Novel applications of urethane/urea chemistry in the field of biomaterials

4

*G.B. Kim, J. Guo, J. Hu, D. Shan, J. Yang**
Department of Biomedical Engineering, Materials Research Institute, The Pennsylvania State University, University Park, PA, USA; The Huck Institutes of the Life Sciences, The Pennsylvania State University, University Park, PA, USA
*Corresponding author: jxy30@psu.edu

4.1 Introduction

Urethane/urea chemistry refers to both isocyanate-based and nonisocyanate-based reactions that form urethane (—HNCOO—) or urea (—HNCONH—) bonds. The reactions between isocyanate groups and hydroxyl (to form urethane bonds, Figure 4.1(a)) or amino (to form urea bonds, Figure 4.1(d)) groups [1–3] are the most commonly found. Nonisocyanate-based urethane reactions include the reactions between cyclic carbonates or activated carbonate/carbamate/chloroformate derivative groups and amine groups (Figure 4.1(b) and (c)) [4–6]. The latter were often used as coupling reactions between hydroxyl and amino groups [5,7–9]. The polyaddition reaction between polyisocyanates and polyols is often used to make polyurethanes (PUs) [1–3], the generic term which represents the most versatile family of synthetic polymers containing repeating urethane (—HNCOO—) linkages in the polymer chains. Polyols used for PUs can be small molecules or macromolecules, biodegradable polyesters or nondegradable polyethers, or other polymers with two or more terminal or pendent hydroxyl groups [1–3].

Segments of polyisocyanates can be aliphatic or aromatic, di-, tri-, or multifunctional, pure carbon chains or containing some biodegradable ester bonds [1–3,10]. A variety of polyols and polyisocyanates make PUs a class of polymers that can display thermoplastic, elastomeric, and thermoset behavior depending on their chemical and morphological characteristics [2]. The unsurpassed physical and chemical properties, along with their biocompatibility, have led to their use in a wide range of biomedical applications, including external applications as catheters, padding and bedding [1,3,11,12], cardiovascular applications [1,3,11,13–16], nerve guides [1,3,11,14,17], bone tissue engineered substrates [14,18], artificial organs [12], tissue replacement and augmentation, breast implantation, and wound dressings and adhesives [11,19,20].

Traditional and most commonly used PUs are linear multiblock polymers made by the polyaddition reaction between diols and diisocyanates. Diols can be polyesters, polyethers, other polymers with two terminal hydroxyl groups, or small molecular diols and their mixtures. Diisocyanates can be aliphatic, such as 1,6-hexamethylene diisocyanate (HDI) and isophorone diisocyanate (IPDI), or aromatic, such as toluene diisocyanate [2]. Using different types of diols and diisocyanates, various thermoplastic, elastic, or thermoset

Advances in Polyurethane Biomaterials. http://dx.doi.org/10.1016/B978-0-08-100614-6.00004-4

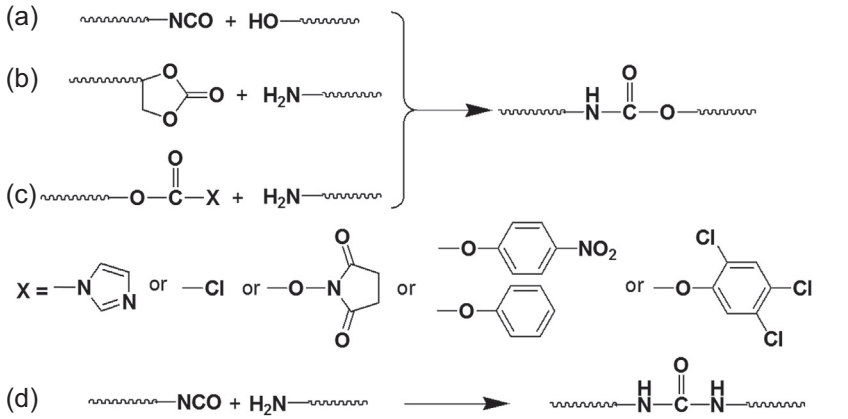

Figure 4.1 Representative urethane/urea chemistry reactions: (a) between isocyanate and hydroxyl groups (to form a urethane bond); (b) between a cyclic carbonate; activated carbonate, carbamate, or chloroformate derivative group and amino group (c); between isocyanate and amino groups (to form a urea bond) (d).

PUs have been developed and thoroughly investigated for various industrial and biomedical applications [1–3]. By alternately connecting soft and hard segments together through urethane bonds, assorted PUs, such as poly(ε-caprolactone) (PCL) containing block PUs [21], polylactide (PLA)-based PUs [22], and poly(ε-caprolactone-co-lactide acid) (PCLA)-based PUs [23], were prepared with useful shape-memory properties.

Since the synthesis and applications of traditional biodegradable PUs have been thoroughly reviewed by many other researchers, we will particularly analyze the biomedical applications of urethane/urea chemistry from a different view in this chapter. We will focus on the development of novel PUs, such as citrate-based urethane-doped polyesters, including cross-linked urethane-doped polyester elastomers (CUPE) [13,16], clickable CUPE (CUPE-click) [24], urethane-doped biodegradable photoluminescent polymers (UBPLPs) [15], photo-cross-linkable CUPE [25], and biodegradable citrate-based waterborne PUs and their clickable counterparts. In addition, their applications in cardiovascular and orthopedic applications, nerve regeneration, and drug delivery will be reviewed. We will also expand our discussion to nonisocyanate-based urethane reactions and nontraditional applications of isocyanate- and nonisocyanate-based urethane/urea chemistry in polymer synthesis, surface functionalization, polymer grafting, polymer cross-linking, peptide, protein, and deoxyribonucleic acid (DNA) bioconjugations.

4.2 Citrate-based urethane-doped polyesters

Different from traditional PUs designed for long-term implantation applications, PUs used for soft tissue engineering (e.g., cardiac, bone tissue, and neural engineering) and drug delivery should be able to decompose to nontoxic degradation products *in vivo*. One of the most common methods to synthesize biodegradable PUs is to incorporate biodegradable polyester macrodiol soft segments that hydrolyze *in vitro* and *in vivo*, such as PLA, poly(lactide-co-glycolide) (PLGA), and PCL.

Polyester is a group of polymers that contain the ester functional group in their chain. Esters are chemical compounds derived from a carboxylic acid and a hydroxyl compound, usually an alcohol. Most esters are considered biocompatible since they are endogenous to the human metabolism and able to break down to natural metabolic products by simple hydrolysis. Elastomers composed of aliphatic polyester chains cross-linked with each other by ester bonds, such as poly(diol citrates) and poly(glycerol sebacate) (PGS), have received much attention because they are soft, elastic, and biocompatible [26,27]. Yang et al. synthesized the first citrate-based biodegradable elastomer (CABE), poly(diol citrates), in 2004 using a convenient and cost-effective polycondensation reaction [26,28].

A key feature of CABEs is that citric acid serves as a robust multifunctional monomer in prepolymer formation through a simple polycondensation reaction while preserving pendant functionality for postpolymerization to produce a cross-linked polyester network with degradable ester bonds [29]. Citric acid is a nontoxic metabolic product of the Krebs cycle and has been used in Food and Drug Administration (FDA)-approved products or devices. Citric acid prevents blood clotting so it can function as an anticoagulant for blood specimens. In biomaterials, citric acid is mainly used to participate in the ester cross-link formation, but also enhances hemocompatibility, balances the hydrophobicity of the polymer network, and provides hydrogen bonding and additional binding sites for bioconjugation to confer an additional functionality such as optical properties. The pendant functionality gives the CABEs their unique degradation, mechanical, and optical properties over existing biomaterials.

However, traditional polyester elastomers lack mechanical compatibility with surrounding living tissues and the strategy for increasing cross-link density to improve their mechanical properties often makes them lose their flexibility. Although these polyester elastomer scaffolds have been proposed for tissue engineering of nerve tissues [30–32] and small diameter blood vessels [33], they are weak and unsuitable for engineering tissues such as ligaments, which require high tensile strength and load bearing ability. For example, the human anterior cruciate ligament has an ultimate tensile strength of at least 38 MPa [34], which is much higher than that of poly(diol citrates) (up to 11.15 ± 2.62 MPa). Sufficient mechanical strength is also desired for an ideal tissue-engineering scaffold especially during surgical handling following initial cell seeding. Maintaining proper mechanical strength becomes even harder when using elastomers for porous scaffolds. Polymers used for tissue engineering tend to lose a significant amount of mechanical strength when fabricated into porous scaffolds. For example, poly(diol citrate) underwent a significant loss in peak stress from 2.93 ± 0.09 MPa (film) to 0.3 ± 0.1 (scaffold) on pore introduction [33].

