended with either lysine or 1,4 BDA exhibit good compatibility with human endothelial cells [50, 94]. Human endothelial cells cultured for 4 days with media containing the degradation products from PUU with either the lysine or 1,4-BDA chain extender showed no toxic effects. Cell adhesion was 85% compared to tissue-culture polystyrene for unmodified PEUU surfaces ($p < 0.01$) and > 160% ($p < 0.001$) of polystyrene on RGDS-modified PUU. The peptide RGDS was coupled to the PUU surface, modified by radio-frequency glow discharge, to improve cell compatibility.

While it is paramount that the scaffold materials have good compatibility with cells and provide the environment conducive to cell growth and proliferation, the blood vessel in-growth (angiogenesis) is also an important factor in proper regeneration of tissues. Laschke *et al*. [166] have studied the ability to stimulate blood vessel in-growth of three different biodegradable PU scaffolds *in-vivo*. The polyurethanes were based on HDI, ε-PCL-diol (MW 530) with three different chain extenders; 1,4,3,6,-dianhydro-D-sorbitol, bis(2-mercaptoethyl) ether and a mixture of 1,4,3,6,-dianhydro-D-sorbitol with 3,7-,11,trimethyl-2,6,10-dodecatrien-1-diaminobutane amide. *In-vitro* assays confirmed that all three PUs are non toxic. Porous PU scaffolds, fabricated using a salt-leaching technique, were implanted into dorsal skin fold chambers of BALB/c mice. The rolling and adherent leukocytes in venules of the dorsal skin fold chamber were found to be in a physiological range and did not differ

much between the three PU types. However, the angiogenic response was poor with low microvessel density in the border and central zones of the scaffold after 14 days of implantation. Histology demonstrated the incorporation of granulation tissue with only a few blood vessels and some inflammatory tissue.

Fibroblasts are a type of cells that synthesize extracellular matrix materials and collagen, and play a critical role in wound healing. Testing of experimental PU scaffolds, designed for dermal tissue regeneration, for compatibility, growth and proliferation of fibroblasts forms an important part of material evaluation. Many studies report on fibroblast compatibility with biodegradable PUs having different chemical structures [67, 138-139, 158-160].

Parrag *et al*. [139] evaluated biodegradable PUU based on chain extenders containing the di-peptide Gly-Leu for fibroblast compatibility. Mouse embryonic fibroblasts were successfully cultured up to 28 days on electro spun scaffolds. Polyurethanes prepared by chain linking three different polyols; α,ω-dihydroxy-oligo- [®-3-hydroxybutyrate-co-®-3-hydroxyvalerate)-block-ethylene glycol] (PHB-diol), ε-PCL and Diorez® (commercial polyester diol) [171] by MLDI or TMDI as chain linking diisocyanates. Macrophages and fibroblasts cultured on these PU films exhibited no morphology difference. However, there were some differences in the adhesion and growth of these cells and it depended on the polymer properties. Both cell types retained their phenotypes, where fibroblasts produced Type I and Type IV collagens and fibronectin, while macrophages produced nitric oxide, and tumour necrosis.

The hydrophobic-to-hydrophilic ratio of polyurethane a surface has an influence on cell compatibility. Harris *et al*. [159] investigated the effect of varying hydrophobic-to-hydrophilic ratios on the compatibility of *staphylococcus aureus*, *staphylococcus epidermitidis* and hTERT human fibroblasts. The PUs used were based on HDI, ε-PCL-diol and PEG-diol chain extended with BDO. The ε-PCL:PEG ratio was varied to prepare PUs with different hydrophobic-to-hydrophilic ratios. Poly(l/dl-lactide) (70/30%) and Thermonex® [poly(ethylene tetraphthalate) cell culture plastic were used as controls. The most hydrophobic PU of the series (100% ε-PCL soft segment) and that with 30% ε-PCL were not cytocompatible, where as the PU with PCL/PEG

(70/30) surface was compatible with hHERT fibroblasts. All surfaces encouraged *S. aureus and S. epidermidis* colonisation.

6.2 In-Vitro degradation

The understanding of the rates of degradation and underlying molecular mechanisms under *in-vivo* conditions is crucial if biodegradable polyurethanes are to be used for clinical applications. Despite many publications reporting on the synthesis, mechanical properties, toxicity, *in-vitro* degradation, cell compatibility, and in some cases animal studies to demonstrate safety, the advancement of these findings to clinically useful products has not progressed significantly, with only a few exceptions.

Artelon®, a PUU based on MDI, ε-PCL-diol and 1,3-BDA has received FDA and CE Mark approval, and has been used clinically for cruciate ligament reconstruction and as a spacer for the trapeziometacarpal joint (TMC) for the treatment of TMC osteoarthritis [110, 112, 172]. Lacthane®, a family of biodegradable PUUs based on BDI and glycolide, lactide and caprolactone polyols, is commercialized by Polyganics, and available for soft tissue surgery [173-174]. NovoSorb™ (PolyNovo Biomaterials), a family of biodegradable polyurethanes, including injectable prepolymer systems is in development for applications in orthopaedic and dermal applications [124, 161, 164].

