Chapter 6
Biodegradable Polyurethanes and Their Biomedical Applications

Chandrani Sarkar and Sampa Saha

1 Introduction

Nowadays, synthetic polymers with defined structures and good processability are attracting the attention of researchers. One of the interesting classes of synthetic polymers is Polyurethanes (PUs). PUs are available in a broad range of segmented block structures. They are generally fabricated by the reaction of isocyanates, polyols (diols or triols), and chain extenders; those are the building materials of PUs (Fig. 1) [1–3]. Various types of isocyanates, diols, and chain extenders are commercially available. A few of them are given in Table 1; particularly used for the fabrication of biocompatible PUs. The physicochemical properties of PUs can be tailored with the selection of appropriate types and molar ratios of building materials. The tuning of the physical properties and biodegradability are associated with the quality and percentage of the soft segment (ester bonds), while the hard segment (urethane bonds) is the main factor affecting the structural strength and mechanical properties [4–6]. Due to this versatility, PU became an attractive biomaterial for engineered structures. The investigation of PUs in the biomedical field has been started since the 1960s. The first generation implantable PU is commercially available in 1967 [5, 7–9]. Traditionally, PU is used as a bio-stable implant like vascular grafts, heart valves, catheters, and prostheses. Some commercially available medical grades PUs are given in Table 2. Since 1990, a major drive in the development of biodegradable PUs has been initiated because the next generation medical implants require excellent biocompatibility with controlled degradation to address the materials need for modern medical utility. A deep understanding of the relationship between the molecular structure of PUs on

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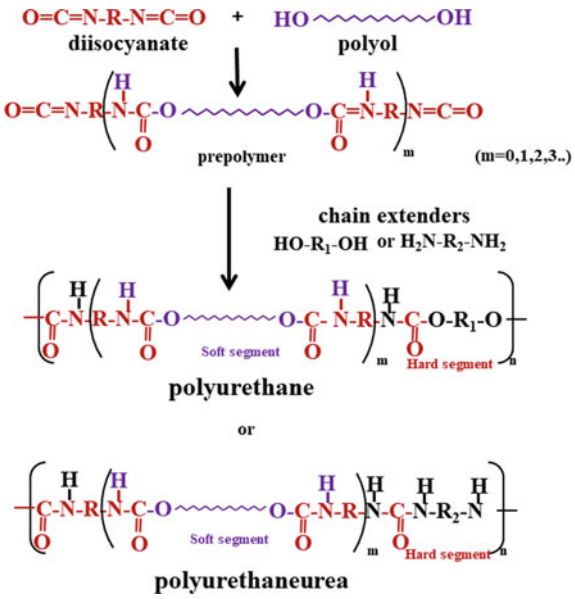


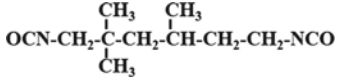
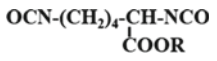
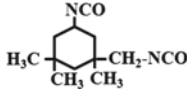
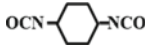
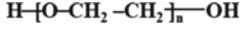
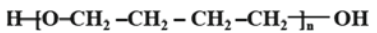
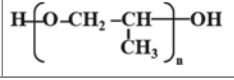
Fig. 1 Formation schemes of PU and PU-urea. Redrawn from [7]

mechanical properties and degradation in in vivo environments plays a key role in designing biodegradable PUs for biomedical applications. In this chapter, we cover the biodegradation and biocompatibility of PUs and their biomedical applications, particularly in tissue engineering and pharmaceutical fields.

2 Biodegradability and Biocompatibility of Polyurethanes

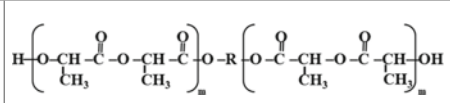
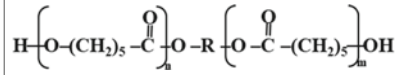
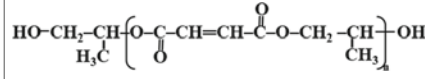
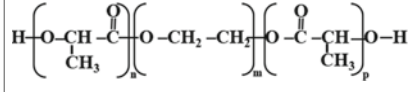
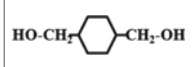
In PUs, degradation mainly relies on the chemical behaviour of its segmented block structure. Each segment link with each other through the urethane or carbamate [−RNHCOOR'−] group in their backbones [2, 4, 5]. As can be seen from Fig. 1, PUs are made up of three constituents: diisocyanate (aromatic or aliphatic), polyol (diols or triols), and chain extender (diols and diamines). They react and form segmented polymer chains with alternating soft and hard segments in their backbones. The soft segments are normally polyester or poly alkyl diol and the hard segments are usually an aliphatic or aromatic diisocyanate [8, 10, 11]. The degradation of PUs is generally tuned with the incorporation of hydrolysable segments into their backbones. In most cases, the degradation rate is governed by soft segments (ester bonds) of PUs; because hard segments (urethane bonds) are not easily hydrolysed. However, incorporating a hydrolysable chain extender made the hard segment of PUs to be degradable [4, 7, 12]. Studies show that the biological degradation of PUs is due to the cleavage of hydrolytic sensitive bonds present in their backbone. The kinetics of the hydrolysis depends on their structural compositions [4, 13]. It is noticed that aliphatic

Table 1 Diisocyanates, polyols, and chain extenders are commonly used in formulating biodegradable PUs

Components	Chemical name	Molecular structure
Diisocyanate	1,4-butanediisocyanate **BDI**	$OCN–(CH_2)_4–NCO$
	1,6-Hexamethylene diisocyanate **HDI**	$OCN–(CH_2)_6–NCO$
	2,2,4-Trimethyl hexamethylene diisocyanate **TMDI**	
	Ethyl 2,6-diisocyanatohexanoate (R=Ethyl) **ELDI** Methyl 2,6-diisocyanatohexanoate (R=methyl) **MLDI**	
	Isophorone diisocyanate **IPDI**	
	1,4-Cyclohexane diisocyanate **CHDI**	
Polyol	Poly(ethylene oxide) **PEO**	
	Poly(tetramethylene oxide) **PTMO**	
	Poly(propylene oxide) **PPO**	

(continued)

Table 1 (continued)

Components	Chemical name	Molecular structure
	Poly(D,L-lactide) **PLA**	
	Poly(ε -caprolactone) **ε-PCL**	
	Poly(glycolide) **PGA**	
	Poly(propylene fumarate) **PPF**	
	Poly(lactic acid-ethylene glycol-co-lactic acid) (PCL-co-PEG-coPCL)	
Chain extender	Ethylene glycol **EG**	$HO–CH_2–CH_2–OH$
	1,4-Butanediol **BDO**	$HO–(CH_2)_4–OH$
	1,4-Cyclohexanedimethanol **CHDM**	
	1,2-Ethanediamine **ED**	$H_2N–CH_2–CH_2–NH_2$
	1,4-Butanediamine **BDA**	$H_2N–(CH_2)_4–NH_2$