Thus, recent effort in biodegradable elastomer designs has focused primarily on developing a soft, strong, and completely elastic (100% recovery from deformation) material with balanced, tunable biodegradability and mechanical properties. For a decade, multifunctional CABEs with tunable mechanical and degradation properties for tissue engineering, drug delivery, bioimaging, and other applications have been developed [17]. The resulting materials have shown a wide range of mechanical properties, degradation profiles, and surface energies, which are all important in controlling the biological response to an implant. Recently, a new class of biodegradable elastomers, cross-linked urethane-doped polyesters (CUPEs), has been developed by doping urethane bonds in the poly(diol citrate) polyester

network [16]. CUPEs fuse the advantages of a fully elastic cross-linked polyester network with the high strength of linear PUs so they are soft and elastic with improved mechanical strength, which make them highly suitable for soft tissue-engineering applications. Briefly, the rationale behind CUPE synthesis was: (1) cross-linking confers excellent elasticity of CUPEs; (2) ester bonds confer degradability of CUPEs, all the cross-links of the polymer's network consist of ester bonds to ensure a degradable cross-linked polymer network; (3) introduction of urethane bonds into the polyester chains between ester cross-links enhances the hydrogen bonding within the polyester network, thus significantly improving the mechanical strength of the CUPE network. The first CUPE prepolymers were synthesized in two steps similar to previously published methods as shown in Figure 4.2 [16]. The first step involves the synthesis of a POC (poly(1,8-octanediol citrate)) prepolymer, which is chain-extended by 1,6-hexamethylene diisocyanate (HDI) in the second PU synthesis step. Briefly, a POC prepolymer was first synthesized by reacting a 1:1.1 monomer ratio of citric acid to 1,8-octanediol [35].

The purified POC prepolymer was then lyophilized for the next step of chain extension. In the second step, chain extension was achieved by dissolving pre-POC in 1,4-dioxane (3 wt%) and allowing it to react with HDI using stannous octoate as a catalyst (0.1 wt%). The reaction was terminated on the disappearance of the isocyanate peak located at 2267 cm^{-1}, which was determined by Fourier transform infrared (FT-IR) analysis. HDI was chosen here as a chain extender as it has previously been used in the synthesis of various biodegradable PUs [36–41]. To obtain cross-linked CUPE, the material was postpolymerized in an oven at 80 °C for predetermined durations (0.5, 1, 2, 3 days). Free carboxylic acids and hydroxyl groups available on CUPEs allow for further biofunctionalization.

Subsequently, the physical and biological properties of CUPE both *in vitro* and *in vivo* [16] have been examined. The tensile strength of CUPE was as high as 41.07 ± 6.85 MPa while still maintaining over 200% elongation at break [16]. The initial modulus ranged from 4.14 ± 1.71 to 38.35 ± 4.5 MPa. It is important to note that a simple chemical modification to the previous polyester network, poly(diol citrate) resulted in over a 10-fold increase in mechanical strength [42]. Mechanical properties are known to be involved with different material and process parameters such as the (1) choice of diol, (2) choice of isocyanate and its molar ratio used during synthesis, and (3) postpolymerization conditions. Consequently, these parameters can be used to modulate the material properties of CUPEs, which ultimately affect their biological performance *in vitro* and *in vivo*.

Higher tensile strength of CUPE was obtained by increasing the amount of isocyanate, polymerization time, or temperature used during the synthesis. Various CUPE prepolymers were synthesized using different molar feeding ratios of the pre-POC:HDI (1:0.6, 1:0.9, 1:1.2 M ratio) to evaluate the influence of HDI on CUPEs. The properties of CUPE polymers can also be controlled by varying the diol content. Various diols can be used to control the material performance and create a family of elastomers with their diols varied in their methylene content. Dey et al. conducted a detailed investigation on the development of CUPE polymers synthesized using diols with 4, 6, 8, 10, or 12 methylene units in an attempt to elucidate the influence of the diol component on the physical properties of the resulting material and assessing

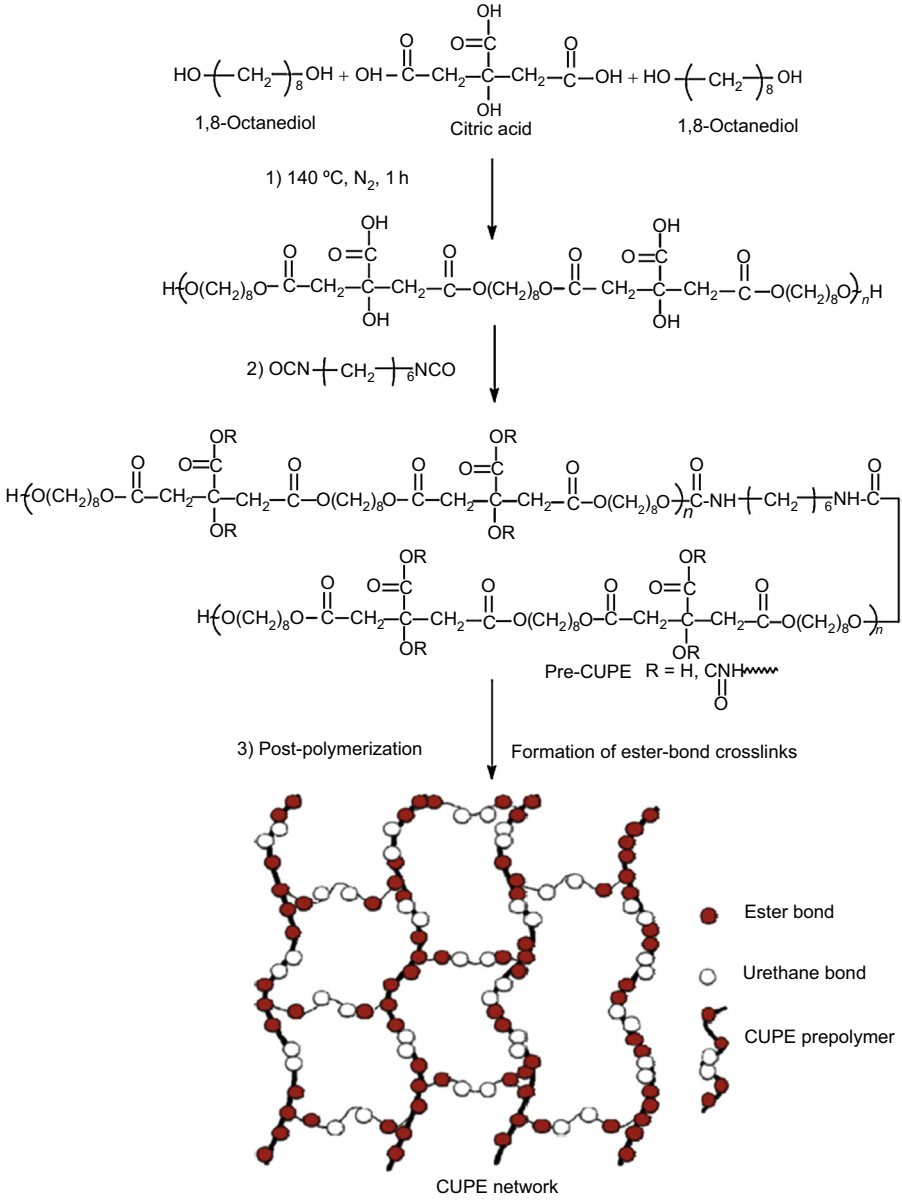

Figure 4.2 Schematic representative of cross-linked urethane-doped polyester (CUPE) synthesis.
Reprinted with permission from Ref. [16]. Copyright © 2008, Elsevier Ltd.

their long-term biological performance *in vivo* [43]. They prepared CUPE polymers using diols with different numbers of carbon atoms, while maintaining the constant ratio 1:1.2 of the soft segment prepolymer/diisocyanate. Along with the diol content, polymerization times were varied from 1 to 4 days. It was found that increasing the diol length leads to a lower cross-linking density, higher hydrophobicity, higher tensile strength and elasticity, and slower polymer degradation.

Initial contact angles of the CUPE prepolymer films were affected by the diol used during the synthesis. Incorporating polyethylene glycol (PEG) into the diol segment of the polymer chain increased the hydrophilicity, thus reducing the initial contact angle. CUPE films made with 1,8-octanediol were more hydrophobic with an average contact angle of 94.20 ± 2.87°. Meanwhile, HDI played a negligible role in affecting the initial contact angles of CUPE films. It is likely due to the fact that the urethane-bonded segment formed a small portion of the polyester chain and did not significantly influence the wettability of the material.

By controlling the temperature and time of postpolymerization, the elastomer's mechanical properties and degradation rate can be tuned to fit a wide range of tissue-engineering applications. An increase in postpolymerization temperature and time resulted in a network with increased mechanical properties due to the increased cross-linking density. The introduction of CUPEs presents new avenues to meet the versatile requirements for tissue engineering and other biomedical applications.

CUPEs demonstrated good *in vitro* and *in vivo* biocompatibility. Hemocompatibility studies indicated that CUPE adhered and activated a lower number of platelets compared to poly(L-lactic acid) (PLLA) [16]. In addition to biocompatibility, CUPEs facilitate processing of the materials into highly porous structures compared to other poly(diol citrates); the higher molecular weights and nonsticky nature of the CUPE prepolymers allow the use of fabrication techniques such as thermally induced phase separation (TIPS) technique and electrospinning. Soft and elastic CUPE three-dimensional porous sheets (150 μm thick) fabricated from a simple TIPS allowed for even seeding, growth, and distribution of 3T3 fibroblasts. Good mechanical properties, processibility, and biocompatibility make CUPE materials well suited for soft tissue-engineering applications.

