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Recent advances in functional polyurethane elastomers: from structural design to biomedical applications

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Polyurethane (PU) is a synthetic polymer with a micro-phase separation structure and tunable mechanical properties. Since the first successful application of thermoplastic polyurethane (TPU) *in vivo* in 1967, PU has become an important biomedical material for various applications in tissue engineering, artificial organs, wound healing, surgical sutures, medical catheters, and bio-flexible electronics. This review summarizes three strategies for regulating the mechanical properties of medical PU elastomers, including monomer design and selection, modification and arrangement of segments, and incorporation of nanofillers. Furthermore, we discuss the feasible strategies to achieve the biodegradability and self-healing properties of polyurethane to meet specific biomedical needs. Finally, this review highlights the latest advancements in functionalized PU for biomedical applications and offers insights into its future development.

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1. Introduction

Since 1967, segmented multiblock thermoplastic polyurethane (TPU) has been reported to be successfully used *in vivo*, marking the beginning of the development of polyurethane biomaterials for biomedical applications.¹ Polyurethane (PU) consists of three components: polymer diols, diisocyanates, and small molecule chain extenders such as diols or diamines. Among these, polymer diols like polyether and polyester form the flexible segments (soft segments) in the main chain, while diisocyanates and small molecule chain extenders form the rigid segments (hard segments) in the main chain. These hard and soft segments alternate, creating the unique microphase-separated structure of TPU.² This unique structure imparts elasticity, strength, and toughness to TPU.³

PU materials with diverse functions can be prepared through monomer design and selection, adjustment of polymerization parameters, modification of polymer chains, and doping with other materials.⁴ Examples include self-healing PU, biodegradable PU, conductive PU, shape-memory PU, antibacterial PU, and anti-thrombosis PU.^{5–9} These

materials also exhibit a wide range of mechanical properties and good biocompatibility. Furthermore, customized strategies can be carefully designed to meet various clinical needs.

Currently, nearly 600 000 tons of medical polyurethane are being produced globally each year.¹⁰ Polyurethane elastomers with different structures and properties have been widely explored and applied in various aspects of biomedicine, including tissue engineering, artificial organs, wound healing, surgical sutures, medical catheters, and bio-flexible electronics. This broad application is due to the adjustable molecular structure and properties of PU, the abundant source of raw materials, efficient synthesis strategies, and its biological safety.^{10,11}

There have been several comprehensive reviews on biomedical PU that cover a range of topics. These include nano-material-modified biomedical PU, self-healing PU, biodegradable PU, structural engineering of biomedical PU, shape memory PU, sustainable PU, tissue engineering PU, bio-based PU biomedical materials, and so on.^{4,10,12–17} The scope of this review is to introduce and summarize the latest research advancements in the property regulation strategies and biomedical applications of polyurethane elastomers. First, we summarize three strategies for regulating the mechanical properties of polyurethane, including the introduction and regulation of multiple sacrificial bonds, modification and arrangement control of polymer segments, and incorporation of nanofillers. For specific applications, such as tissue engineering, polyurethane may also need to possess biodegradability or self-healing properties. Therefore, we present and sum-

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marize the current strategies for regulating both properties. Second, we provide a comprehensive overview of the latest developments in the biomedical applications of functionalized polyurethane, including tissue engineering, artificial organs, wound healing, bio-flexible electronics, and other implantable and interventional medical devices. Finally, we offer an outlook on the future development of polyurethane materials for biomedical applications (Fig. 1).

2. Regulation strategies of the mechanical properties of polyurethane elastomers

The mechanical properties of polyurethane elastomers determine their industrial applicability and prospects. Strength and toughness are the most important indicators of mechanical performance, directly affecting the material's service life, applicability, reliability, and safety. However, high strength and high toughness are mutually exclusive.¹⁸ Furthermore, regarding the mechanical properties of biomedical PU elastomers, in addition to focusing on strength and toughness, various factors must be considered depending on the specific application. For instance, artificial heart valves require high fatigue resistance, artificial blood vessels or muscles demand excellent tear resistance, and long medical catheters necessitate low hysteresis. Currently, many methods are being used to improve the mechanical properties of polyurethane, including the introduction of multiple sacrificial bonds, segment modification and arrangement control, and the incorporation of nanofillers.

2.1 Monomer design and selection: introduction of multiple sacrificial bonds

Increasing energy dissipation in structures has been shown to be an effective strategy to improve the mechanical properties of elastomers. Inspired by the structures of numerous natural materials, such as spider silk,¹⁹ mussels,²⁰ and muscle fibers,²¹ sacrificial bonds, represented by non-covalent interactions such as hydrogen bonds and host-guest interactions, have been widely introduced into material structural designs. In these structures, sacrificial bonds preferentially break, extending the localized damage at the crack tip throughout the entire polymer network. The fracture and reorganization of sacrificial bonds effectively improve the energy dissipation efficiency during steady-state propagation.²²

In recent years, hydrogen-bond-based sacrificial bond strategies have been widely explored due to the ease of introducing and regulating hydrogen bonds. Guo *et al.*²³ prepared a PU elastomer by blending polycaprolactone (PCL) and isophorone diisocyanate (IPDI) with *N,N*-bis(2-hydroxyethyl) oxamide (BHO) (Fig. 2a–c). This elastomer exhibited a complex arrangement of five hydrogen bonds, achieving gradient and efficient energy dissipation, suppressing PCL segment crystallization, and promoting a uniform distribution of hard and soft segments. As a result, it exhibited a significant tensile strength of 92.2 MPa and a toughness of 480.2 MJ m⁻³. Due to effective stress dispersion and dissipation, the crack tolerance reaches a high level, with a fracture energy of up to 322.2 kJ m⁻². Furthermore, the elastomer exhibits excellent fatigue resistance and recovery capability, making it a polymer material with outstanding overall mechanical properties. In addition to the introduction of layered hydrogen bonds, other studies have reported dense hydrogen bond arrays,²⁴ rigid-flexible hydrogen bond units,²⁵ and chiral hydrogen bonds.²⁶ The design of hydrogen bonds has guided the development of advanced PU elastomers with excellent mechanical properties (strength > 50 MPa and toughness > 200 MJ m⁻³).²⁷

Moreover, with the rise of mechanochemistry, it has been found that the mechanical properties can be improved by incorporating mechanically interlocked structures into polymer networks.^{29,30} Shi *et al.*²⁸ proposed the supramolecular concept of molecular zippers, introducing zipper-like cross-linking agents, pseudo[2]rotaxane (PS), into the PU network (Fig. 2d). The synergistic effect of ring-sliding and hydrogen-bond networks allows for the energy dissipation mechanism through simultaneous breaking of the hydrogen-bond network *via* the molecular zipper's sliding motion. Even a small amount (0.5 mol%) of the PS crosslinking agent can improve the mechanical strength by 950% (45.06 MPa) and elongation by 650% (1890%). Cyclic tensile tests indicate that the elastomer also exhibits excellent fatigue resistance. Li *et al.*³¹ incorporated pillar[5]arene-based pseudo[1]rotaxane, with hydroxyl and amino groups at both ends, into linear polyurethane to develop a class of polyurethane elastomers with a spring-like structure. The results demonstrate that the sliding motion of the pseudo[1]rotaxane along the polymer backbone signifi-



Fig. 1 Schematic diagram of different properties and biomedical applications of polyurethane elastomers.