(continued)

Table 1 (continued)

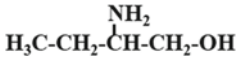
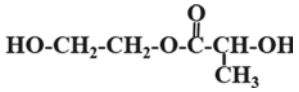
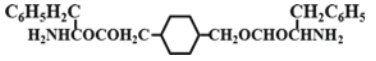
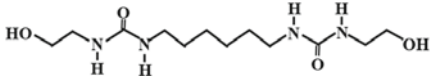
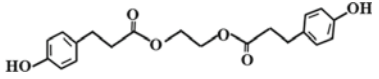
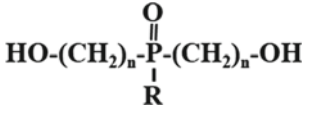
Components	Chemical name	Molecular structure
	2-Amino-1-butanol **ABDO**	
	2-Hydroxyethyl-2-hydroxypropanoate	
	4-((1-(1-amino-2-phenylethoxy)ethoxy)methylcyclohexyl)methyl-2-amino-3-phenylpropanoate	
	1,1-(Hexane-1,6-diyl)bis(3-(2-hydroxyethylurea	
	Ethane-1,2-diyl bis(3-(4-hydroxyphenyl)propanoate	
	Bis(2 hydroxyethyl)phosphate [R=H, n=2] BEP Bis(2-hydroxyhexyl)phosphate [R=H, n=2] BHP	

Table 2 Commercially available medical grade PUs

Comercial name	Manufacturers
Texin®, Texin®4210, Desmopan® DP 2590A, Desmopan® DP 9370A,	Bayer material science
Tecoflex®, Carbothane®, Pellethane®	Lubrizol
Elastollan® SP806	BASF
ChronoFlex®	AdvanSource biomaterials
Bionate®	DSM biomedical
Elast-Eon®	RUA biomaterials
Artelon®	Lavender medical
Lacthane®	Polyganics
NovoSorb BTM	PolyNovo

ester bonds are more susceptible to hydrolytic cleavage than aromatic ester linkages [2, 4, 14]. Moreover, the degradation rate depends on the composition of polyesteric soft segments of PUs. PUs with hydrophilic soft segments [e.g., polyethylene glycol (PEG)] degrade more rapidly than PUs with hydrophobic soft segments [e.g., PCL] [2, 12, 15]. If soft segments are aliphatic polyesters like PCL, PLA, and PGA, then PUs are readily biodegradable. The crystallinity of soft segments also affects the degradation rate of PUs, amorphous segments degrade more rapidly than semicrystalline segments. Because the high content of crystallinity reduces water absorption capacity and restricts polymer chain mobility, thereby reducing the degradation rate of PUs [2, 12, 16, 17]. Tang et al. observed that the degradation rate also depends on the hydrogen bonding of the segmented structure. The hydrogen-bonded urethane degrades slower than the non or less hydrogen-bonded urethanes [18, 19].

Understanding the rates of degradation and bioresorbable mechanisms in biological environments is essential for clinical applications of PUs. The main functional groups susceptible to hydrolytic or enzymatic degradation are ester and urethane in biodegradable PUs [2, 7]. The degradation rate of the ester group is considerably higher than urethane which results high concentration of oligomeric products of PUs during the early stage of the degradation. These oligomeric molecules are excreted from the body via filtration through the kidneys. The safety of these oligomeric molecules is crucial to assess because of the difficulties in their isolation steps [7, 12]. Various studies on in vitro degradation of PUs have been conducted in PBS (phosphate buffer solution) medium at pH 7.4 and 37 °C for mimicking hydrolytic environment. The change in mass of PUs and pH of the medium are generally measured as a function of degradation [7]. Few studies showed that PUs made with aromatic isocyanates are less biocompatible due to the release of aromatic amines after degradation [2]. However, in vitro degradation tests are only applicable for the initial screening of materials. A well-designed in vivo study is essential for site-specific applications of PUs. Numerous in vitro and in vivo studies have evidenced the biocompatibility of aliphatic PUs, which is favourable in biological environments. Standard cytotoxicity assays and in vitro cell studies with different cell lines

like chondrocytes [20–27], fibroblasts [27–32], osteoblasts [15, 33–39], endothelial [15, 40–43], and stem cells [40, 44–47] on biodegradable PUs with a broad range of chemical composition have been reported. Studies demonstrated that biodegradable PUs have acceptable cytocompatibility. Researchers extensively studied the biomedical application of biodegradable PUs both in tissue engineering and drug delivery field which are critically reviewed in subsequent sections.

3 Polyurethanes in Tissue Engineering Applications

In tissue engineering, biological substitutes should facilitate the regeneration of tissue and help in the restoration of its function. For this, the material should mimic the microstructure, physicochemical and mechanical properties of natural tissue [48, 49]. In our body, different tissues possess different structures and properties. Most studied tissues and adequate material properties are concise in Table 3. In the tissue engineering process, biodegradable materials play a critical role to support and accelerate the new tissue formation. They should be biocompatible and have tunable degradation rates with nontoxic degradation products [50]. Biodegradable PUs are promising materials used in the synthesis of scaffolds to regenerate tissues. Numerous studies on the design and fabrication of PUs for tissue engineering applications have been reported [7, 51–53]. Biodegradable PUs have been studied for both soft tissue and hard tissue, details of which are given below.

Table 3 Most studied tissues and adequate material properties

Tissues	Adequate modulus	Adequate porosity and pore sizes	References
Cardiac tissues	5–50 kPa	75–96%, $\leq$300 μm	[53–55]
Skeletal muscle	5–170 kPa	90%, 50–200 μm	[53, 56, 57]
Cartilage	2.8–18.6 MPa	75–87%, 75–175 μm	[58, 59]
Nerve guide	0.30–30 MPa	60–80%, 30–50 μm	[60]
Vein	34 kPa (circumferential) 102 kPa (longitudinal)	6.5–7.6 nm	[61, 62]
Aorta	128 kPa	1–20 μm	[62, 63]
Bone	1.28–1.97 GPa, (cancellous) 10.4–20.7 GPa (cortical)	75–90%, 140–600 μm (cancellous) 5–10%, 10–50 μm (cortical)	[53, 64]

3.1 Polyurethanes in Soft Tissue Engineering Applications

Soft tissues are found throughout the human body. They support, connect and protect all the organs of the body, and give shape/structure to the body. There are different types of soft tissues—muscle, fibrous tissue, vessels, and nerves. Extreme activities lead to soft-tissue damage which causes pain, swelling, and bruising. Sometimes, it needs autografting. Due to certain limitations of autografting, biodegradable synthetic materials are used as alternatives [65, 66]. In this chapter, various biodegradable PUs for soft tissue engineering applications have been discussed.