4.2.1 Photo-cross-linkable citrate-based urethane-doped polyesters

Photo-cross-linkable biomaterials can be of interest in biomedical applications (i.e., as they may allow *in situ* polymerization directly in or on tissues). They may provide advantages including localized drug delivery for site-specific action, ease of application, and a reduction in the dosage amount. A citrate-based photo-cross-linked biodegradable elastomer was developed, poly(octamethylene maleate citrate) (POMC), derived from the previously reported POC material [44]. POMC preserves pendant hydroxyl and carboxylic functionalities even after cross-linking, keeping both available for potential conjugation of biologically active molecules.

POMC films promoted the adhesion and proliferation of human aortic smooth muscle cells and NIH-3T3 fibroblast cell lines and demonstrated minimal inflammatory response when subcutaneously implanted in Sprague–Dawley rats. The success in

designing POMC prompted the development of another novel photo-cross-linkable urethane-doped polyester elastomer (CUPOMC) by reacting POMC prepolymers with HDI followed by thermo- or photopolymerization [25].

The synthesis of CUPOMCs was carried out in the following three steps (Figure 4.3). The monomers, citric acid and 1,8-octanediol, and maleic acid underwent

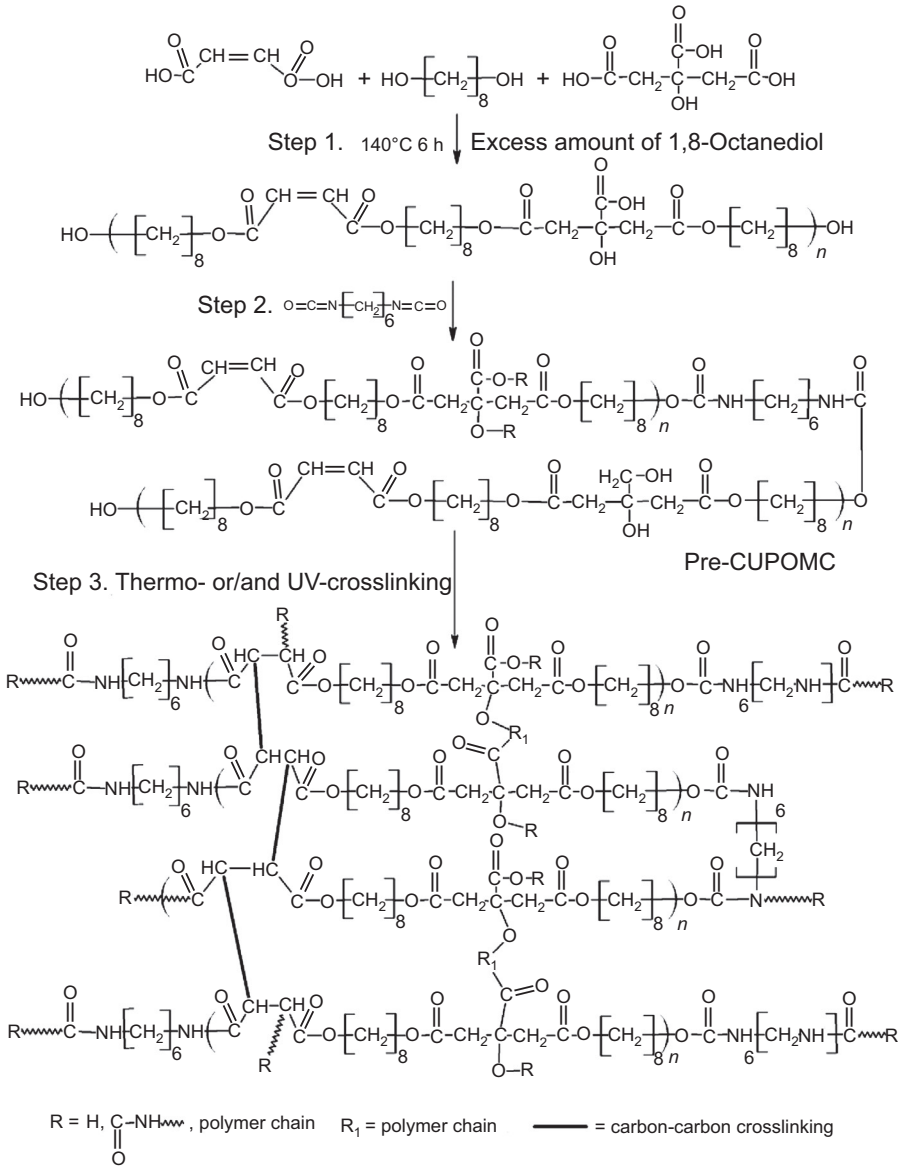

Figure 4.3 Schematic diagram for the synthesis of CUPOMC.
Reprinted with permission from Ref. [25]. Copyright © 2011, ICI Global.

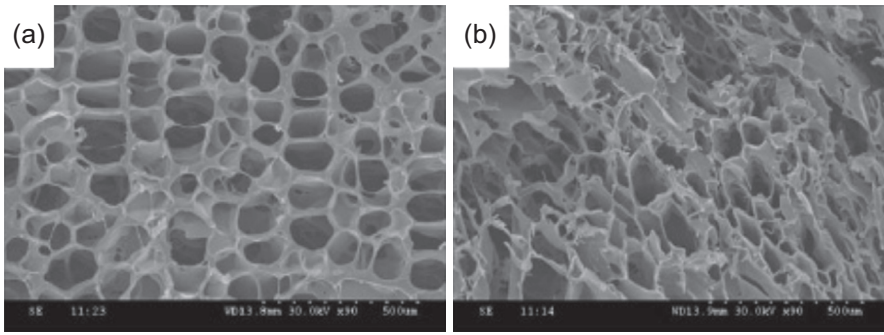

Figure 4.4 SEM images of (a) the surface and (b) cross-section of a CUPOMC-0.2–0.8–1.1–1.0 scaffold thermally cross-linked at 80 °C for 1 day. Reprinted with permission from Ref. [25]. Copyright © 2011, ICI Global.

polycondensation to yield hydroxyl group capped pre-POMC in step 1. In step 2, 1,6-hexamethylene diisocyanate (HDI) was used to extend the pre-POMC chain. In step 3, pre-CUPOMC was thermo- and/or UV-cross-linked to obtain the CUPOMC network. Similar to CUPEs, mechanical properties of the CUPOMCs can be tuned by varying the molar ratios of pre-POMC monomers and the prepolymer:HDI ratios. The mechanical strength and elongation at break of the CUPOMCs range from 0.73 ± 0.12 to 10.91 ± 0.64 MPa and from 72.91 ± 9.09% to 300.41 ± 21.99%, respectively.

The results suggest that doping urethane bonds in photo-cross-linkable POMCs to make CUPOMCs did not compromise the elasticity, thus making CUPOMCs a candidate for soft tissue engineering. CUPOMCs can be cross-linked into a three-dimensional network via either polycondensation or UV polymerization. Using thermal polymerization, a highly interconnected porous CUPOMC structure was built (Figure 4.4). Tensile tests on the pre-CUPOMC scaffolds confirmed the elastic property of the material (Young's modulus, 0.09 ± 0.01 MPa; elongation at break, 192.44 ± 24.76%).

4.2.2 Urethane-doped biodegradable photoluminescent polymers

CABEs have demonstrated excellent biocompatibility *in vivo* animal studies [16–18,43]. Although it is recognized that the scaffold degradation rate should match the rate of new tissue formation [45], biomaterial designs to control the *in vivo* scaffold degradation rate remain empirical due to the lack of *in vivo* quantitative validation. Histological analysis is commonly used for probing such processes, but it is an end-point measurement and requires sacrifice of an animal for each time point [46]. It is imperative to find an *in situ* real-time method to facilitate tracking or monitoring tissue regeneration and scaffold degradation processes without sacrificing animals. This issue has been rarely addressed previously.

To meet this unmet need in regenerative tissue engineering, a breakthrough was recently made in developing soft and elastic biodegradable photoluminescent polymers (BPLPs) with tunable and *in vivo* detectable fluorescence with emission from

blue to near infrared (up to 725 nm) that can function as a noninvasive, real-time imaging probe to monitor the scaffold degradation and tissue infiltration/formation by measuring the fluorescence decay over time *in vivo* [15,47,48]. It is notable that BPLPs' tunable fluorescence emission results by the use of different natural amino acid residues. For example, BPLP-serine (BPLP-Ser) emits strong red fluorescence.

Although BPLPs are attractive materials for tissue engineering and drug delivery, the tensile strength of BPLPs is 6.5 ± 0.8 MPa, which is not sufficient for certain tissue-engineering applications (e.g., vasculature grafts). To address the above challenges, UBPLPs were synthesized [15]. As shown in Figure 4.5(a), BPLPs were first synthesized via condensation polymerization of 1.0:1.1:0.2 monomer ratios of citric acid, 1,8-octanediol, and L-cysteine, respectively. Next, the BPLP prepolymer (3 w/v% in 1,4-dioxane) was chain-extended at 55 °C with HDI to obtain UBPLP using stannous octoate as a catalyst. The reaction was terminated on the disappearance of the isocyanate peak located at 2267 cm^{-1}, determined by FT-IR analysis. The resulting UBPLP was cross-linked in an oven maintained at 80 °C for predetermined periods to obtain cross-linked urethane-doped BPLP or CUBPLP.