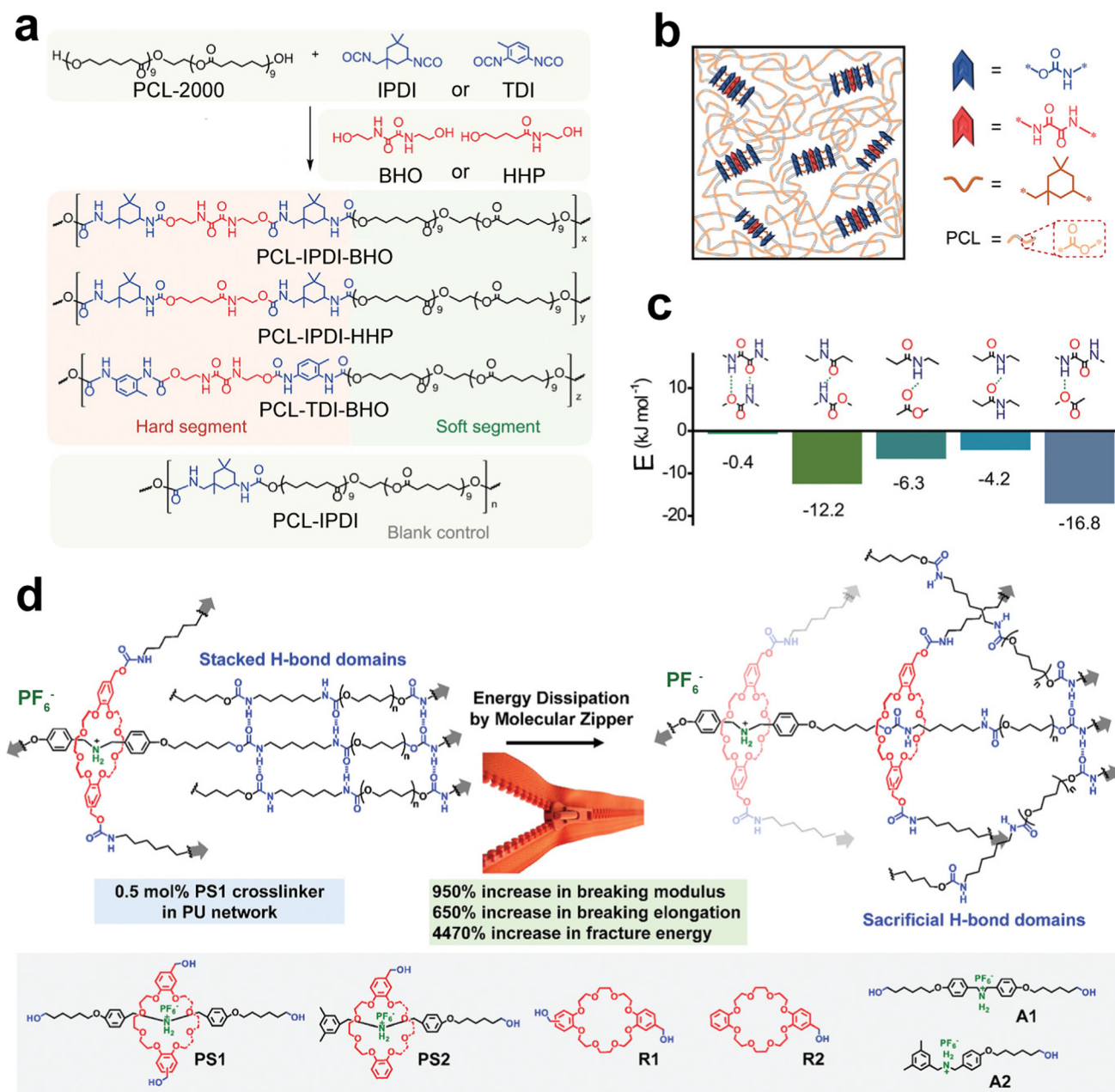


Fig. 2 (a) Synthetic routes employed for the preparation of the elastomers PCL-IPDI-BHO, PCL-IPDI-HHP, PCL-TDI-BHO, and PCL-IPDI. (b) Schematic structural diagram of the PCL-IPDI-BHO elastomer, which is composed of hard phase microdomains and soft segments. (c) Binding energies for the various hydrogen bonds in the elastomers as calculated from DFT. Reproduced from ref. 23 with permission. Copyright 2023 Wiley. (d) Molecular zipper mechanism of the PU network crosslinked by PS1 and PS2. Mechanical force induces ring sliding and synchronously breaks the partial hydrogen-bond stacking domains as sacrificial bonds to dissipate the mechanical energy. Non-interlocked crosslinkers R1, R2, A1, and A2 were used as reference compounds. Reproduced from ref. 28 with permission. Copyright 2020 Wiley.

cantly dissipates energy, thereby endowing the elastomer with enhanced toughness and improved fatigue resistance.

2.2 Chain segment regulation: modification and optimization of arrangement

Traditional TPU synthesis relies on soft segments primarily consisting of specific macromolecular diols, such as polyether, polyester, and polycarbonate polyols. However, Yu *et al.*³²

developed a new method with enhanced performance compared to traditional TPU. They polymerized defect-free α,ω -hydroxyl end-functionalized polyacrylates (ph-PBA) using visible light-driven photoinitiators. In the presence of IPDI (hard chain segment), ethylene glycol (chain extender), and dibutyltin dilaurate (catalyst), ph-PBA was partially used to replace 5 mol% of poly(tetramethylene ether glycol) (PTMEG), resulting in acrylate-based TPU (Fig. 3a). The side chains of

mation, TPU exhibits excellent instantaneous resilience, as well as outstanding fatigue and tear resistance, with a fracture energy of up to $77.8 \text{ kJ}\cdot\text{m}^{-2}$. Qin *et al.*³³ selected PCL as the soft segment and hexamethylene diisocyanate as the hard segment and used chain extenders with different alkyl chain lengths to adjust the arrangement of hard segment clusters (Fig. 3b–d). Compared to PU prepared with adipic dihydrazide (AD), PU prepared using dodecanedioic dihydrazide (DD) as the chain extender had smaller and more uniformly distributed hard segment clusters within the soft segments, resulting in better mechanical properties with a tensile strength of 63.3 MPa, a toughness of 431 MJ m^{-3} , and outstanding crack resistance, as evidenced by a measured fracture energy of 531.1 kJ m^{-2} . Cyclic tensile tests indicate that both elastomers exhibit excellent fatigue resistance. After being heated at $80 \text{ }^\circ\text{C}$ for 5 minutes, the elastomers maintain good elastic recovery performance even after 100 tensile cycles, with minimal residual strain.

2.3 Incorporation of nanofillers

The addition of nanofillers leads to the formation of nanopores in the out-of-domain regions under high strain, while also gaining significant attention due to their ability to

enhance energy dissipation through crosslinking and entanglement within the matrix.^{36,37} For instance, the incorporation of natural polyols (such as lignin and cellulose) can enhance the mechanical properties of PU materials due to their ability to form hydrogen bonds with the polymer matrix.^{38,39} Additionally, the rigid structure of aromatic polyols also contributes to improving the mechanical properties of the composites. Currently, nanoparticle reinforcement strategies are often used in waterborne polyurethane (WPU) to enhance the performance of bio-based WPUs and expand their practical applications.^{40,41} Deng *et al.*⁴² incorporated tunicate cellulose nanocrystals (TCNCs) into castor oil-based WPU using a simple solution mixing method, and a highly stable entangled dispersion system was formed between the TCNCs and WPU (Fig. 4). Based on the unique high crystallinity, high aspect ratio, and high modulus of TCNCs, the composite films exhibited significant strengthening and toughening effects. The tensile strength and Young's modulus of WPU-T_{10%} were significantly increased to 18.29 MPa (three times that of the original WPU film) and 312.17 MPa.