Cardiovascular Applications

Cardiac tissues are found in the wall of the heart which allows the heart to pump blood. Biodegradable materials with high tensile strength and elasticity are generally required for cardiovascular tissue engineering. For this, biodegradable PUs comprised of polyols like PCL, PEG, and their copolymers along with diisocyanates such as ELDI (Ethyl 2,6-diisocyanatohexanoate), HDI(1,6-Hexamethylene diisocyanate), and BDI (1,4-butanediisocyanate) have been designed. PCL generally improves the elastomeric properties of PU whereas PEG makes it hydrophilic and affects the degradation rate [24, 67, 68]. Structural modification of PUs by chain extender is one of the prominent strategies used by researchers to develop biodegradable PUs for soft tissue engineering. The incorporation of chain extenders based on amino acids has been explored by several groups to develop PUs for soft tissue engineering [69–71]. Rechichi et al. designed chain extenders by reacting phenylalanine with 1,4-cyclohexanedimethanol and synthesized a series of PUs using MLDI, PCL or PCL-PEG-PCL [28]. Fromstein et al. showed the effect of blending amino-acid-based PUs with other components like MLDI/PCL or MLDI/PEG on properties and degradation rate to assess their suitability for soft tissue engineering. The mechanical properties of the blends varied from 6 to 20 MPa, while elongation at break varied in the range of 512–690% [44, 72]. Gorna et al. designed a series of PUs using PCL, PEG, HDI, IPDI, and chain extenders BDO and 2-amino-1-butanol in different ratios. They showed a wide range of tensile strength from 4 to 60 MPa, whereas the elongation varied from 100 to 950% [66]. Earlier studies were mainly focused on the development of materials that possess elastomeric properties which provide sufficient mechanical support to the cardiac system. Nowadays, biocompatible and bioactive materials having good mechanical properties are in demand. Many biocompatible cardiac materials made up of PCL-based PUs having urethane and/or urea groups in their backbone have been studied. Guan et al. fabricated a series of PU-urea elastomers using PCL-PEG-PCL, BDI, and 1,4-butanediamine. These showed good endothelial cell adhesion due to the immobilization of Arg-Gly-Asp on its surface. Moreover, these PUs have good mechanical properties (tensile strengths ~8–20 MPa, strains ~325–560%) [15]. Sometimes, researchers incorporated gold nanotubes/nanowires in PUs in order to improve the electroactivity of

material, and stimulate cardiomyocyte cells for accelerating cardiac tissue regeneration [73]. Researchers also fabricated highly porous PUs for soft tissue engineering applications. Guan et al. fabricated a highly porous PUs scaffold (porosity ~80–97%) by a thermally induced phase separation process. Porous scaffold supported good cell adhesion and proliferation. However, the tensile strength of the scaffold was 1 MPa, which is sufficient for soft tissue engineering applications [67]. Researchers prepared an elastomeric porous cardiac patch from biodegradable PU based on butyl diisocyanate, PCL, and putrescine, and showed degradation in the rat model. At 4 weeks, ingrowth of fibroblast into PU patch was found and cellular infiltration of the implant enhanced. At 12 weeks, the PUU patch was completely degraded [74]. The same authors investigated PU cardiac patch for its effectiveness to promote vascular remodelling and improve function by implanting the patch onto sub-acute infarcts in Lewis rats. It was observed that the left ventricular wall was thickened and the patch was mostly remodelled [75]. PU patch accelerated the formation of new contractile phenotype smooth muscle tissue and enhanced contractile function. Researchers also synthesized myoblast seeded PUs scaffolds from MDI, 1,3-diaminopropane and ε-PCL-diol (530 Da) for direct intramyocardial cell transplantation [76, 77]. Hashizume et al. designed porous biodegradable PU and applied in a rat model of ischaemic cardiomyopathy for 16 week and found degradable cardiac patch benefit in treating ischaemic cardiomyopathy [78] (Fig. 2).

Musculoskeletal Applications

Since 1990s, biodegradable PUs scaffolds have been evaluated for the knee-joint meniscus. In the early years, MDI-based PUs were investigated for the healing of meniscal lesions. However, its toxic degraded product, i.e., MDA limits its applications. So, PUs scaffolds based on aliphatic diisocyanate BDI, poly(ε-caprolactone-co-l-lactic acid) diol, and 1,4-BDA or 1,4-BDO have been studied for cartilage tissue regeneration and found suitable for regeneration of fibrocartilage [79]. Spaans et al. fabricated microporous PUs-based scaffold for replacement of knee-joint meniscus. They used 50/50 l-lactide/PCL polyol for soft segment and BDI/adipic acid/water for hard segment formation. The reaction between water and BDI forms CO_2 gas which creates micropores (porosity ~70–80%). This microporous PUs scaffold facilitated fibrocartilage formation in the lateral meniscus of dogs after 18 weeks of implantation [80, 81]. Similarly, Grad et al. demonstrated porous PU fabricated from HDI, ε-PCL, and isosorbide diol favoured chondrocyte attachment, proliferation and provide mechanical support to grow functional cartilage-like extracellular matrix [23]. Field et al. formulated an in situ curable biodegradable PU based on dl-LA/GA and ELDI to repair meniscal cartilage tissue [82]. Researchers fabricated PU-based nanofibers using the wet-spinning process for anterior cruciate ligament reconstruction. PU-based fibres showed high strength and stiffness and retained almost 50% of their tensile strength for 9 months at physiological temperature [83]. In vivo studies