Mechanical properties of UBPLPs were manipulated by (1) postpolymerization conditions, (2) feeding ratio of diisocyanates, and (3) choice of amino acids. A dramatic improvement was made by doping with urethane bonds (tensile strength, 49.41 ± 6.17 MPa; elongation at break, 456.60 ± 62.49%) from the previously reported mechanical strength of cross-linked BPLP (tensile strengths, 6.50 ± 0.80 MPa; elongation, 240 ± 36%) [47]. UBPLPs synthesized with different amino acids retained their fluorescent properties. This confirms that the fluorophores of BPLPs remained intact during the synthesis of UBPLPs, although the chain extension of BPLPs caused some loss of fluorescence intensity after urethane bond doping, due to the increased average number of fluorophores per polymer chain. Degradation properties can also be modulated by varying the feeding ratios of diisocyanate to prepolymers and the choice of amino acids.

The potential of using UBPLPs as an organic dye-free theranostic system has been evaluated. Using a nanoprecipitation technique, UBPLP-Ser 1.2 was able to form nanoparticles in PBS (Figure 4.5(b)). Nanoparticles have a spherical shape with an average diameter of 103 nm. The cytocompatibility of UBPLP nanoparticles was also found to be significantly higher than quantum dots at all dilutions and comparable to PLGA nanoparticles at 2, 10, and 50X dilutions. Tubular triphasic scaffolds made of CUBPLP-Cys and CUBPLP-Ser 1.2 were subcutaneously implanted in the back of black mice for *in vivo* fluorescence imaging (Figure 4.5(d)). Fluorescence was detected with a concentration of the UBPLP-Ser 1.2 at 5 mg/mL (Figure 4.5(e)). UBPLPs present new avenues for noninvasive and real-time assays to advance the fields of tissue engineering and drug delivery.

4.2.3 Click chemistry to enhance citrate-based urethane-doped polyesters

Click chemistry represents a rapid, selective, and high-yielding bioorthogonal reaction that is also capable of immobilizing materials on cell surfaces [49,50]. To further expand click chemistry-based elastomers, Guo et al. introduced click chemistry into

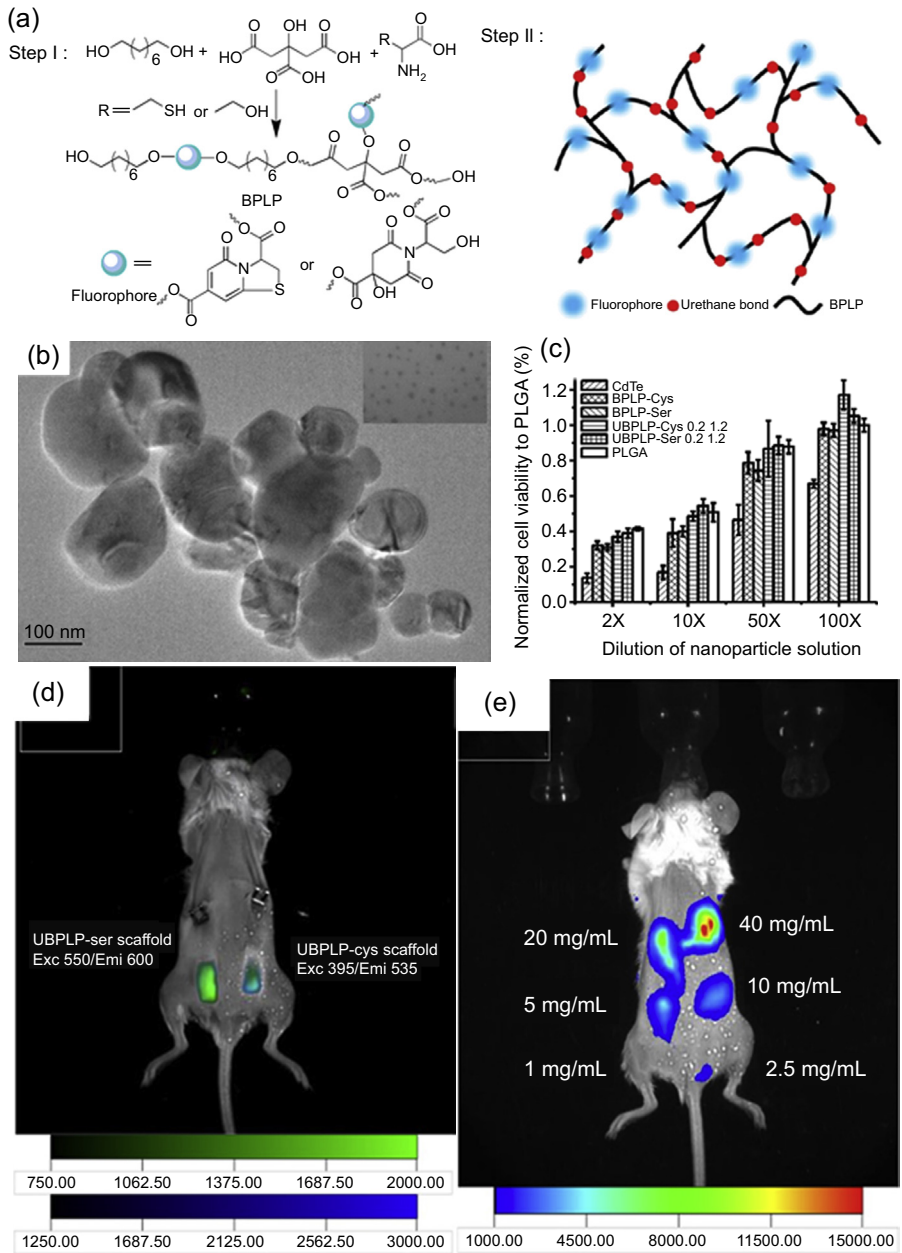

Figure 4.5 (a) Synthesis of UBPLP polymers; (b) TEM images of UBPLP-Ser 1.2 nanoparticles. Inset image was captured under higher magnification showing evenly dispersed nanoparticles; (c) cytotoxicity evaluation of BPLP and UBPLP nanoparticle solutions at different dilutions. PLGA nanoparticles as a control; (d) combined fluorescence images of CUBPLP-Cys and CUBPLP-Ser triphasic scaffolds implanted in a black mouse; (e) *in vivo* fluorescence images of UBPLP-Ser nanoparticles at various concentrations injected subcutaneously in the back of a black mouse.
Reprinted with permission from Ref. [15]. Copyright © 2013, Elsevier Ltd.

CABEs as a strategy to both improve mechanical properties and enable facile surface site-specific bioconjugation [24].

Azide and alkyne groups were introduced to POC prepolymers to synthesize pre-POC-N_3 and pre-POC-Al, respectively (Figure 4.6(a)). Pre-POC-N_3 and pre-POC-Al were cross-linked via a thermal synchronous binary (TSB) cross-linking mechanism to make POC-clicks (Figure 4.6(b)). In the TSB cross-linking, thermal click reaction between azide groups and alkyne groups and esterification between –COOH and –OH groups took place simultaneously to form TSB cross-linked POC-click polymers. The introduction of click chemistry into POCs improved their mechanical properties significantly. For example, the wet mechanical strength of POC-click was stronger than that of CUPE [16].

Cross-linked urethane-doped polyester clickable prepolymer (UPE-click) was synthesized by chain-extending pre-POC-click macromolecules (pre-POC-N_3 and pre-POC-Al) with HDI as a chain extender using the weight ratio 1:0.22 of pre-POC-click:HDI followed by TSB cross-linking. The TSB cross-linked polymer (CUPE-click) showed significantly enhanced mechanical strength compared to normal CUPE. As shown in Figure 4.6(c) and (d), click chemistry also fortified the mechanical strength of CUPE and CBPLP materials after chemical modification with azide and alkyne groups and TSB cross-linking.

The residual azide groups on the surface of click materials can be sites for convenient and efficient bioconjugation. As an example, collagen mimetic peptide p15 was conjugated onto the surface of POC-click-3 films by strain-promoted azide–alkyne cycloaddition (SPAAC) and the viability and proliferation of human umbilical vein endothelial cells (HUVECs) on POC-click-3-p15 films were investigated. Based on the methylthiazolyldiphenyl-tetrazolium bromide (MTT) results, HUVEC proliferation on POC-click-3-p15 films was much faster than that on untreated POC-click-3 films. The HUVEC cell density on POC-click-3 films was nearly twice that of the control POC-click-3 films. The results suggest that the same SPAAC method can be utilized for conjugating CUPE-click materials with such biomolecules for various biomedical applications.

The triazole rings formed by click reactions were recently found to possess antimicrobial properties. The large dipole moment of triazole modulates N-2 and N-3 nitrogen atoms present in the triazole ring as good H-bond acceptors [51]. The hydrogen-bonded triazole acts as a biologically active site that protects the material from bacterial and fungal attacks. The antimicrobial property of triazoles is expected to make CUPE-click more promising for future applications in tissue engineering.