In recent years, researchers have enhanced the mechanical properties of PU by utilizing mechanically responsive carriers that alter their chemical structure under external forces.^{43–45}

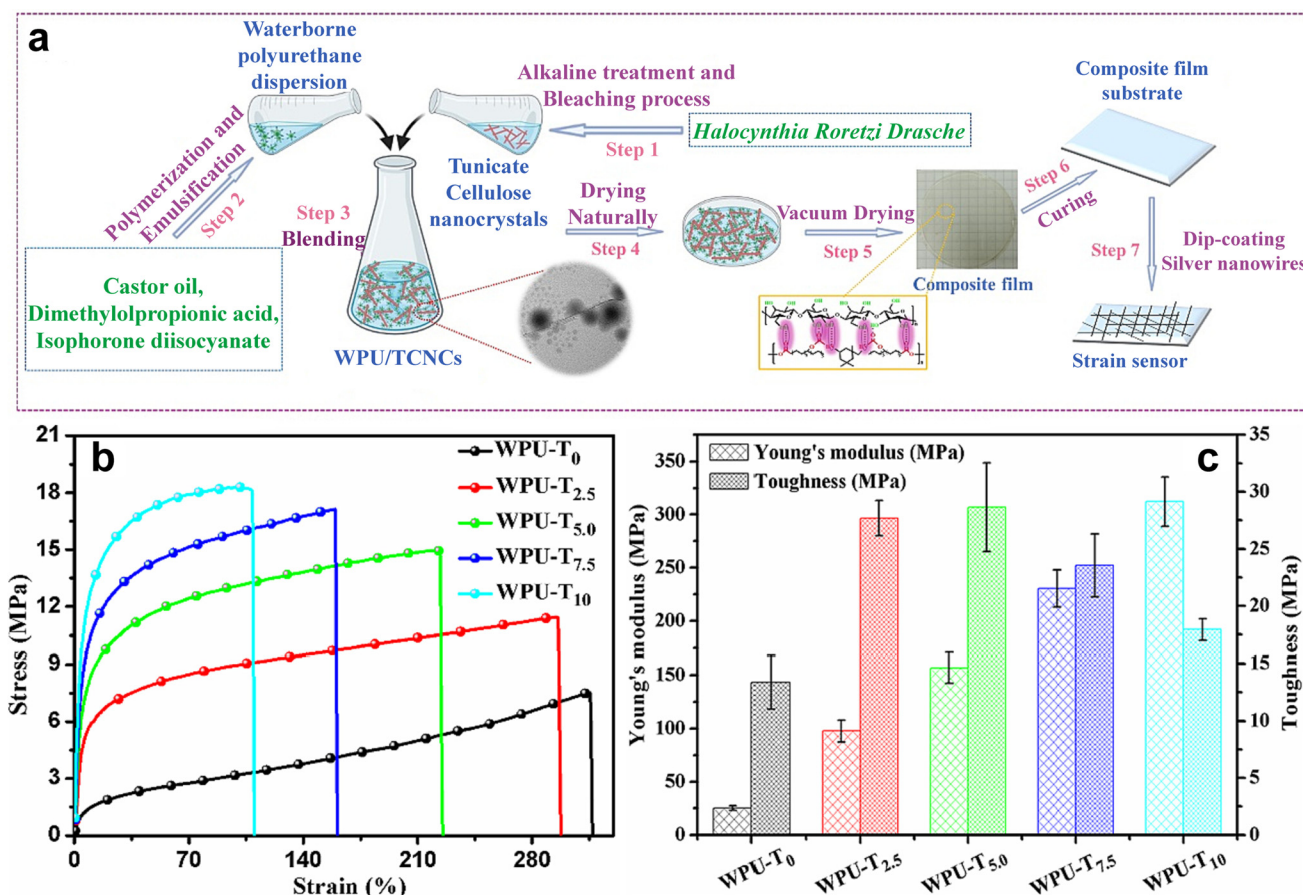


Fig. 4 (a) The whole process from the raw material to strain sensor fabrication. (b) Representative stress–strain curves and (c) mechanical data of WPU films with different ratios of TCNCs. Reproduced from ref. 42 with permission. Copyright 2022, Elsevier.

For example, Chen *et al.*⁴³ incorporated diundecyldiselenide moieties into both the polymer backbone and polymerizable side chains. The Se–Se units act as potential initiators, generating selenol radicals under mechanical stimuli, which subsequently trigger radical transfer and *in situ* crosslinking reactions. The resulting covalent crosslinking endows PU with increased modulus, mechanical self-healing, and mechanical reconfigurability.

3. Self-healing performance of polyurethane elastomers

Endowing materials with self-healing capabilities not only extends the lifespan of materials and reduces waste generation but also opens more diverse application scenarios. However, self-healing performance and mechanical properties are often contradictory.^{46,47} Therefore, manufacturing polyurethane elastomers that have excellent strength, elasticity, toughness, and good self-healing ability is challenging. Current research has shown that by introducing dynamic bonds (dynamic covalent bonds and non-covalent interactions), it is possible to effectively prepare self-healing and recyclable polyurethanes.

3.1 Dynamic covalent bonds

Dynamic covalent bonds are a class of chemical bonds that can undergo reversible exchange under certain conditions (such as light, heat, humidity stimulation, *etc.*). Dynamic covalent bonds possess the stability of covalent bonds while allowing reversible bond cleavage and formation under specific conditions, enabling intermolecular exchange and the creation of new structures or molecules. This characteristic makes them particularly suitable for designing materials with enhanced mechanical properties.⁴⁸ The reversible nature of the reaction makes the synthesis process of dynamic covalent chemistry have the intelligent function of self-healing. Dynamic covalent bond strategies include Diels–Alder reactions,⁴⁹ disulfide bonds,⁵⁰ oxime–urethane bonds,⁵¹ imine bonds,⁵² and metal coordination bonds.⁵³ For example, Yang *et al.*⁵⁰ used IPDI and bis(4-hydroxyphenyl) disulfide as the hard segments and PTMEG 1000 as the soft segments. Hydrogen bonds are introduced into TEMPO-oxidized cellulose nanofibers (TCNF) by modification with 2-ureido-4[1H]-pyrimidone (UTCNF), while disulfide bonds are introduced in the polyurethane (PU) main chain, leading to the formation of dual dynamic cross-linking networks. The resulting PU–SS–UTCNF elastomer could fully self-heal within 4.0 hours at 50 °C. Compared to the original elastomer samples, its tensile strength and toughness increased by 401% and 257%, respectively, reaching 50.0 MPa and 132.5 MJ m⁻³. Zhang *et al.*⁵¹ developed a new copper(II)–butanedione oxime–urethane composite polyurethane elastomer (Cu–DOU–CPU) with synergistic triple dynamic bonds (reversible DOU covalent bonds, Cu–DOU coordination bonds, and hydrogen bonds) (Fig. 5a and b). The dissociation of the weaker bonds (hydrogen bonds and Cu–DOU coordination bonds) can significantly dissipate