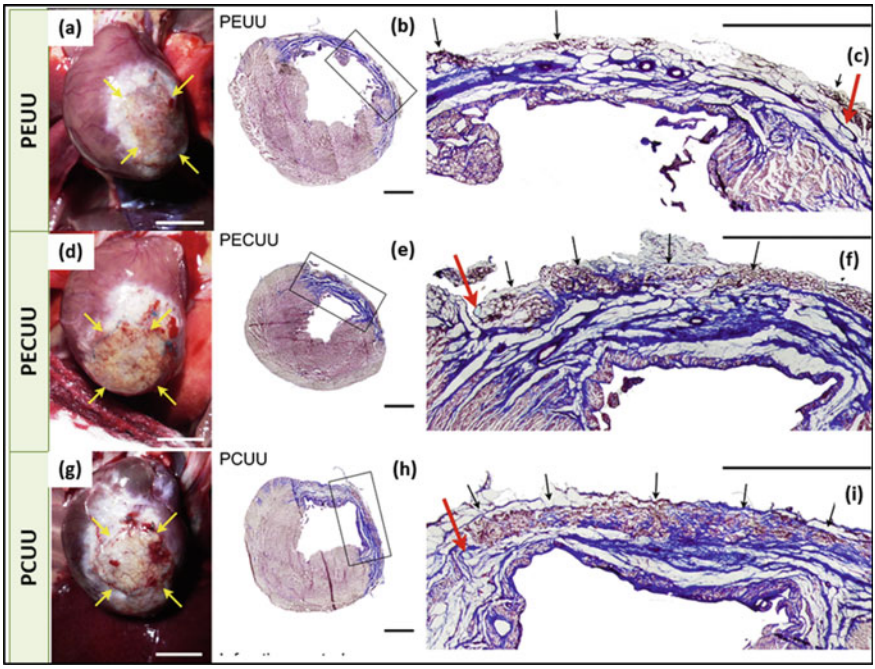


Fig. 2 Representative macroscopic images **a**, **d**, **g** of using different polyurethane [polyester urethane urea (PEUU), polyester carbonate urethane urea (PECUU), polycarbonate urethane urea (PCUU)] cardiac patches after 16-week study in a rat model of ischaemic cardiomyopathy [scale bar ~5 mm]. The corresponding images **b**, **e**, **h** of Masson's trichrome stained cross-sections of the heart after 16-week implantation of PEUU, PECUU, and PCUU [**c**, **f**, and **i** are magnified images] [scale bar ~2 mm]. Yellow and black arrows indicate the edge and regions of the implanted PU. Red arrows indicate the suture lines. Reprinted with copyright permission from Elsevier [78]

supported its biocompatibility and safety issues. The trade name of this material is Artelon® commercialized by Artimplant® AB, Goteborg, Sweden. This material has also been developed as a spacer for the trapeziometacarpal joint for the treatment of osteoarthritis [84].

Neural Applications

Nerves are soft tissues of the human body that control the movement and functions of the whole body. Nerve tissue collectively in the brain and spinal cord creates the central nervous system of the body, and nerves outside the brain and spinal cord create the peripheral nervous system. Peripherical nerve injury is the most common clinical problem. Researchers focus on the development of tubular structures that guide nerve regeneration [52, 85]. Biodegradable PUs offer attractive properties like tunable mechanical strength, flexibility, and high

biocompatibility in fabricating tubular grafts for nerve regeneration. Borkenhagen et al. designed PU-based tubular structures made up of poly[glycolide-co-(ε-caprolactone)]-diol, poly[(R)-3-hydroxybutyric acid-co-(R)-3-hydroxyvaleric acid]-diol and 2,2,4-trimethylhexamethylene diisocyanate. This nerve conduit (10 mm long) was implanted in rats for 4, 12, and 24 weeks. They found regeneration of nerve tissue in the implanted site with no inflammatory reaction with degraded product [86]. Dezhznz et al. fabricated nerve conduits from biodegradable PU based on ε-PCL-diol, HDI, and PEO-diol. In in vivo study, myelinated axon regeneration and PU degradation were observed after 4 weeks and 12 weeks of implantation in rabbits, respectively [87]. Nowadays, researchers mainly focus on the development of fully functional nerve reconstruction in the minimum time span. The porous PU scaffold exhibited good nerve regeneration potential due to high interconnectivity and varied pore sizes in the outer (42 μm), inner surfaces (9 μm), and cross-sectional (23 μm) area. Asymmetrical pores facilitate good wound inflammation waste drainage and better permeability for growth factor that leads quick nerve regeneration [88]. Researchers demonstrated new electroactive nerve conduits made up with PU based on poly (glycerol sebacate) and aniline pentamer. Its higher electroactivity accelerated neuronal Schwann cells for high release of nerve growth factor that induced neurite growth and fast nerve regeneration [89].

Vascular Applications

Blood vessels (veins, arteries, and capillaries) are functionally dynamic tissue with minimal regeneration potential. These vessels are long, elastic hollow tubes with varying thicknesses and architecture. Blood passes through these vessels and transports oxygen, nutrients, and waste products around the body. Various polymeric materials have been developed for blood vessel replacement. Clinical use of synthetic vascular grafts is limited mainly due to thrombosis and intimal hyperplasia. Thrombus formation is occurred by platelet adhesion and slow endothelialization that leads to abnormal accumulation of vascular tissue in the graft lumen [90–93]. In order to solve these problems, a strategic approach like surface modification of synthetic vascular grafts has been adopted which enhanced the hemocompatibility and long stability of vascular grafts [91, 94]. PU is the most common polymer used for the production of blood-containing devices like blood bags and artificial hearts valve due to its good hemocompatibility and mechanical properties [90, 94]. Researchers modify the surface of PU with PEG and peptides in order to compliance with natural blood vessels [95–97]. Modified PU showed good mechanical stability and less thrombogenicity. Researchers have designed PU film based on PCL, MDI, and poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV). PHBV incorporation increased the mechanical properties and surface hydrophilicity of the film. Moreover, PU film showed exceptional cytocompatibility and hemocompatibility with poor platelet adhesion and haemolysis, suitable for vascular grafts [98].

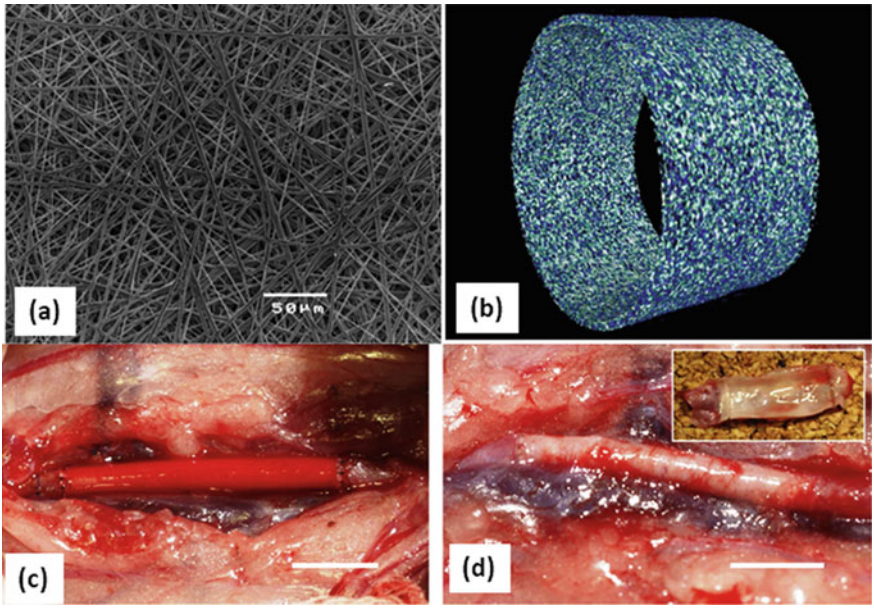


Fig. 3 **a** Scanning electron microscopic image and **b** 3D μCT image of electrospun PU vascular graft. Images of PU grafts just after implantation (no blood leakage observed) (**c**) and after 12 months implantation (well integrated with adjacent tissue with no inflammation and no thrombus formation) (**d**) [scale bars ~6 mm]. Reproduced with permission from Elsevier [100]

Long-term mechanical stability of vascular graft is needed for complete regeneration and restoration of the vascular wall structure. Researchers developed mechanically robust, long-lasting PU-based elastomeric scaffolds for vascular grafts [99]. Bergmeister et al. fabricated vascular grafts from biodegradable PU and these grafts showed good performance at the implant site of Sprague Dawley rat for one-year study [100] (Fig. 3).