In polyester polyol-based biodegradable PUs and PUUs, the main functional groups susceptible to hydrolytic or enzymatic degradation are ester, urethane, urea, and amide. When polyether polyols such as PEG are used in PU formulations, the oxidative degradation of the ether linkages may also contribute to PU degradation [6]. The hydrolytic degradation rate of ester group is significantly faster than urethane, urea or amide functional groups. This results in relatively high percentage of oligomeric products due to preferential degradation of ester groups within the PU structure, particularly during the early stages of the degradation. Depending on the solubility of these oligomeric molecules in biological fluids, they may be released from the body via filtration through the kidneys. The safety of these oligomers is

difficult to assess, due to difficulties associated with their isolation and characterisation.

Numerous studies report on *in-vitro* degradation of biodegradable polyurethanes based on standard test procedures [175], often the degradation medium is PBS buffer (pH 7.4) at 37°C to simulate the hydrolytic environment. The change in mass, mechanical strength, molecular weight and pH of the medium is measured as a function of degradation time to assess the susceptibility of the materials for hydrolytic degradation. While *in-vitro* degradation tests are useful for initial screening of materials, well-designed *in-vivo* evaluations are required at appropriate sites to assess the materials for specific applications.

Bruin *et al*. [176] investigated the degradation of polyurethane networks based on ELDI and poly(glycolide-co-ε-caprolactone) under both *in-vitro* and *in-vivo* conditions. The PU network with a higher fraction (GA:CL: 1:1.7) of ε-caprolactone degraded faster *in-vitro* with only 12 % weight loss after 26 weeks *in-vitro* compared to 90% loss for a PU network with GA/CL 1:1. The degradation rate was faster *in-vivo* compared to *in-vitro* where both polymers degraded completely after 4-8 weeks implantation in the dorsum of guinea pigs. Zhang *et al.* [154, 177] evaluated the *in-vitro* degradation of PU networks based on ELDI, glycerol and water at 100, 37, 22 and 4°C temperature in aqueous solutions. The rate was fastest at 100°C and yielded lysine, ethanol, and glycerol as degradation products, whereas the degradation at 4°C was negligible. The degradation products lysine and glucose were quantitatively analysed by a ninhydrin colorimetric reaction [178] (by the method described by Idahl *et al*. [179]), respectively. The degradation rate in *in-vivo*, (subcutaneous implantationa in rat) was three times faster than under *in-vitro* conditions.

The effect of soft segment composition and the chemical structure of the chain extender have been shown to strongly influence the rate of PU degradation. Gorona *et al.* [57] prepared series of polyurethanes based on ε-PCL diol, pluronics (Pluronic E-68), HDI and chain extenders BDO, and 2-amino-1-butanol. PU based on ε-PCL diol soft segment absorbed up to 2% water but those with a ε-PCL-diol and other polyether diols absorbed up to 212% water and behaved as hydrogels. Under *in-vitro*

degradation test conditions (PBS at 37°C) the PCL-based PU exhibited only 1.1 to 3.8 % mass loss after 76 weeks, while in those based with mixed polyols, the mass loss was higher in the range 1.6 to 96 %. PUs that were chain extended with BDO degraded faster than those based on 2-amino-1-butanol.

The incorporation of an amino-acid chain extender into the PU structure makes the PU susceptible to enzyme mediated degradation. Skarja *et al*. [24] prepared polyurethanes based on two different soft segments (ε-PCL-diol and PEO-diol) with phenylalanine diester chain extender and evaluated susceptibility to enzymes chymotrypsin and trypsin *in-vitro*. SEM analysis confirmed progressive surface erosion mediated by the enzymes. Enzyme mediated erosion of L-phenyl alanine-based PUs was also demonstrated by Ciardelli *et al.* [180].

Van Minnen *et al*. [173] have investigated both short (12 weeks) and long term (52 weeks) *in-vitro* degradation of PU foams prepared from BDI and dl-lactic acid/ε-PCL copolymer polyols. Under *in-vitro* test conditions, the mass loss was only 3-4% after twelve weeks. In another study by the same authors [174], PU foams were degraded at 60°C for 52 weeks in distilled water and the degradation medium collected at different time intervals. The undiluted test medium exhibited cytotoxicity after a 3-5 week degradation period and became more cytotoxic toward the end stage of the degradation. While in this study, degradation products have not been identified, it raises an important issue with respect to the toxicity of degradation products, particularly if these are accumulated in sufficient concentrations to illicit a tissue response.