Fig. 5 (a) Molecular structure of the Cu–DOU–CPU elastomer. (b) Schematic structure of the Cu–DOU–CPU elastomer. Triple dynamic bonds including reversible covalent (green arc and gray stick), metal–ligand (gray stick and orange circle), and hydrogen bonds (blue polygons) constructed using hybrid dynamic networks. Reproduced from ref. 51 with permission. Copyright 2019 Wiley. (c) Schematic illustration of the muscle-like DA–PU elastomers with the capabilities of being super-tough, anti-fatigue, thermal repairable, and self-healable based on the D–A self-assembly structure. Reproduced from ref. 54 with permission. Copyright 2021 Wiley.

energy during mechanical deformation, thus obtaining high toughness. Their reformation leads to effective self-healing. The relatively strong covalent bonds ensure structural integration to achieve stable mechanical properties. Cu–DOU–CPU exhibited a tensile strength and toughness of 14.8 MPa and 87.0 MJ m⁻³ at room temperature. Meanwhile, the elastomer self-healed spontaneously at room temperature, with the instantaneous recovery tensile strength reaching 1.84 MPa, gradually increasing to 13.8 MPa.

3.2 Dynamic non-covalent bonds

Dynamic non-covalent bonds have low binding energy, allowing them to quickly respond to repair at room temperature without any external stimuli.⁵⁰ Compared to covalent bonds, non-covalent bonds offer the advantage of largely avoiding issues associated with side reactions and may exhibit greater stability over time.¹³ However, most non-covalent interactions

are weaker than typical covalent bonds. Therefore, one of the primary goals in utilizing non-covalent bonds for self-healing materials is to maximize the strength of these interactions to develop materials that possess both self-healing capabilities and excellent mechanical properties. Common dynamic non-covalent bonds include hydrogen bonds,⁵⁵ supramolecular self-assembly,⁵⁴ π - π stacking interactions,⁵⁶ and ionic bonds.⁵⁷ Ying *et al.*⁵⁴ introduced electron-donating (D) and electron-withdrawing (A) structures containing naphthalene rings and amide groups, respectively, into the main chain of polyurethane to design and synthesize DA-PU, where D and A groups alternate along the main chain to achieve donor-acceptor self-assembly both within and between chains (Fig. 5c). The fracture elongation of DA-PU was 1900%, with a toughness of 175.9 MJ m⁻³. In the temperature range of 60–80 °C, its self-healing speed reached 1.0–6.15 $\mu\text{m min}^{-1}$, and the speed gradually increased with temperature.

As can be inferred from the above studies, in recent years, the research paradigm of self-healing PU elastomers has shifted from a singular mechanical mechanism to the study of synergistic repair systems involving multiple dynamic bonds and supramolecular interactions.

4. Biodegradable polyurethanes

With the rapid development of biomedical science and engineering, along with the increasing demand for environmental protection, biodegradable materials are gradually replacing permanent materials as a new trend.^{58,59} Biodegradable polyurethanes are designed to degrade at a controlled rate into safe, non-cytotoxic by-products and are widely used in fields such as tissue engineering and controlled drug release. Biodegradable PUs are synthesized by incorporating hydrolyzable or enzyme-degradable bonds, such as esters, amides, anhydrides, and carbonates, into the polymer network.¹⁷ Several proteases, including cholesterol esterase, lipase, papain, and urease, have been studied owing to their ability to promote the degradation of certain PU elastomers.⁶⁰

The introduction of degradable bonds into soft segments is a common method for constructing biodegradable PUs. Polyesters are the most frequently used polyols in biodegradable PUs. For instance, soft segments such as polycaprolactone (PCL) diol,^{61,62} poly(glycolic acid) (PGA) diol,⁶³ and polylactic acid (PLA) diol,⁶⁴ which are prone to hydrolysis, have been utilized in the fabrication of biodegradable PUs. In addition to the selection of polyol, the choice and design of isocyanates and chain extenders are also critical. For biodegradable PUs, aliphatic diisocyanates (*e.g.*, 1,4-butane diisocyanate (BDI), 1,6-hexamethylene diisocyanate (HDI), and lysine-based diisocyanate (LDI)) or cycloaliphatic diisocyanates (*e.g.*, isophorone diisocyanate (IPDI) and 4,4'-methylene bis(cyclohexyl isocyanate) (HMDI)) should be chosen because their degradation products are non-toxic.^{65–69} LDI-based PUs typically exhibit a higher rate of hydrolytic degradation, which is attributed to the presence of side groups containing hydro-

lyzable bonds.⁷⁰ Small molecule diols or diamines are commonly employed as chain extenders, such as 1,4-butanediol (BDO), ethylene glycol (EG), ethylenediamine (ED), and 1,4-butanediamine (BDA).¹⁴ A crucial function of chain extenders is to facilitate the formation of highly ordered hard segments within the PU backbone. However, chain extenders with hydrolyzable bonds can also accelerate the degradation of hard segments, such as degradable chain extenders based on lactic acid and ethylene glycol.⁷¹ Furthermore, peptide-based chain extenders can be utilized to enhance the enzymatic degradation of PUs.¹⁷

5. Biomedical applications of functionalized polyurethane elastomers

5.1 Tissue engineering

Tissue engineering refers to the repair or replacement of tissues through the use of cells, biomaterials, and appropriate molecular or physical factors, either individually or in combination, to improve clinical outcomes.⁷² The mechanical properties of human tissues vary widely, with differences in elasticity modulus spanning several orders of magnitude. The modulus of central nervous system tissues, as well as most soft tissues such as abdominal organs and skin, ranges between 1 and 100 kPa, while the modulus of hard tissues like cartilage and bone spans from 10² to 10⁶ kPa.^{73,74} The modulus mismatch between biomaterials and adjacent tissues can trigger unwanted inflammatory responses, exacerbate foreign body reactions, and hinder the tissue regeneration process.⁷⁵ Therefore, it is essential to develop a range of mechanically adaptable elastomers suitable for various tissue engineering applications. PU offers adjustable mechanical strength, flexibility, and elasticity, making it capable of mimicking the biomechanical behavior of hard tissues, soft tissues, and elastic tissues. Furthermore, PU's flexible synthetic chemistry allows for the generation of various biodegradable PUs to meet the specific needs of different tissues.

PUs applied to bones and muscles require a modulus similar to that of tissue to serve as a cell culture matrix for human muscles.⁷⁶ Ker *et al.*⁷⁷ synthesized a photochemically cross-linked polyurethane (QHM) from quadrol (Q), hexamethylene diisocyanate (H), and methyl methacrylate anhydride (M) as a graft for rotator cuff repair. QHM exhibits light-controllable tensile and compressive properties that resemble bone and tendon (12–74 MPa tensile strength, 0.6–2.7 GPa tensile modulus, 58–121 MPa compressive strength, and 1.5–3.0 GPa compressive modulus), capable of withstanding 10 000 physiological stretching cycles and reducing stress concentration through stiffness gradients. Additionally, it possesses favourable biophysical and chemical properties for clinical translation, including slow degradation, minimal cytotoxicity, and excellent suture retention, and functions as a tendon substitute. Zhang *et al.*⁷⁸ developed a 3D-printed

scaffold made of shape-memory PU and Mg particle composites (SMPU/Mg), which promotes bone formation, near-infrared responsiveness, and close contact (Fig. 6a). The prepared SMPU/4 wt% Mg scaffold with a graded porous structure significantly improved mechanical properties compared to the original SMPU scaffold (compressive strength of ~ 5.9 MPa and modulus of ~ 16.8 MPa), achieving a compressive strength of ~ 6.7 MPa and a modulus of ~ 23.0 MPa. This method addresses the limitations of traditional shape-memory implants in terms of low porosity, response temperature, mechanical properties, and bioactivity.