3.2 Polyurethanes in Hard Tissue Engineering Applications

Calcified tissue like bone is categorized as hard tissue of the body. It has good healing ability under specific biological environments. Throughout our life, it undergoes a continuous process of remodelling. However, severely damaged bones need immediate replacement with functional bone substitutes. The suitability of bone substitutes depends on their mechanical and structural properties such as strength, modulus, porosity, and size of pores that support cell mobility, vascular ingrowth, and bone tissue formation [48, 49, 101]. In the next section, we have discussed various biodegradable PUs scaffolds for bone tissue engineering.

Polyurethane Scaffolds

Since last decade, the development of biodegradable PU scaffolds has increased dramatically due to their tailorable physicochemical and mechanical properties. These biodegradable PU scaffolds have certain limitations like poor cell adhesion, differentiation, and biomineralization properties that may be due to pH changes around the scaffold after degradation. Although it is known that osteoblasts proliferate and differentiate at physiological pH 7.4 [102], researchers have attempted to control pH changes in the microenvironment by designing a 3D printed PU-urea scaffold based on poly (D, L-lactic acid) diol with piperazine moieties and isosorbide-HDI/HDI. In the in vivo study, the scaffold exhibited excellent cytocompatibility and bone tissue formation ability after 8 weeks of implantation. This is due to the stable neutral pH maintained by piperazine after the degradation of the scaffold [103–107]. In another study, researchers designed chondroitin sulfate sodium (bone extracellular matrix component) grafted PU-based scaffolds to promote osteoblast adhesion and bone tissue regeneration [108, 109]. Inorganic fillers were incorporated to gain mechanical properties as compared to bare polymers. Researchers have incorporated bioactive particles like hydroxyapatite (Hap, an inorganic component of bone) into the PU matrix and enhanced the mechanical properties as well as the bioactivity (e.g., osteoconductivity, supports bone tissue formation) of scaffolds [110–112]. Liu et al. incorporated Hap in PU during the PU formation step and designed a highly porous (pororsity ~83%) scaffold with good mechanical properties (compressive strength ~554 kPa) [112]. Similarly, Nasrollah et al. prepared PU-Hap scaffolds via in situ polymerization and described the role of Hap in pore creation as well as cell attachment and proliferation on the scaffold [113]. In another study, researchers showed that Hap-incorporated PU scaffolds significantly enhanced cell adhesion and proliferation both in cell study and animal study. Researchers demonstrated the suitability of highly porous (porosity ~78–81% and pore size ~300–1000 μm) Hap-incorporated PU foam in the biomineralization and bone tissue regeneration process. They found the formation of bone matrix and trabecular regeneration in their study that showed excellent biocompatibility and osteogenic differentiation of cells in presence of Hap incorporated PU foam [114]. Scientists implanted citric acid (calcium-complexing agent) incorporated PU scaffolds in oestrogen-deficient sheep and found high bone regeneration after 18–25 months [115]. All these studies showed that PU composite scaffolds can be potentially used in bone tissue engineering applications (Fig. 4).

Injectable Polyurethane Prepolymer Systems

The injectable bone void fillers loaded with/without growth factors are commonly used for the treatment of bone defects. The formulation of two-component prepolymer systems that react upon mixing under mild conditions has the advantage of such delivery to the defect site through minimally invasive procedures. Researchers extensively investigated the potential of liquid two-part urethane formulation in such biomedical applications. The injectable prepolymer systems are formulated to form

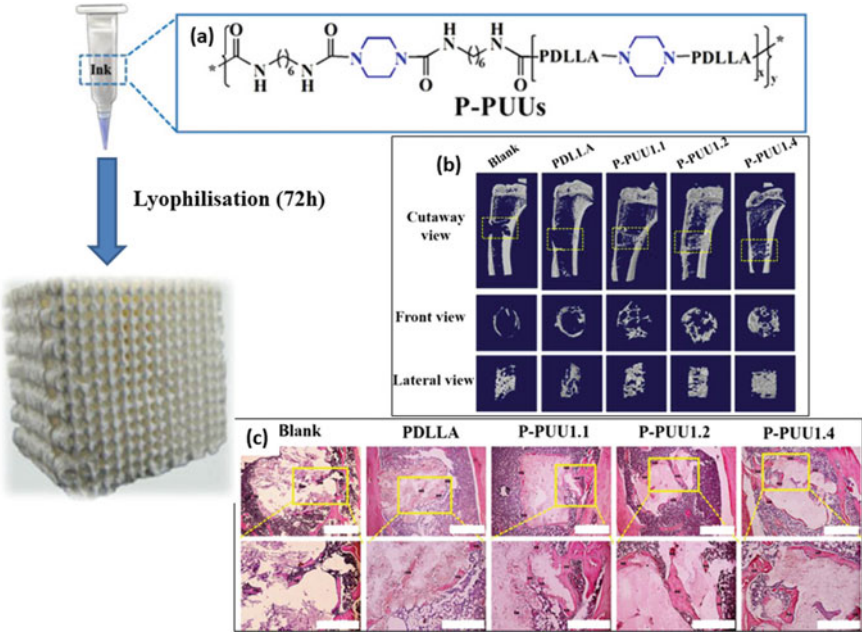


Fig. 4 Schematic presentation of piperazine-based PU-urea (P-PUUs) **a** Chemical formula of P-PUUs, **b** 3D μCT images, and **c** H&E staining images [Scale bar ~1 mm (top image) and 500 μm (bottom images)] after 8 weeks implantation of scaffolds (different content of piperazine) in rat model. Reproduced with permission from the American Chemical Society [103]