4.2.4 Applications

4.2.4.1 Vascular grafts

To demonstrate the feasibility of using CUPEs as a tissue engineered vascular graft (TENG), Dey et al. developed biphasic CUPE scaffolds prepared as previously reported [33]. The nonporous phase was created by dip coating a glass rod (outer diameter 3 mm) in a 3 w/w% CUPE0.9 in 1,4-dioxane. The prepolymer coated glass rods were air-dried and cross-linked for 12 h in an oven at 80 °C. The porous phase

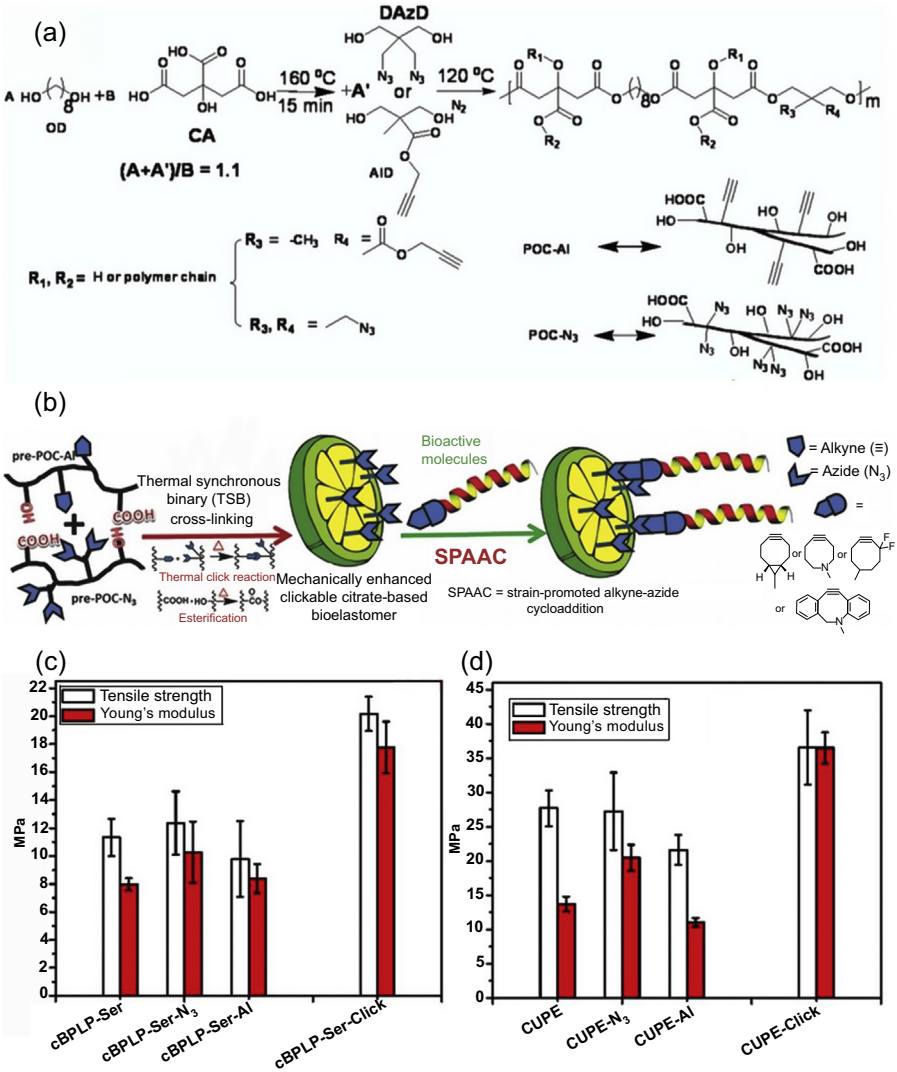

Figure 4.6 (a) Synthesis of functional POC prepolymers: POC-N_3 and POC-Al; (b) cartoon illustration of a new class of citrate-based biodegradable clickable elastomers (CABEs) with greatly improved mechanical strength and easily clickable surface for biofunctionalization; (c) mechanical properties of cBPLP-Ser, cBPLP-Ser-N_3, cBPLP-Ser-Al, and cBPLP-click (cBPLP-Ser-N_3, Al) polymers; (d) mechanical properties of CUPE, CUPE-N_3, CUPE-Al, and CUPE-click (CUPE-N_3, Al) polymers. The polymers used in (c) and (d) were cross-linked at 100 °C for 3 days.

consists of a 3 w/w% solution of CUPE0.9 in 1,4-dioxane mixed with salt particles (150–250 μm) in a 1:9 ratio by weight. The biphasic scaffolds were prepared by (1) casting the slurry into tubular poly(tetrafluorethylene) molds (inner diameter 6 mm), or by (2) inserting the partially polymerized nonporous phase, consisting of the glass rod with the prepolymer coats, concentrically into the mold. Purely porous salt-leached scaffolds were used as controls.

The prepared CUPE material was evaluated for its mechanical properties (tensile strength, burst pressure, and suture retention) and hemocompatibility as a potential blood-contacting vascular graft material. The tensile strength of CUPE biphasic scaffolds (5.02 ± 0.70 MPa) was greater than that of native vessels (1.43 ± 0.60 MPa). CUPE scaffolds showed tunable burst pressure between 1500 and 2600 mm Hg and their suture retention values were 2.45 ± 0.23 N. CUPE scaffolds exhibited mechanical properties similar to those of native veins and arteries. Hemocompatibility of CUPE *in vitro* was evaluated by assessing blood clotting characteristics, leukocyte activation, inflammatory cytokine release, and red blood cell hemolysis. The results showed that CUPE is less prone to thrombosis and inflammation, compared to PLLA. CUPE also behaved similarly to PLLA in terms of leukocyte activation. Suitable mechanical properties combined with a reduced tendency to cause thrombosis make CUPE a promising material for implantation in *in vivo* vascular tissue-engineering applications.

4.2.4.2 Bone tissue engineering applications

In the field of bone tissue engineering, it is highly desirable to design mechanically strong and osteoconductive scaffold materials for orthopedic applications. A class of citrate-based polymer blends (CBPBs) with hydroxyapatite (HA) (CBPBHAs) was developed for bone regeneration [18]. Citrate makes up about 5 wt% of the organic component in bone, and is responsible for regulating and stabilizing apatite nanocrystals. Additionally, a study has shown that citrate has an innate ability to induce the HA formation in simulated body fluid (SBF) [52]. It was hypothesized that the mechanically strong CUPE material increased the strength of the resulting material to meet the load-bearing requirements of orthopedic devices. In addition, the introduction of an optimal percentage of carboxyl-rich POC into the CUPE network helps the polymer/HA interactions to better mimic the inorganic composition of bone.

For these reasons, HA was used in CSPBs to better replicate the natural bone citrate and inorganic mineral content to produce a more biomimetic material and to enhance bone formation (Figure 4.7(a)).

CBPBHA composites were fabricated in three steps. First, a mixture of CUPE and POC prepolymers was prepared by dissolving POC prepolymer in 1,4-dioxane and mixing with various weight ratios of CUPE prepolymer to form a homogeneous CSPB. In the second step, various CBPBs were mixed with 65 wt% HA and stirred in Teflon dishes, which were prewarmed to 50 °C to help solvent evaporation, until a homogeneous mixture was formed. Following solvent evaporation, the mixture was inserted into machined cylindrical metal molds and compressed into rod-shaped samples. In the final step, the resulting cylindrical composites were postpolymerized for

1 day to form a cross-linked CBPBHA-X composite (where X denotes the weight ratio of CUPE in CBPB).

The CBPBHA composite material possesses a compressive strength of 116.23 ± 5.37 MPa, comparable to human cortical bone (100–230 MPa). *In vitro* mineralization of CBPBHA composites was assessed in SBF. CBPBHA exhibited a rapid mineralization in SBF and showed promising osteoconductivity results (Figure 4.7(b)). As shown in Figure 4.7(c) and (d), it also increased osterix gene (obsteoblast-specific transcription factor required for osteoblast differentiation and bone formation) and alkaline phosphatase (an early osteoblast differentiation gene marker for bone formation) gene expression in C2C12 (a typical pluripotent mesenchymal cell line) cells. The role of soluble citrate was also investigated to show that exogenous