Biodegradable PUs are attractive for the repair and regeneration of soft tissues (nerve tissue, blood vessels, *etc.*) because they have good biocompatibility, flexibility and high elasticity, mimicking the mechanical behavior of soft tissues. Yang *et al.*⁷⁹ designed a PU nerve guidance conduit modified with gastrin for continuous and sustained release of gastrin, creating a favourable microenvironment for reducing inflammation and stimulating axonal regeneration (Fig. 6b). The pre-

pared 5% gastrin/PU exhibited suitable pore structures and biocompatibility *in vitro*, significantly enhancing Schwann cell proliferation, migration, and myelination *in vivo*, upregulating the expression of neurotrophic factors, and inducing PC12 cell differentiation, which greatly promoted the morphological and functional recovery of regenerated sciatic nerves. Li *et al.*⁸⁰ developed a hydrophilic PU elastomer by crosslinking hard segment chains containing 2,2'-diselenoethanol with diamino-pyrimidine-capped polyethylene glycol (PEG) and glycol terminated with diamino pyrimidine (Fig. 6c). By adjusting the crosslinking density of the elastomer, its elasticity was tailored to resemble that of natural blood vessels. The hydrophilicity of PEG and the bioactivity of aminopyrimidine and diselenoether groups endowed the PU with biological functions similar to those of natural endothelium, including stable NO release at physiological levels, anti-platelet adhesion and activation, inhibition of smooth muscle cell migration, adhesion, and proliferation, antimicrobial properties, and reduced immune response and calcification *in vivo*.

5.2 Artificial organs

PU materials are widely regarded as feasible candidates for the fabrication of artificial tissues and organs due to their excellent mechanical properties, chemical stability, and highly tunable performance and applicability. Heart valve disease affects millions of people globally each year. Valve replacement surgery is a major therapeutic intervention, with options ranging from mechanical heart valves to biological heart valves.^{81,82} However, both types present various issues, including mismatched mechanical properties, calcification, and thrombosis, which limit their service life.^{83,84} Therefore, achieving both biocompatibility and mechanical stability is a key challenge in the development of artificial heart valves.⁸⁵ Zhao *et al.*⁸⁶ designed and synthesized a uniformly integrated polyurea-polyurethane elastomer (PSCU) for use as an artificial heart valve (Fig. 7). The molecular structure of PSCU features a dense hydrogen bond network between oxygen-rich helical chemical rings and polyurethane urea segments, granting excellent fatigue resistance and damage tolerance. By incorporating silane-structured TDBA into the hard segments of the polyurethane, the complexity of the protein adhesion process was enhanced, and the degree of Ca^{2+} adsorption was significantly reduced. *In vivo* implantation experiments showed good blood compatibility.

Furthermore, PU also shows promise in the fabrication of artificial bone membranes and artificial ligaments. Zhang *et al.*⁸⁷ used a one-pot method to prepare a catechol aldehyde + zinc ion (PCA + Zn ions) metal-phenol network coating on TPU films, resulting in a novel bone membrane with excellent biocompatibility. This membrane regulates oxidative stress and promotes osteogenesis and mineralization, thus facilitating bone regeneration. Zhao *et al.*³⁸ extracted natural lignin polyols (LP) with a unique aromatic skeleton and numerous reactive sites from lignocellulosic waste. The obtained LP was directly incorporated into a polyurethane matrix synthesized from IPDI, PTMEG, and adipic hydrazide (ADH). The resulting

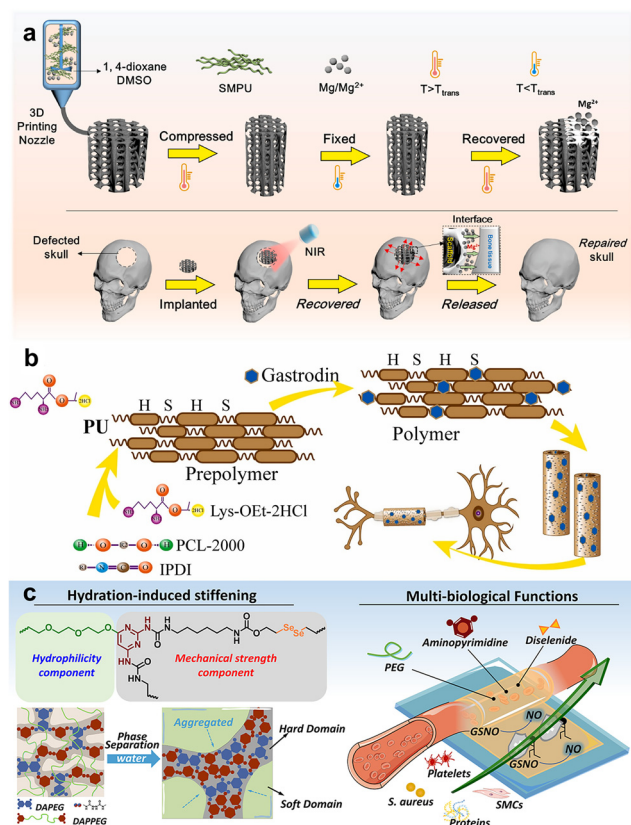


Fig. 6 (a) 3D printed SMPU/Mg scaffold and its Mg^{2+} releasing process for repairing defective bone. Reproduced from ref. 78 with permission. Copyright 2022, The Author(s). (b) Illustration of the preparation of gastrin/PU NGCs and their application in a peripheral nerve repair strategy. Reproduced from ref. 79 with permission. Copyright 2021, The Author(s). (c) Schematic diagram of the synthesis of the polyurethane-based hydrophilic elastomer and its application to small-diameter vascular grafts. Reproduced from ref. 80 with permission. Copyright 2024, Elsevier.