cross-linked polymer networks upon completion of the urethane formation once the components are mixed together. These liquid two-part urethane systems should be formulated in such a way that no by-products (low molecular weight) are released during curing, and they cure with a low reaction exotherm (not exceeding body temperature) [7]. Gunatillake et al. developed multiple PU prepolymers systems for varied applications in the biomedical field including tissue engineering [116]. They mixed diisocyanates ELDI or MLDI (liquids at and above ambient temperature) with multifunctional core molecules (pentaerythritol, glucose or glycerol) and produced isocyanate end functional prepolymers (Prepolymer A) which were viscous liquids at ambient temperature. Polyester polyol like PCL /PLA /PGA /PLGA polyols was used as the second component (Prepolymer B). The reaction of the two prepolymers (Prepolymer A and Prepolymer B) produced a cross-linked polymer network at ambient temperature. With the appropriate choice of polyols and diisocyanates, they produced a cross-linked PU network with a wide range of mechanical properties (Compressive strength ~260 MPa, compressive modulus ~2 GPa) [25, 35, 116, 117]. PU prepared by this approach showed good compatibility with osteoblasts. It is found that highly viscous liquids create some miscibility and injectability issues. To eradicate these issues, Guelcher et al. have employed a quasi-prepolymer approach and end-capped all the polyol hydroxyls with excess use of polyisocyanate (NCO:OH

equivalent ratio >5:1). The excess diisocyanate kept the viscosity low of the quasi prepolymer, and formed PU networks by the reaction of the available isocyanate groups with a polyester polyol. The compressive strength and modulus of PU films were in the range of 82–111 MPa and 1200–1430 MPa, respectively. PU films were found to release nontoxic degraded products and supported the attachment and proliferation of MC3T3 cells [118]. The degradation, safety, and suitability of injectable prepolymer systems were also evaluated in an animal model (in sheep). PE and ELDI were used as Prepolymer A, and PE and DL-lactic acid (molecular weight 456) or PE and glycolic acid (molecular weight 453) were used as Prepolymer B. The cured polymers in this study exhibited compressive strength and modulus in the range of 100–190 MPa and 1600–2300 MPa, respectively. So, researchers had used both precured scaffolds and prepolymer liquid mixture for in vivo study. Precured cylindrical scaffolds (diameter ~10 mm) were implanted in sheep femurs, and prepolymer mixture in liquid form was injected to fill the voids and allowed to set for 8–10 min before closing the surgical site. This study demonstrated that PU in both forms (injectable and precured) did not show any surgical issues, even new bone tissue formed and PU degraded gradually [117] (Fig. 5).

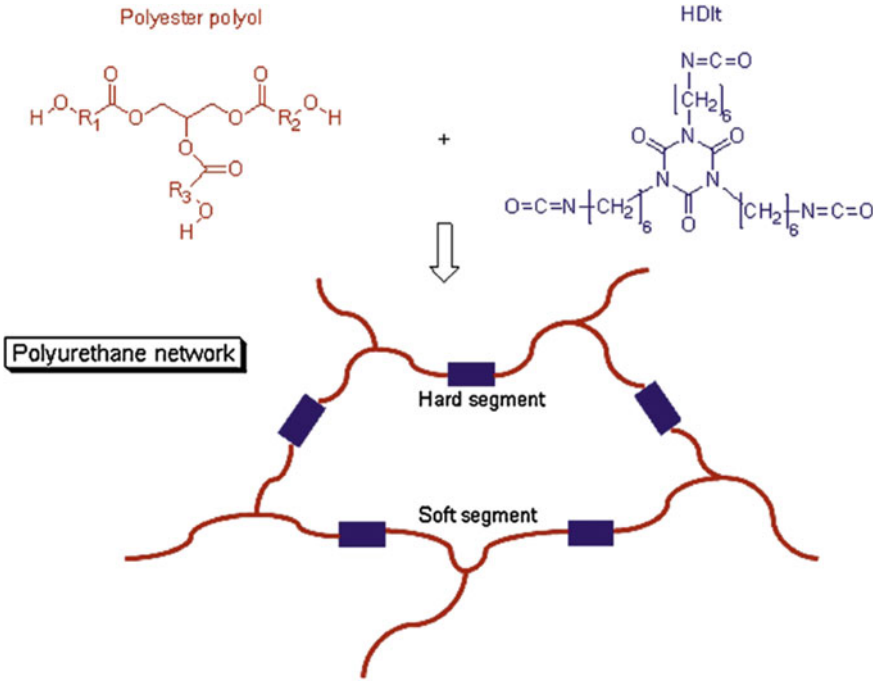


Fig. 5 Formation of PU network [119]. Adapted with permission from Elsevier [2]

4 Polyurethanes in Drug Delivery Applications

PUs are a common choice for the synthesis of drug delivery vehicles due to their tunable composition and tailor-made properties. Several drug delivery systems in different forms like micro/nanosystems (micelles, micro/nanoparticles), membrane/film systems, and matrix systems such as gels or scaffolds based on degradable PUs have been reported [2–6, 119–121]. Various forms of PU-based drug delivery systems are tabulated in Table 4. In numerous reports, the release behaviour of PU systems is generally correlated with the composition, swelling, and degradation rate at different pH. The drug release from PU matrices relies on the loading content and solubility of the drug as well as the degradation rate and swelling of the matrices [2, 122]. Water swollen PU system showed a linear relationship between cumulative drug release of a hydrophilic drug such as tenofovir with time [123]. Moreover, a more linear release of dapivirine (another anti-retroviral agent) was observed from water-absorbed PU matrices than from non-water-absorbed PU matrices due to controlled dapivirine diffusion [123].

The stimuli-responsive structure of PU facilitated the modulation of the drug release profile by tuning the degradation and/or adjusting the glass transition temperature of PU. Temperature increases the mobility of the PU chains, weakening the interactions between PUs and drugs; thereby leading to enhanced drug diffusivity [4, 122]. Fast degradation of PU matrix shows a more rapid drug release compared to non-degrading or slowly degrading PU matrix. Drug delivery vehicles based on PUs with quick degradation have been developed by introducing highly degradable PLA or PLGA into PU chains; tuning the degradation rates by changing their molar ratio in the final PU [124–127] (Fig. 6).

Multiresponsive such as temperature, pH, redox, or enzyme-sensitive PU drug delivery systems have been also reported. The first stimulus, i.e., the temperature normally permits drug carriers to enter into cancer cells, and the second stimulus (for example enzyme attack) initiates the disassembly of polymers leading to final drug release [52]. Redox-responsive PU (PLA-dithiodiethanol-PLA diol) based self-assembled micelles were stable at physiological pH, whereas drug release occurred in the microenvironment of the cancer cells (acidic pH) [128]. Another stimuli assisted degradation is currently being explored and a major focus is on the development of enzymatic intracellular responsive PU systems for anticancer drug release [129]. A summary of several drug delivery systems based on PUs has been tabulated below.