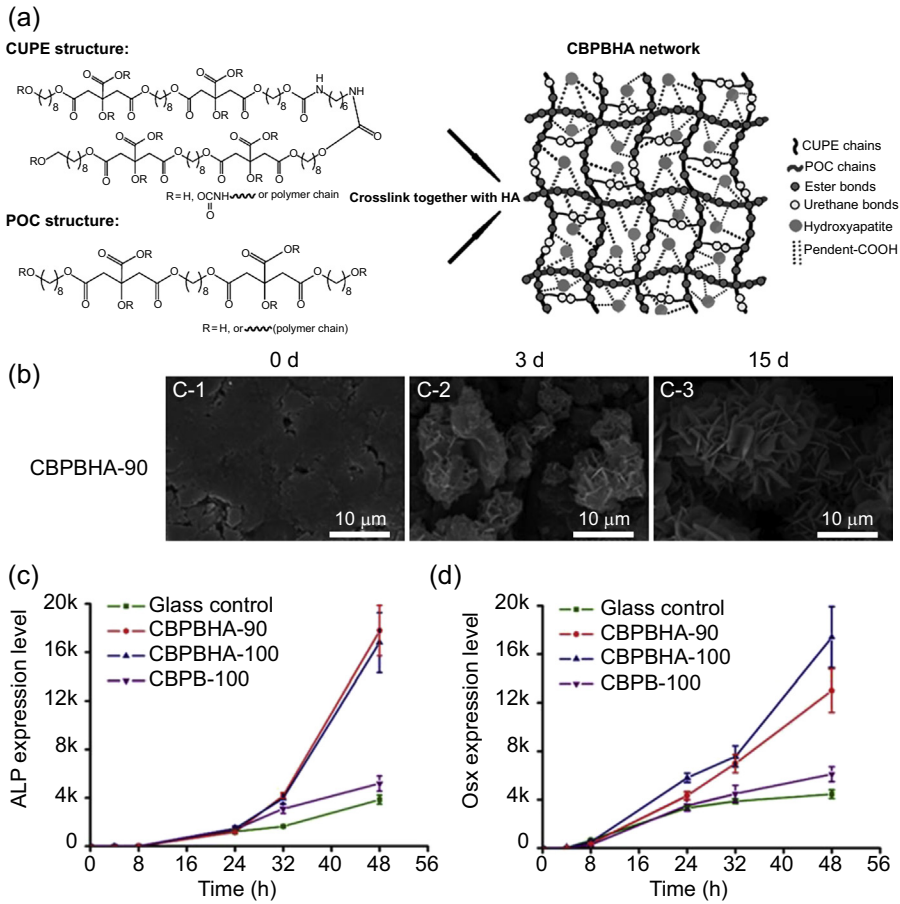

Figure 4.7 (a) Schematics of CBPBHA composites; (b) representative SEM images of CBPBHA-90 composites mineralized in 4X simulated body fluid (SBF) at 0, 3, and 15 days; (c) alkaline phosphatase (ALP); and (d) osterix (Osx) gene expression of C2C12 cells cultured on CBPB and CBPBHA films.
Reprinted with permission from Ref. [18]. Copyright © 2014, Wiley Periodicals, Inc.

citrate supplemented into cell media improved the *in vitro* phenotype progression of MG-63 (a *Homo sapien* bone osteosarcoma) osteoblasts. CBPBHA composites induced minimal fibrous tissue encapsulation and were well integrated with the surrounding tissues after 6 weeks of implantation in a rabbit lateral femoral condyle defect model. This study highlighted the role of citrate molecules that had previously been overlooked.

4.2.4.3 Nerve applications

To demonstrate the applicability of using our soft, elastic, and biodegradable CUPE for nerve tissue engineering, TENGs for peripheral nerve regeneration were designed [17]. Porous, suturable, and multichanneled CUPE TENGs were fabricated using microengineering approaches and particulate leaching (Figure 4.8). Elastic CUPE TENGs showed an ultimate peak stress of 1.38 ± 0.22 MPa and a corresponding elongation at break of 122.76 ± 42.71%, which were comparable to those of native nerve tissue. Our CUPE TENGs were successfully implanted to repair a 1 cm sciatic nerve defect. They showed comparable performance with nerve autografts and outperformed

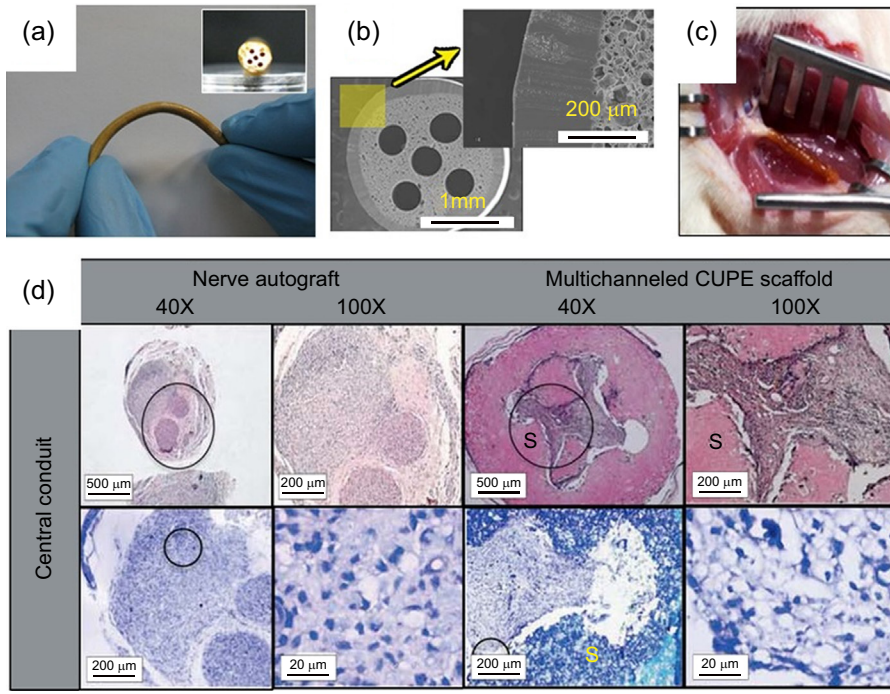

Figure 4.8 (a) Multidirectional bend without kinks to show soft and elastic nature of CUPE materials; (b) scanning electron microscope images of porous and elastic multichannel CUPE TENG with five channels; (c) surgical image of a rat with the implantation of CUPE scaffold; (d) microscopic images of a semithin cross-sections of tissue explants stained with H&E (top row) and toluidine blue (bottom row).
Reprinted with permission from Ref. [17] Copyright ©2014, Wiley Periodicals, Inc.

PCL hollow tubes in terms of fiber population and densities 8 weeks after their implantation. The elastic and biomimetic CUPE TENGs could serve as off-the-shelf nerve conduits for peripheral nerve regeneration.

4.3 Waterborne polyurethane biomaterials

4.3.1 Waterborne polyurethane technology

Traditional solvent-based PUs have long established the standard for high performance systems. However, due to high levels of volatile organic compounds (VOCs) in solvent-based PUs, serious concerns have emerged about environmental and application safety in the use of typical solvent-based PUs [53]. Waterborne PU technology uses water as the primary dispersion solvent. The resultant waterborne PU materials have many advantages: (1) zero or very low levels of VOCs (environmentally friendly), (2) absence of isocyanate residues (nontoxic), and (3) good applicability, versatility, and a wide range of superior properties, such as abrasion resistance, impact strength, and low temperature flexibility. As such, waterborne PUs have rapidly become important materials used in diverse applications [54].

An aqueous waterborne PU dispersion is a binary colloid system in which PU particles range in size from 0.01 to 5.0 μm [55]. The effective method for making PU dispersible in water is to introduce ionic and/or nonionic hydrophilic moieties into its backbone structure. The most important and practical type of waterborne PU is the anionic type. This type of waterborne PU possesses pendant ionized carboxylic acid groups [56]. Anionic waterborne PUs with carboxylic acid groups can be synthesized by a four-step process, which is schematically presented in Figure 4.9.

In the first step, macromonomer diisocyanate is prepared by reacting excess diisocyanate with a long-chain polyol and/or low-molecular-weight glycol. Then, carboxylic acid-containing macromonomer diisocyanate is prepared through the hydrophilization of macromonomer diisocyanate in a second step, where bis-hydroxycarboxylic acid, such as dimethylolpropionic acid (DMPA), is incorporated into the backbone of macromonomer diisocyanate. The next step involves the neutralization of carboxylic acid with tertiary amine. Finally, the anionic PU prepolymer is vigorously sheared and stirred in water with diamine. Chain extension in water causes the residual isocyanate groups to transform into urea linkages resulting in an anionic PU that is stably dispersed in water.

4.3.2 Design and synthesis of waterborne polyurethane biomaterials

Most conventional waterborne PUs derived from petroleum resources are not biorenewable or biodegradable. The most common method to obtain biorenewable and/or biodegradable waterborne PU is to incorporate bio-based and/or biodegradable components into a waterborne PU backbone during polymer synthesis.