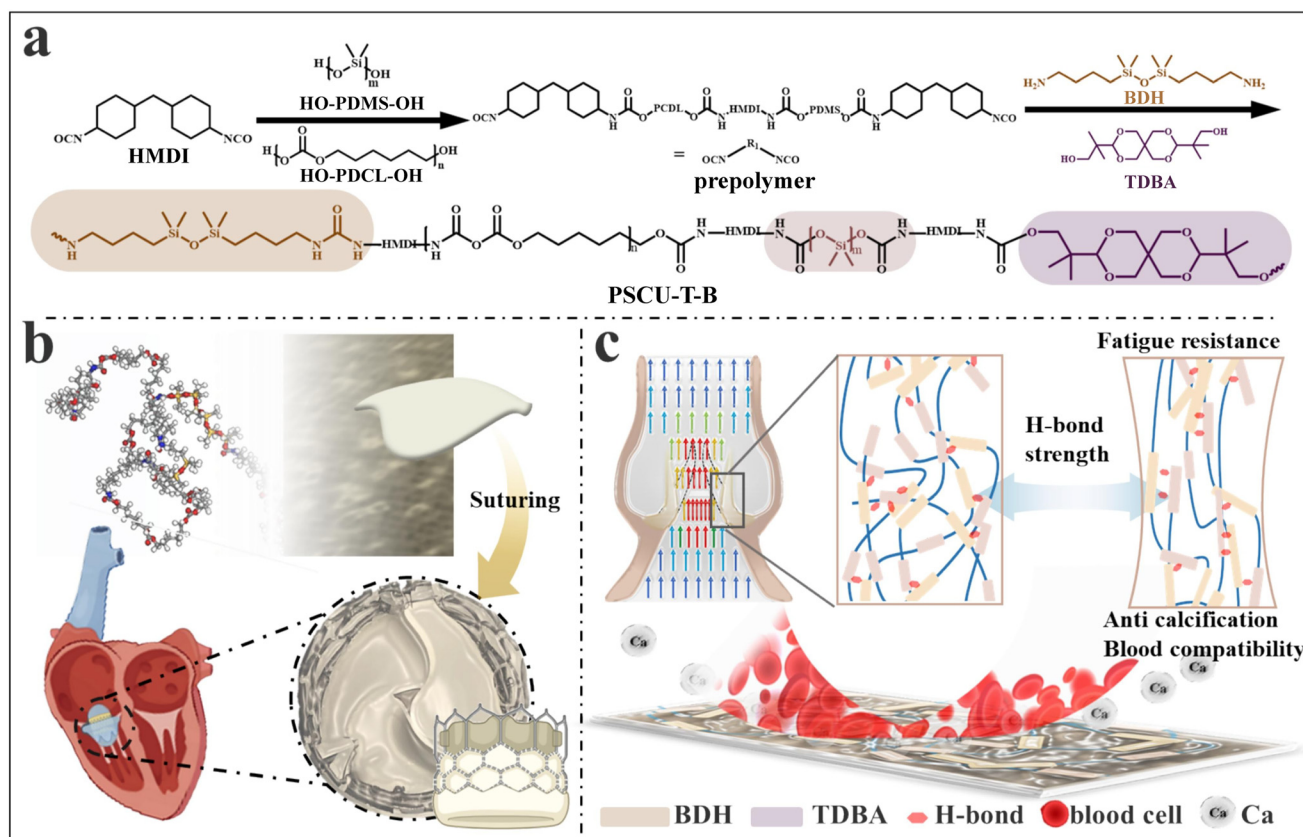


Fig. 7 Design and synthesis of polyurethane with enhanced fatigue resistance, anti-calcification and blood compatibility for heart valves. (a) Structure of polyurethane. (b) Processing of artificial heart valves. (c) Polyurethane heart valves having fatigue resistance, anti-calcification, and blood compatibility. Reproduced from ref. 86 with permission. Copyright 2024, Elsevier.

elastomer, ADH-LP-PU, demonstrated significant improvements in tensile strength and toughness with good biocompatibility, making it suitable for the manufacturing of artificial ligaments.

5.3 Promoting wound healing

As the largest organ of the human body, the skin is not only an essential part of the immune system but also plays a role in absorption, excretion, and sensation.⁸⁸ For small wounds in a healthy body, simple treatments can allow the skin to heal and restore its function in a short period. However, for patients with large-area skin burns or chronic diseases, wound healing may take days or even months, and abnormal phenomena such as wound infections, ulcers, or scarring may occur.^{89,90} Chronic wound care standards include wound debridement (removal of necrotic or infected tissue), cleaning the infected area, and finally dressing the wound with appropriate materials.⁹¹ Therefore, the development of suitable wound dressings is crucial for chronic wound healing to prevent infection and provide an appropriate environment (promoting oxygen penetration, sufficient moisture, and absorbing exudate). PU is commonly used in wound dressings due to its good biocompatibility, barrier properties, elasticity, and oxygen permeability.^{92,93}

Incorporating electroactive materials into PU matrices, and using electrical stimulation to promote cellular movements such as adhesion, migration, and proliferation, is a feasible strategy for preparing PU-based wound dressings.⁹⁴ Yang *et al.*⁹⁵ designed a new biocompatible composite wound dressing (LGPU) by blending PU with a liquid metal (LM) modified with the bioactive tripeptide compound glutathione (GSH) (Fig. 8). This dressing allows for stable and uniform electrical stimulation (ES) treatment of the wound. Using GSH, which promotes skin immunity and hair follicle growth, as a dispersing agent, multiple hydrogen bonds are formed at the interface, overcoming the high surface tension ($>550 \text{ mN m}^{-1}$) of the LM and achieving good dispersibility. This improves the uniformity and stability of ES treatment. At the same time, benefiting from the hydrogen bond network in PU and the remodeling properties of LM, the dressing has excellent self-healing capabilities, with conductivity fully restored in a short period (<1 second). Furthermore, the results show that the dressing has good biocompatibility, and 3.6 V direct current electrical stimulation promotes fibroblast migration, significantly enhancing wound healing, and can stimulate hair follicle activation to promote scar-free wound repair.

In addition, bioactive agents such as amino acids,⁹⁶ asiaticoside, nano-silver,⁹⁷ and ciprofloxacin⁹² can also be incorpor-