5 Tissue Adhesives Applications of Polyurethanes

In most of the surgical procedures in the world, stapling/suturing is used for the purpose of tissue binding that keeps the tissues attached for healing and lessens bleeding. Uncontrolled bleeding and air/gas leaking are the few complications of these techniques. There is an emergence to develop an advanced tissue closure

Table 4 Polyurethane-based drug delivery systems

Delivery system	Drug incorporated	Outcome
PU nanoparticles	Adriamycin	– Temperature-responsive PU nanoparticles were created by using PEG and LDI (L-lysine ester diisocyanate) – Drug release behaviour depends on the transition temperature of LDI-PEG600 [130]
PU nanoparticle	Doxorubicin (DX)	pH and temperature-responsive PU nanoparticles were synthesized using HDI and MDI [131]
PU nanoparticles	DX	pH sensitive PU nanoparticles showed high cellular internalization and high anti-proliferative effects on MCF-7 cells (human breast cancer) [132]
PU nanoparticles	paclitaxel	Paclitaxel-loaded PU nanoparticles showed good distribution in healthy mice [133]
PU microparticles	Epigallocatechin gallate	Epigallocatechin gallate-loaded PU showed a toxic effect on Detroit 562 cells (human pharyngeal carcinoma) and SCC-4 cells (squamous carcinoma) [134]
PU microparticles	DX	PU microparticles showed effective transportation of DX into cells and high anti-tumour activity towards cancer cells and 3D multi-cellular tumour spheroids [135]
PU conjugates	DX	DX-loaded PU conjugates showed a high release of the drug under acidic conditions. It showed pH and ultrasound triggered drug release and inhibit tumour growth [136, 137]
PU nano micelles	Paclitaxel	PU nano micelles are easily internalized into the cells and released paclitaxel within tumour cells under an acidic environment [138]
PU nano micelles	DX	– Showed sustained release of DX at different pH. DX-loaded PU micelles exhibited high toxicity against RAW 264.7 and MCF-7/ADR cancer cells [139–143] – They also showed high anti-tumour efficacy in in vivo studies – Folic acid-conjugated DX-loaded PU micelles easily internalized into KB cells (human epidermoid carcinoma cell), and showed high toxicity with the release of DX – Thermoresponsive PU nano micelles have a lower critical solution temperature at 41–43 °C comparable to cancer tissue temperature. DX-loaded PU nano micelles exhibited high toxicity (almost 90%) towards MCF 7 cells

(continued)

Table 4 (continued)

Delivery system	Drug incorporated	Outcome
PU micelles	DX	– Redox-sensitive PU micelles showed controlled release of DX in the presence of glutathione (a reducing agent) and high cytotoxicity towards cancer cells [144–150] – DX-loaded PU micelles showed high anticancer activity and toxicity against C6 cells (rat glioma cells), Saos–2 cells, MCF-7 cells, and HeLa cells due to the quick release of DX under an intracellular reducing environment – Redox and pH-responsive PU micelles also showed toxicity to C6 cells due to the controlled release of DX – At low pH, DX was rapidly released and effectively transported into the cell nuclei and showed cytotoxic effects to cancer cells – The enzymatic degradation of PU micelles chiefly occurred at the ester linkage under the physiological condition for 8 weeks
PU micelles	Paclitaxel	Showed pH-responsive release of paclitaxel from PU micelles into H460 cancer cells [151]
PU micelles	DX and paclitaxel	Redox-responsive PU micelles exhibited high cytotoxicity towards tumour cells (HepG2) [128]
PU microcapsules	DX	– pH-sensitive PU microcapsules showed a controlled drug release profile – Those microcapsules are easily internalized into Hela cells and BGC 823 [152]
PU matrix	Cefamandole nafate	– Showed controlled release of drug and prolonged antimicrobial activity upto day 9 [153, 154]
PU matrix	Metoprolol tartrate	– Drug loading efficiency ~65% – Can be administered through the oral route [155]
PU pellet	Model drugs	– Double-coated PU pellets fabricated by using (carboxymethyl)(ethyl)-cellulose and azo polymer for controlled release of drug – Colon-specific delivery [156]
PU thermogel	DX	– Showed sustained release of DX and an anti-melanoma effect on tumours [157]
PU core–shell nanogel	DX	– Redox-responsive PU gels were designed with hydrophilic PEG [158] – Reducing agent, Glutathione triggered the drug release at pH = 7.4
PU film	Chlorhexidine diacetate	– Showed antibacterial activity against *Staphylococcus species* [159]

(continued)

Table 4 (continued)

Delivery system	Drug incorporated	Outcome
PU film	Gemcitabine	– Initial burst release [160] – Local drug delivery applications
PU films	Methotrexate	– Methotrexate was released with almost zero-order kinetics for 96–144 h [161]
PU core–shell nanofiber	5-fluorouracil and paclitaxel	Drugs were released in a controlled manner at both acidic and physiological pH [162]
Gold-coated PU nanofibers	Temozolomide	Sustained release of temozolomide was observed for 30 days which inhibit the growth of U-87 MG human glioblastoma cells [163]
Amphiphilic block segmented PU nanofiber	Curcumin	Curcumin-loaded triblock (PEG-PCL-PEG) segmented PU nanofibers were fabricated. These nanofibers showed a steady release of curcumin for 18 days and good antibacterial activity against Escherichia coli and *Staphylococcus aureus* [119]
PU membranes	Paclitaxel	Temperature responsive PU membranes were fabricated with a lower critical solution temperature of 44 °C. Below this point, the PU matrix prevented the diffusion of paclitaxel; upon heating above this temperature, the matrix suddenly switched on and diffusion of the drug occurred [164]
Waterborne PU membrane	DX	Waterborne PU membranes showed fine biodegradability, favourable cytocompatibility, hemocompatibility and sustained release of DX caused high toxicity to tumour cells [121]
Waterborne PU	5-fluorouracil	The release rate of 5-fluorouracil was tuned with the length of the chain extender and molecular weight of PEG [165]
PU foam	Gefitinib	Gefitinib was released in a controlled manner for nine months. This can be used for the treatment of broncho tracheal cancer [166]
PU foam	Anticancer compounds DB-67 and DX	– Drugs were covalently attached to PU foam – Differential release of drugs depends on the chemical structure of the drug and temperature [167]
PUs scaffold	Platelet-derived growth factor (PDGF)	– Biphasic release of growth factor – PDGF-loaded PU showed wound healing potential in in vivo study [168]
PU scaffold	Recombinant human bone morphogenetic protein (rBMP)	– Sustained release of rBMP enhanced new bone tissue formation [169]

(continued)

Table 4 (continued)

Delivery system	Drug incorporated	Outcome
PU adhesive	Thiamazole diclofenac and ibuprofen	– Pressure-sensitive PU adhesive showed excellent stabilization of the drugs without any irritation in the skin [170]
Modified PU	Ibuprofen	– Ibuprofen was incorporated in the polymeric backbone via ester linkages, and release was based on the degradation of ester bonds [171]
PU dual delivery system	Dapivirine, tenofovir	– Sustained release of drugs over time [123]
PU implant	Cyclophosphamide	– Controlled release of the cyclophosphamide [172]