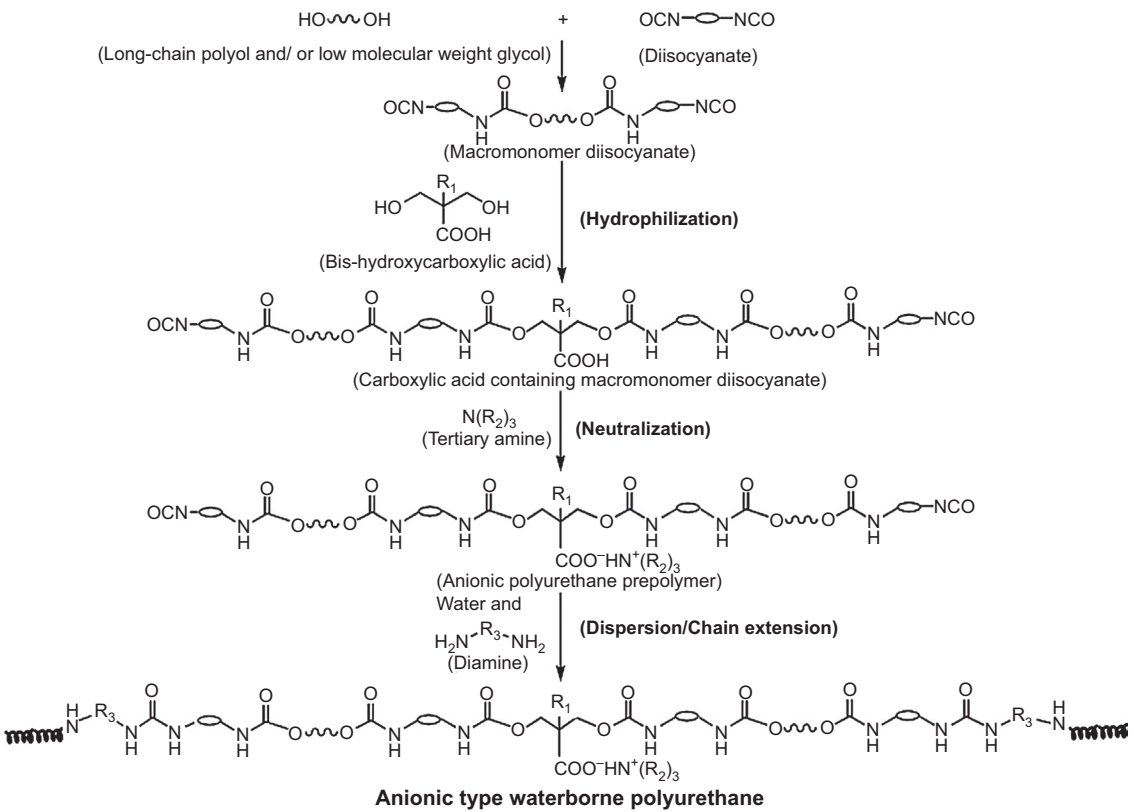

Figure 4.9 Representative schematic synthesis process of carboxylic acid-type anionic waterborne polyurethane.

4.3.2.1 Introduction of bio-based materials into waterborne polyurethanes

Vegetable oils are widely used bio-based renewable resources due to their low toxicity, inherent biodegradability, ready availability, and relatively low price. As such, a great deal of effort has been made to develop waterborne PUs from vegetable oils [57,58]. Castor oil, which has inherent hydroxyl groups in its structure, was the first vegetable oil directly used in the synthesis of waterborne PUs. Other vegetable oils, such as sunflower, corn, palm, rapeseed, soybean, and linseed oils, must be modified into polyols for synthesizing waterborne PUs [59,60].

Vegetable oil-based polyols are long-chain polyols that offer promise in producing biorenewable waterborne PUs. Castor oil-based waterborne PUs show good mechanical properties in terms of both tensile strength (9.3 ± 1.5 MPa) and elongation at break (520 ± 20%). Thus they have been used to modify plasticized starch to prepare novel biodegradable materials with high performance [60]. Waterborne PUs containing 50–60 wt% of biorenewable components have been prepared using methoxylated soybean oil polyols (MSOLs) with hydroxyl functionality ranging from 2.4 to 4.0 by Lu and Larock. Particle sizes of the resultant waterborne PUs range from 12 to 130 nm. An increase in the hydroxyl functionality of the MSOL significantly improved the cross-link density of the waterborne PUs and resulted in biorenewable PUs ranging from elastomeric polymers to ductile plastics [61]. A challenge in the synthesis of vegetable oil-based, environmentally friendly waterborne PU is the high cross-linking of the PU prepolymers caused by high hydroxyl functionality of the vegetable oil-based polyols. Vegetable oils are also susceptible to hydrolytic breakdown due to the three ester bonds in their structure. Vegetable oil-based waterborne PU bonds may degrade when exposed to excessive humidity, releasing amines and carbon dioxide and they are also susceptible to microorganism attack [62].

Chain extenders can also be substituted with bio-based components in the synthesis of waterborne PUs. For example, chitosan, a derivative of abundant naturally occurring polysaccharides that has active amino groups, can be used to chain-extend waterborne PUs in water. Chitosan possesses unique biological properties such as nontoxicity, biocompatibility, anticoagulant properties, and biodegradability. Waterborne PU films synthesized with chitosan as a chain extender exhibited excellent mechanical and anticoagulating properties, as well as antibacterial and antifungal activities [63].

Gelatin from cold fish skin also can be introduced into waterborne PUs by covalent bonding, to reinforce and render biodegradability. Lee et al. chemically modified gelatin with vinyltrimethoxysilane and incorporated the modified gelatin into waterborne PU with terminal hydroxyl ethyl acrylate groups by UV polymerization. The waterborne PU showed excellent mechanical properties and water-resistant properties along with significantly enhanced biodegradability both in trypsin solution and in soil [64].

4.3.2.2 Introduction of biodegradable polyesters into waterborne polyurethanes

To render waterborne PUs biodegradable, researchers have attempted to incorporate biodegradable polymeric materials into the backbones of waterborne PUs. The biodegradable polymeric materials can be long-chain polyols, chain extenders, or

diisocyanates. Among biodegradable long-chain polyols, PCL diols, PLA diols, poly(lactic acid-caprolactone) (PLCL) diols, and PLGA diols are often used for the synthesis of biodegradable waterborne PUs. However, it is reported that satisfactory mechanical properties (e.g., elongation higher than 25%) are not obtainable by merely reacting a single PLA diol as a long-chain polyol component [65]. Biodegradable long-chain polyols and conventional polyether/polyester polyols are often synergistically used in the synthesis of waterborne PUs to adjust the biodegradability and the film-forming properties of waterborne PUs [66].

Recently, a breakthrough on the development of biodegradable photoluminescent prepolymers (BPLPs as described in Figure 4.10(a)) with superior inherent photoluminescence and photostability has been made [47]. BPLP–cysteine, a hydroxyl-terminated aliphatic polyol, is fully biodegradable and biocompatible. It can be used as a long-chain polyol to produce biodegradable BPLP-based waterborne polyurethane (BPLP-WPU as in Figure 4.10(b)). The emission spectra of the obtained BPLP-WPU excited at different wavelengths of 335, 365, 380, 425, 455, and 485 nm are shown in Figure 4.10(c), which demonstrates the versatile and strong photoluminescence of BPLP-WPU. Nanomicelles of BPLP-WPU are distributed evenly in water with the average size of 20–30 nm as shown in Figure 4.10(d). The resulting photoluminescent waterborne polyurethane can be used as noninvasive bioimaging elastomeric films and porous scaffolds in tissue engineering, as well as amphiphilic fluorescent nanomicelles for theranostic drug delivery.

Many amino acid derivatives can be used as chain extenders for the synthesis of PUs in bulk or in organic solvents. Among natural amino acids, water soluble L-lysine, which contains two active amino groups and one carboxyl group, is a good extender candidate for waterborne PUs [36]. Low-molecular-weight L-lysine can be incorporated as a biodegradable component to help the degradation of high-molecular-weight waterborne PUs. Waterborne PUs made from isophorone diisocyanate (IPDI), DMPA, and PCL were prepared and chain-extended in water using L-lysine by Chen et al. [67]. Results demonstrated that the prepared waterborne PU films exhibited excellent mechanical properties, good anticoagulating characteristics, desirable water swellability, and hydrolysis properties. Jiang et al. have successfully prepared nontoxic waterborne biodegradable PU by using IPDI, 1,4-butandiol (BDO), and L-lysine as hard segments, and PEG and PCL as soft segments with a molar feed ratio of IPDI/PCL/PEG/BDO/L-lysine = 3/0.75/0.25/0.85/0.85. Three-dimensional interconnected porous scaffolds fabricated with the waterborne PU showed better adhesion and proliferation of endothelial cells and can be utilized in soft tissue engineering [68].

To achieve biodegradability and nontoxicity, there has been intensive research on replacing common isocyanates with amino acid diisocyanates in the development of waterborne PUs [69]. L-Lysine diisocyanate and L-lysine ethyl ester diisocyanate have gained attention because lysine is nontoxic, less prone to inflammation, and easy to connect with bioactive molecules. Lysine ethyl ester diisocyanate was prepared with an improved method that avoids the use of gaseous phosgene, elevated temperature, and strongly acidic conditions as described by Nowick et al. [70]. L-Lysine diisocyanate and PCL diol were used as main components to prepare nontoxic and