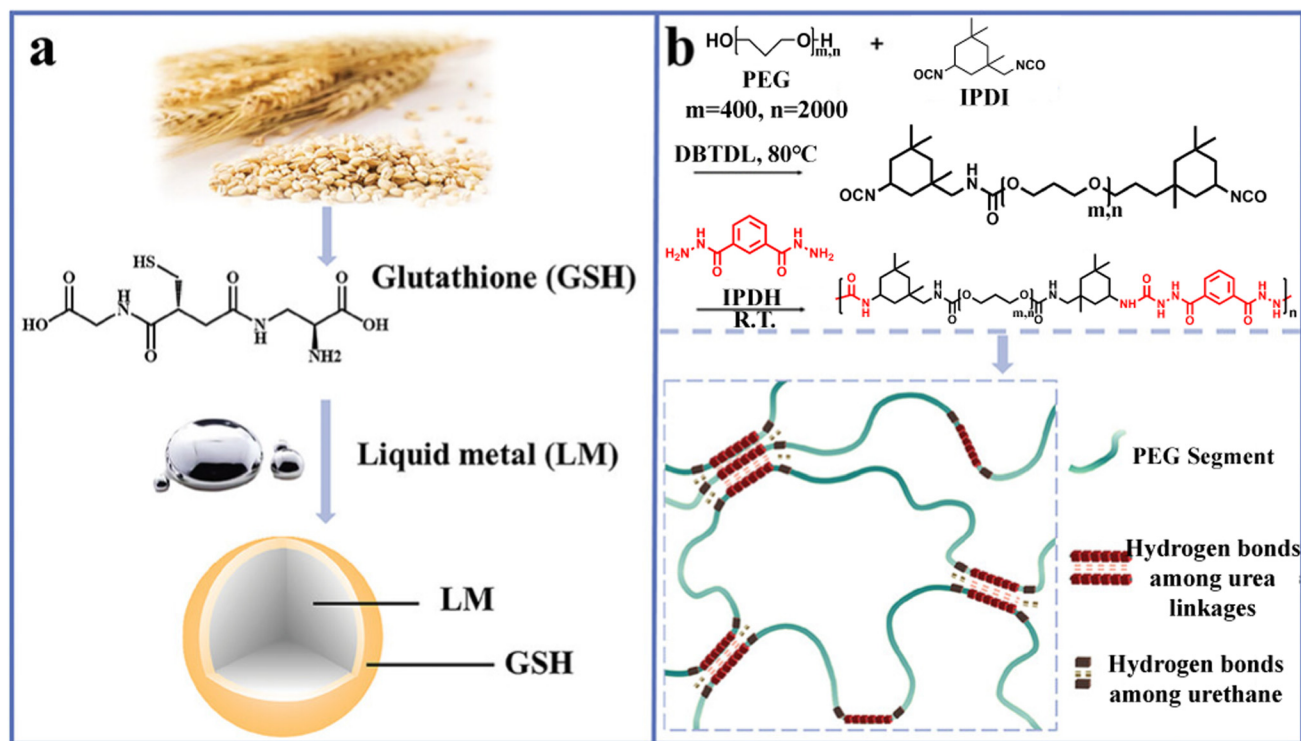


Fig. 8 Design strategy of the electric stimulation patch for scarless wound healing. (a) GSH-coated LM for the formation of a core-shell structure. (b) Synthetic routes and schematic illustration of PU. Reproduced from ref. 95 with permission. Copyright 2024 Wiley.

ated into degradable PUs, allowing controlled drug release during the slow degradation process of PU, thereby promoting wound healing. As a pivotal mediator in the wound healing process, L-arginine (L-Arg) possesses pro-angiogenic properties. Zou *et al.*⁹⁶ endowed PU with multifunctional tissue adhesion and biodegradable properties for wound healing by incorporating L-Arg, drug-loading chain extender β -CD, and the soft segment PEG into the PU molecular chain. Asiaticoside is a herbal wound healing agent known to stimulate collagen synthesis and reduce oxidative stress in wounds. Therefore, Ritthidej *et al.*⁹⁷ developed a PU foam dressing containing silver and asiaticoside for the healing of skin wounds.

5.4 Bio-flexible electronics

In the past few decades, flexible electronic sensors have attracted widespread attention due to their portability, flexibility, real-time sensing response, and low detection limits, making them ideal for multifunctional electronic skin, wearable human-machine interfaces, and healthcare monitoring.⁹⁸ Although flexible electronic sensors have made significant progress, there remain substantial challenges in simultaneously achieving ultra-high sensing sensitivity, a wide working range, and fast response/recovery.^{99,100} Among various flexible materials, TPU is a commonly used stretchable material that offers high elasticity and ductility, along with excellent tensile strength, toughness, and aging resistance. These properties make it an ideal material for fabricating flexible sensors.¹⁰¹ By incorporating sensing material layers such as ionic liquids,

graphene, carbon nanotubes, metal nanoparticles, or MXenes onto TPU matrices, multifunctional flexible electronic sensors can be fabricated, including strain sensors, temperature/light sensors, and piezoresistive sensors.^{102–104}

Liu *et al.*¹⁰⁵ drew inspiration from the highly sensitive microstructure of human skin (protective epidermis/spiny sensory structure/nerve conduction network) and combined a polyurethane elastomer matrix with MXene nanosheet-coated microsphere arrays, which were assembled using a clever templating method (Fig. 9). This configuration served as a biomimetic protective epidermal layer/sensing layer, with a conductive cross-electrode-coated PU substrate acting as the signal transmission layer, resulting in a multifunctional biomimetic skin electronic device. The newly prepared polyurethane elastomer matrix, functionalized with three dynamic bonds (reversible hydrogen bonds, carbamate oxime bonds, and copper(II) ion coordination bonds), exhibited high healing efficiency, strong recyclability, reliable antibacterial properties, and good biocompatibility. The assembled flexible electronic device demonstrated satisfactory sensing performance: ultra-high sensitivity (up to 1573.05 kPa^{-1}), wide sensing range (up to 325 kPa), good reproducibility, fast response time ($\approx 4 \text{ ms}$), and low detection limit ($\approx 0.98 \text{ Pa}$). These features make it an excellent candidate for human health monitoring, with remarkable repairability and reliable antibacterial properties. It shows significant potential in next-generation electronic skin, personalized medical detection, smart disease diagnosis, and wearable human-machine interfaces.

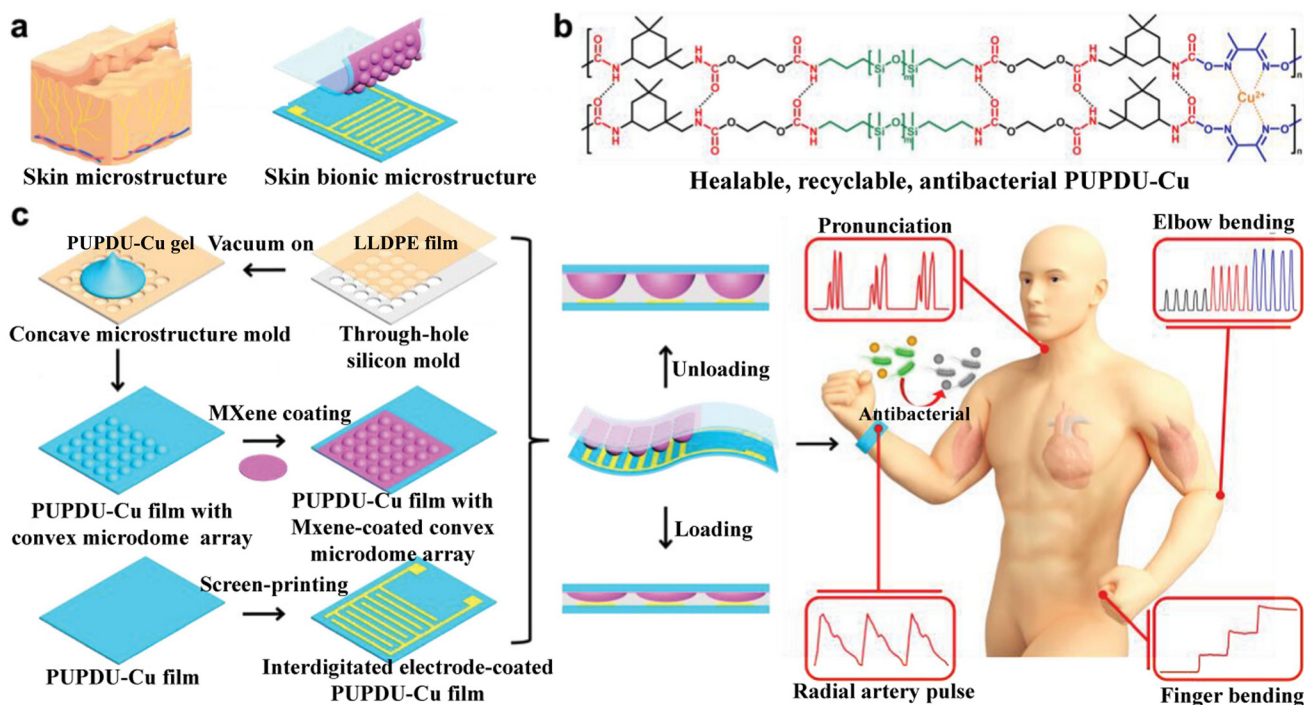


Fig. 9 Schematic illustration of the preparation of a skin bionic ultrasensitive multifunctional flexible electronic sensor with excellent healability and reliable antibacterial function. (a) Schematic of a skin bionic multifunctional flexible electronic sensor with a human skin-like microstructure. (b) Molecular structure of the newly prepared healable, recyclable, and antibacterial polyurethane elastomer (PUPDU-Cu). (c) Fabrication of the skin bionic ultrasensitive multifunctional flexible electronic sensor with reliable antibacterial capability for personalized healthcare monitoring and intelligent human-machine interface. Reproduced from ref. 105 with permission. Copyright 2023, The Author(s).