Tatai *et al.* [28] have investigated the degradation of polyurethanes based on ε-PCL-diol, with either ELDI or HDI as the diisocyanate and novel chain extenders with ester linkages. These chain extenders were prepared from dl-lactic acid and ethylene glycol to enhance hydrolytic degradation of hard segments. The *in-vitro* (PBS) degradation of these PUs was assessed by periodic measurement of mass loss, change in molecular weight and amine group concentration in the degradation medium over a one year period. The hard segment was the most susceptible group to the hydrolytic

degradation reactions in these PUs and under the test conditions used; there was no degradation of the PCL soft segment.

In another study, Zuidema *et al.* [181] studied the degradation of PU foams based on BDI, dl-lactic acid/ε-PCL copolymer polyol and BDO for up to three years in *in-vitro* (Sorensen buffer, pH 7.4) at 37 and 60°C. PU foams retained their dimensions for 20 weeks at 37°C and lost 80% of initial the PU mass at both 37 and 60°C after three years. H-NMR results showed that the hard segment of the PUs does not degrade under the *in-vitro* condition used in the study.

6.3 In-vivo degradation

Most literature studies indicate that polyurethanes degrade faster in the *in-vivo* environments compared to *in-vitro* test conditions developed to simulate biological environments [124, 177]. The results are influenced by the animal models used, the sample geometry and volume as well as the location of implant site. Several literature studies provide information on the degradation behaviour of the polyurethanes under different *in-vivo* environments [124, 171, 176, 182]

Biodegradation of rigid polyurethanes formulated for orthopaedic applications was investigated by Adhikari *et al*. [124] by implanting prefabricated cylindrical porous plugs and as injectable liquids designed to cure *in-situ,* in an *in-vivo* implant study (sheep). The polyurethanes were based on ELDI, pentaerythritol, and star polyester polyols based on glycolic and lactic acids. The pre-cured polymers were rigid and high strength with compressive strength in the range 100 to 190 MPa and modulus 1600 to 2300 MPa. Examination of histology sections harvested from explants at different time intervals up to six months, revealed new bone growth within the pores and gradual degradation of the polyurethanes. While this study does not provide data to quantify the extent of the degradation, polyurethane with glycolic acid-based PU had the fastest degradation rate and showed almost complete polymer disappearance in 12 months.

In a three-year subcutaneous study in rats and rabbits, van Minnen *et al*. [182] demonstrated near complete resorption of BDI based polyurethane foams with no observable toxicity issues due to the degrading material and its degradation products. The foams, the surrounding tissues and the draining lymph nodes were evaluated with light and electron microscopy to evaluate the explants. At the first stage of degradation, the number of macrophages and giant cells increased, and as the resorption of the material set in, their numbers gradually decreased. After three years, PU samples had been resorbed almost completely. This is one of the few literature reported studies where the polyurethane has been implanted for a longer term to demonstrate near complete degradation. This study however, does not provide data as to the nature of the degradation products formed and how those products are resorbed or released from implant site.

Complete degradation *in-vivo* of a polyurethane network based on ELDI and, poly(glycolide-co-ε-caprolactone) (multi-arm polyol prepared by initiation with myoinisitol) was demonstrated by implanting subcutaneously in guinea pigs [176]. The porous scaffolds (porosity 80%) showed signs of degradation after four weeks and were completely degraded in 8 weeks, based on assessment by examination of histology sections of the explants.

7.0 Conclusion

Over the last two decades many research groups world wide have explored the potential of biodegradable polyurethanes for applications in regenerative medicine and biomedical implants. These studies have confirmed their inherently good biocompatibility, formulation versatility to tailor mechanical properties ranging from soft elastomers to rigid materials and the many processing options to fabricate scaffolds for tissue engineering. Among the synthetic biodegradable polymers, PURs stands out as perhaps the most versatile class of polymers for fabrication of scaffolds with a wide range of pore size, architecture and mechanical properties. PUR scaffolds have been prepared using processing techniques such as electrospinning and thermally induced phase separation. PUR scaffolds provide cell friendly environments for growth and proliferation of many different cell types including fibroblasts,

osteoblasts, endothelial cells, chrondrocytes, smooth muscle cells and stem cells. Both *in-vitro* and *in-vivo* studies have demonstrated that the PUR scaffolds support the in growth of cells and tissue under controlled degradation conditions to give non-cytotoxic degradation products. A number of long-term studies have demonstrated the safety of PUR in several different animal models as well as examples of their complete degradation.

The development of reactive injectable PUR prepolymer systems that can be delivered by minimally invasive surgical procedures has opened new opportunities in developing biodegradable bone cements and orthopaedic fracture fixation products.

With many supporting studies to confirm biocompatibility, ability to tailor mechanical properties and degradation kinetics coupled with numerous processing options, PURs offers many attractive future opportunities to fulfil demanding material needs for tissue engineering and next generation medical implants.

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