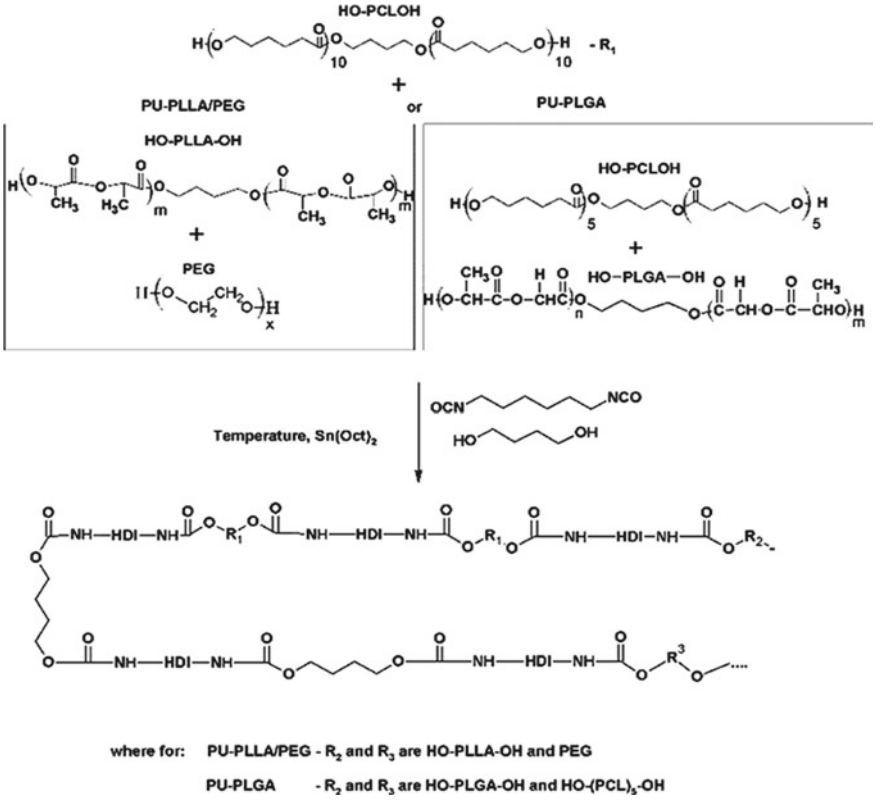


Fig. 6 Formation scheme of PU-PLGA and PU-PLLA-PEG. Reproduced with permission from Elsevier [127]

that replaces sutures. Therefore, tissue adhesive materials have been developed and are available in the market in different forms [52]. Based on the purpose, tissue adhesives are categorized in three different forms: (a) Haemostats are commonly used when blood loss occurs due to tissue damage, this material stops bleeding by involvement in the clotting process; (b) Sealants are commonly applied as a physical barrier during blood leaking. They act as a mid-range adhesive to tissues; (c) glues strongly adhere to tissues [173–175]. The performance of these materials is usually better in a dry environment; however, it is required to perform well in wet conditions also [176]. Besides this, a few other properties like fast curing time, no or low swelling, mechanical stability, and biocompatibility are the key requirements for tissue adhesive [177]. Polymeric tissue adhesives, chiefly PUs-based adhesives, have been extensively studied due to the reactivity of –NCO group in the PU backbone. The –NCO group reacts with water and –OH groups and accelerates tissue adherence in wet conditions. Thus, –NCO terminated PU adhesives can be easily cured in aqueous environment. However, the exothermic reaction water with –NCO group and toxic effects of these materials limit their applications [173, 178–182]. So, researchers developed saccharide based PU solutions for tissue adhesives applications. Numerous –OH groups from saccharide facilitated the adhesion process via hydrogen bonding because no free –NCO groups were available in the material [183] (Fig. 7). Researchers also improved curing time (cured with minutes) by designing biobased photo-crosslinkable networks based on oxidized urethane-modified dextran [184] or methacrylate end-capped PLA [185]. A few systems on biobased PU tissue adhesives have been developed so far. Still, research needs to be carried out to develop biobased PU adhesives for surgical adhesive applications. TissuGlu® is the PU-based (Lysine-derived Urethane) tissue adhesive which is commercially available in the market [52, 176]. Recently, Zou et al. designed a multifunctional wound adhesive using L-Arginine-based degradable polyurethane and gelatin-methacryloyl. It showed shape-adaptive adhesion and haemostatic effect of the damaged organ on rat liver haemorrhage model [186].

6 Conclusion and Future Prospective

Over the last two decades, many research groups have widely explored the potential of biodegradable PUs for biomedical applications, especially in tissue engineering and drug delivery field. In this chapter, we have discussed the tailor-made properties of biodegradable PUs with varied soft and hard segments; their biocompatibility both in vitro and vivo environments. The biomedical applications of biodegradable PUs have been discussed in detail covering tissue engineering, drug delivery, and tissue adhesive applications. With many supporting studies to confirm biocompatibility, the ability to tailor mechanical properties, and degradation kinetics coupled with numerous processing options, biodegradable PUs offer attractive future opportunities to fulfil needs for next generation biomaterials. For translation research, studies should be more emphasized on preclinical evaluation because of the limited number

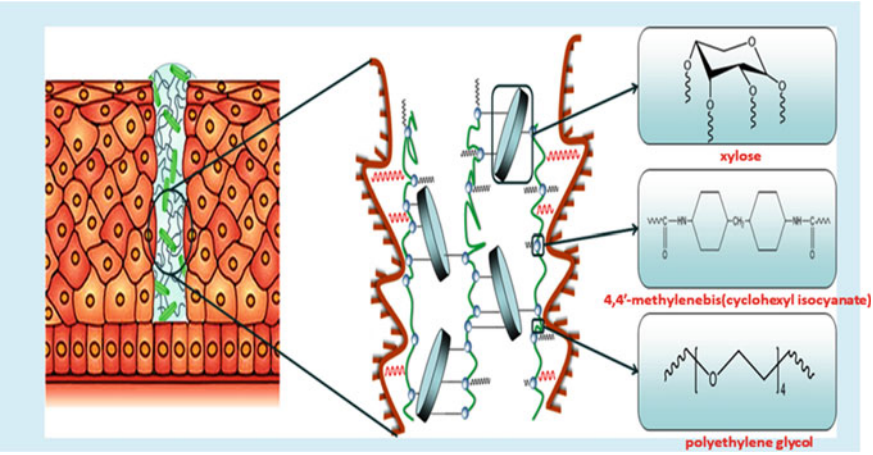


Fig. 7 Xylose-based PU for tissue adhesives applications. Reproduced with permission by Balcioglu et al. [183]

of in vivo studies available on biodegradable PU. The efficacy and safety of PU system should be demonstrated. The clearance of degraded products by metabolizing organs should also be thoroughly assessed.

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