5.5 Other implantable and interventional medical devices

PU has become an indispensable material for implantable and interventional devices due to its unique advantages, including excellent mechanical properties (good toughness and strength, tear resistance, and fatigue resistance), favourable biocompatibility, and adjustable degradability. The previous sections have discussed the applications of PU in implantable and interventional medical devices such as tissue scaffolds, artificial organs, and nerve guidance conduits. Beyond these, PU is also utilized in implantable/interventional devices like medical catheters and surgical sutures. Xu *et al.*¹⁰⁶ modified PU with an efficient imidazole-type ionic liquid (IL) cationic antimicrobial agent, Mim-BU, and developed a long-lasting anti-infective PU catheter on an industrial scale that can withstand autoclaving. Guo *et al.*¹⁰⁷ designed and fabricated a recyclable, degradable (approximately within 2 months by lipase), high-toughness, and tear-resistant PU elastomer based on PCL, utilizing biologically relevant Fe³⁺ and protocatechualdehyde (PA, chain extender) to achieve iron-catechol coordination. Biological experiments have demonstrated that this elastomer has good biocompatibility and can promote wound healing in mice when used as sutures.

6. Conclusions and perspectives

The adjustable molecular structure and properties as well as the biocompatibility of PU endow it with unique potential as a bio-

medical material. This review discusses in detail the strategies for regulating the mechanical properties, self-healing properties, and biodegradability of PU, providing insights for customizing PU materials for specific biomedical applications. Furthermore, we summarized the latest advances in the application of PU materials in tissue engineering, artificial organs, wound healing, bio-flexible electronics, and other implantable and interventional medical devices, highlighting the adaptability and wide applicability of PU materials in the biomedical field.

Looking forward to the future development of biomedical PU materials, we believe that the following issues need to be focused on.

1. Environmentally friendly and sustainable PU materials. So far, the synthesis of PU has primarily been through the step-growth polymerization of polyisocyanates with polyols. Although the chemical reactions involved in PU synthesis are simple and the final product exhibits excellent properties, the raw materials used for synthesis have inherent toxicity and are non-renewable resources. For instance, isocyanates are synthesized from highly toxic phosgene, which is closely associated with health issues such as asthma and dermatitis. Therefore, research on non-isocyanate polyurethane (NIPU) has garnered significant attention. Currently, NIPU is mainly synthesized through three methods: transurethanisation, aziridine copolymerization with CO₂, and ring-opening polymerization of cyclic carbamates, with the latter being the most widely used and researched.¹⁶ Although NIPU faces drawbacks such as slower synthesis kinetics and lower

molecular weights than isocyanate-based PU, it still offers advantages, such as avoiding the toxic isocyanates and phosgene, as well as being less sensitive to moisture.¹⁰⁸ Literature studies have reported the biomedical applications of NIPU, such as artificial heart valves, wound healing dressings, and biosensors.^{52,109,110}

In addition, WPU has also attracted increasing attention owing to its multifunctional and environmentally friendly characteristics. WPU is formed by dispersing polyurethane prepolymers containing isocyanate functional groups into water, either directly or through an emulsion process, and then chain-extending the dispersed polyurethane in the aqueous phase using diamines.¹¹¹ The resulting WPU material has several advantages: zero or extremely low content of volatile organic compounds (VOCs) (environmentally friendly); no isocyanate residues (non-toxic); excellent applicability, multifunctionality, and a broad range of superior properties.¹⁶ Due to these advantages and good biocompatibility, WPU has been widely used in biomedical fields such as tissue repair, drug delivery, wound dressings, and antibacterial applications.^{112–115}

2. Smart PU materials and 4D printing. Shape-memory polyurethane (SMPU)-based 4D printing has gradually emerged as a promising smart material and technology. Shape-memory polymers can recover from the deformed state to the initial shape under various stimuli and have broad application prospects in biomedical equipment for minimally invasive surgery.¹¹⁶ 4D printing refers to the ability of 3D printed materials to trigger changes when exposed to stimuli such as temperature, electricity, light, pressure, or humidity. 4D printing involves time, stimuli, programming, and smart materials, indicating that printed parts will continue to change over time after the manufacturing process and further restore their original shape when subjected to external stimuli, such as heat, applied loads, light, pH changes, evaporation, magnetic fields, and electric fields.¹⁵ 4D printing typically uses TPU due to its excellent shape-memory behavior. Currently, 4D printing based on SMPU overcomes the limitations of traditional manufacturing methods (such as extrusion and injection molding), enabling the creation of various intricately designed and complex geometries, which can be used in applications such as tissue scaffolds, flexible sensors, and wearable or biomedical devices.^{117–119}

In conclusion, the future trend of PU materials for biomedical applications will focus on the development of environmentally friendly, sustainable, bio-based, and non-isocyanate PU. In addition, smart, multifunctional PU materials may spark significant interest. Moreover, with the rapid development of 3D/4D printing technologies, customized medical devices are likely to become more widespread, which will require increased attention to the biocompatibility and biodegradability of PU, including the characterization of degradation products and their toxicity.

Abbreviations

PU	Polyurethane
TPU	Thermoplastic polyurethane

PCL	Polycaprolactone
IPDI	Isophorone diisocyanate
BHO	<i>N,N</i> -Bis(2-hydroxyethyl)oxamide
PS	Pseudo[2]rotaxane
ph-PBA	α,ω -Hydroxyl end-functionalized polyacrylates
PTMEG	Poly(tetramethylene ether glycol)
AD	Adipic dihydrazide
DD	Dodecanedioic dihydrazide
WPU	Waterborne polyurethane
TCNs	Tunicate cellulose nanocrystals
PDMS	Polydimethylsiloxane
PGA	Poly(glycolic acid)
PLA	Poly(lactic acid)
BDI	1,4-Butane diisocyanate
HDI	Hexamethylene diisocyanate
LDI	Lysine-based diisocyanate
HMDI	4,4'-Methylene bis(cyclohexyl isocyanate)
BDA	1,4-Butanediamine
BDO	1,4-Butanediol
SMPU	Shape-memory polyurethane
PEG	Polyethylene glycol
LP	Lignin polyols
ADH	Adipic hydrazide
LM	Liquid metal
GSH	Glutathione
ES	Electrical stimulation
NIPU	Non-isocyanate polyurethane
VOCs	Volatile organic compounds
EG	Ethylene glycol
ED	Ethylenediamine
L-Arg	L-Arginine
IL	Ionic liquid
PA	Protocatechualdehyde.

Author contributions

Jinhua Qiu: investigation, methodology, formal analysis, and writing – original draft. Hui Zhao: investigation and formal analysis. Shifang Luan: writing – review & editing and conceptualization. Lei Wang: conceptualization, project administration, supervision, funding acquisition, and writing – review & editing. Hengchong Shi: supervision, funding acquisition, and writing – review & editing.

Data availability

Data availability is not applicable to this article as no new datasets were generated or analyzed in this study.

Conflicts of interest

There are no conflicts to declare.

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