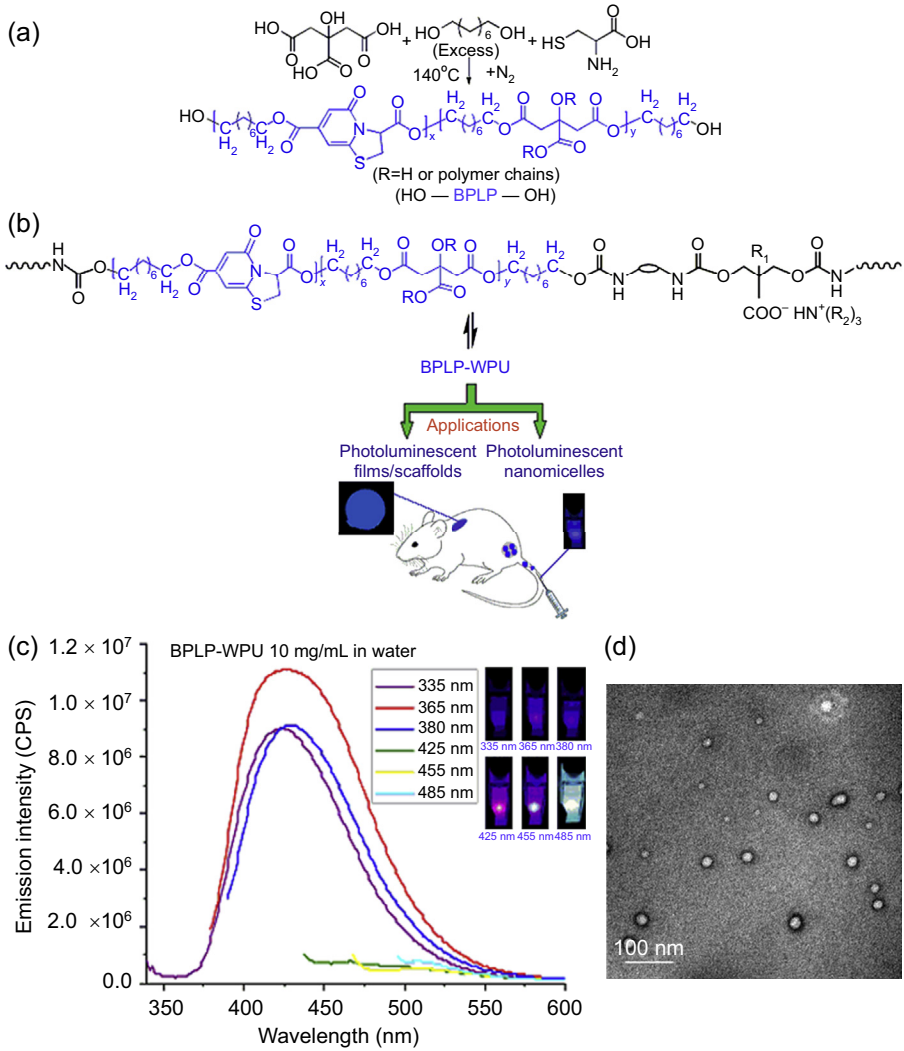

Figure 4.10 Synthesis and properties of BPLP and biodegradable BPLP-based biodegradable waterborne polyurethane (BPLP-WPU). (a) Synthesis of BPLP. (b) Structure and application of BPLP-WPU. (c) Emission spectra of BPLP-WPU excited at wavelengths of 335, 365, 380, 425, 455, and 485 nm. (d) Particle size distribution of BPLP-WPU dispersed in water.

biodegradable waterborne PUs. The materials showed tensile strength up to 46.5 MPa and 42% hydrolytic degradation after 80 days [71].

In conclusion, waterborne PU biomaterials have the advantages of low viscosity at high molecular weight, nontoxicity, and good applicability over conventional PU biomaterials. Driven by the continuous reduction in costs and the control of VOC emissions, the development of waterborne PUs as biomaterials has significantly increased.

4.3.3 Applications of waterborne polyurethane biomaterials

Much effort has been made to improve the biocompatibility and biodegradability of waterborne PUs, thus making them suitable for a wide range of medical applications. For example, waterborne PUs have great potential in the field of tissue engineering. Xu et al. studied the response of bladder smooth muscle cells (BSMCs) on biodegradable waterborne PUs. BSMCs showed better attachment, proliferation, and α-actin distribution behavior on waterborne PU membranes than on PLGA membranes [72]. Waterborne PUs have also been developed as nanoparticles for drug delivery. Biodegradable waterborne PU nanocomposites containing clay nanoparticles have been used to deliver dexamethasone acetate for the treatment of ocular diseases [73]. Researchers also prepared bioactive waterborne PU nanomicelles for breast cancer treatment. The nanomicelles successfully caused apoptosis of human breast cancer MCF-7 cells [74]. In addition, waterborne PUs could be used in wound healing [75] and antibacterial materials [76]. Hsu et al. have developed biodegradable elastomeric nanoparticles that could self-assemble into hydrogels, microspheres, nanofibers, sponges, and films, all of which have great value in biomedical applications [77].

4.4 Functionalization of polyurethanes and novel applications of urethane/urea chemistry

The properties of biodegradable PUs (e.g., hydrophobicity/hydrophilicity, biocompatibility, biodegradability, and conjugation with proteins, drugs, or biological agents) can be tailored by the introduction of different functional groups for various biomedical applications. Urethane/urea reactions (isocyanate-based and nonisocyanate-based reactions) can be used to impart specific functionalities to polymers or biomaterials. The reactions between polyisocyanates and polymers/proteins that contain abundant hydroxyl or amino groups have also been applied as a room temperature cross-linking method to fabricate tissue-engineering scaffolds or 3D printed patterns. In the following sections, applications of urethane/urea chemistry in biomaterials will be discussed in detail.

4.4.1 Functionalization of polyurethanes

4.4.1.1 An overview of functionalization methods for polyurethanes

The introduction of functionalities into PUs can be made before, during, or after polymerization. Traditional linear PUs are made by the polyaddition reactions between diols and diisocyanates. One route to obtain functional PUs is to use monofunctional compounds (alcohol or isocyanate, b1, b2, and c1 in Figure 4.11(a)), but they lead to a limited number of terminal functionalities and reduced molecular weight [78]. Although there are some examples of introducing specific functionalities using functional diisocyanates, such as diisocyanates derived from L-lysine (e.g., L-lysine methyl

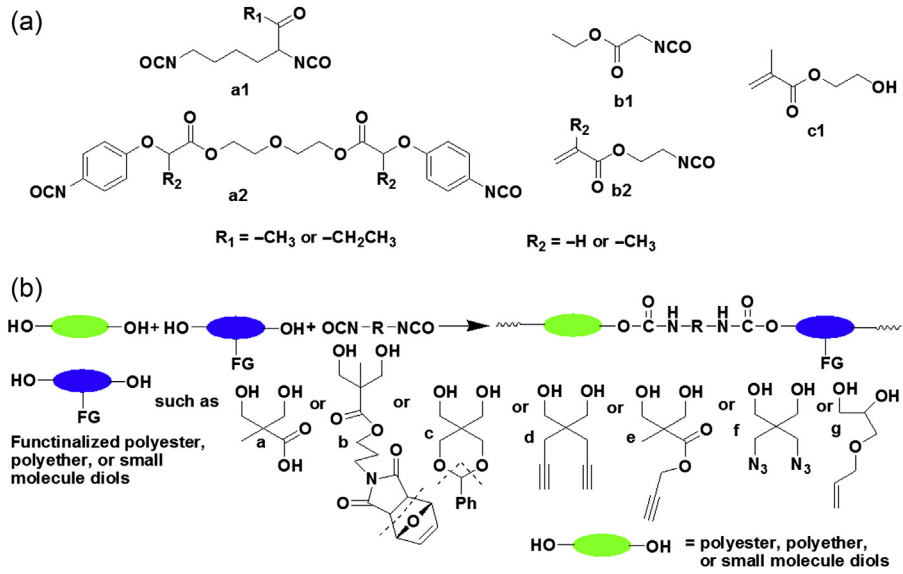

Figure 4.11 (a) Examples of functional diisocyanates (a1, a2), functional monoisocyanates (b1, b2), and monofunctional alcohol (c1) used for polyurethane functionalization before, concurrent, or post polymerization; (b) introduction of functional groups into polyurethane through functional diols.

ester diisocyanate [LDI], a1 in Figure 4.11(a)) [79], or biodegradable diisocyanates (a2 in Figure 4.11(a)) [10], the sources of functional diisocyanates are limited and their synthesis processes are inconvenient. By controlling the feed ratios of diols and diisocyanates, desired terminated groups, such as isocyanates, can be obtained and can be used for functionalizing PUs through postmodification [78]. Side ester groups introduced by either LDI or ethyl isocyanatoacetate (b1 in Figure 4.11(a)) [79,80] can be further modified through aminolysis by amino group-containing compounds, such as *N*,*N*-dimethylenediamine [79] or poly(ethyleneimine) [80], to obtain cationic polymers. The cationic polymers can then be used for gene delivery. All of the functionalization methods noted above are limited by a complex reaction process or limited raw material sources. In contrast, the incorporation of functionalities into PUs through the addition of functional diols is convenient and straightforward (Figure 4.11(b)).

4.4.1.2 *Introduction of functional groups into polyurethanes using functional diols*

The introduction of hydrophilic carboxyl groups by the addition of 2,2-bis(hydroxymethyl) propionic acid (DMPA, a in Figure 4.11(b)) followed by salt formation of carboxyl groups with amines, such as triethylamine, is frequently applied as a functionalization method, to obtain waterborne PUs [81]. Du Prez and colleagues developed maleimide-functionalized PUs by adding furan-protected maleimide-containing diols (FMD, b in Figure 4.11(b)) followed by simple heating at 100 °C under

vacuum overnight. Maleimide-functionalized PUs can be further used to conduct thiol–maleimide reactions without the use of UV light or any toxic catalyst [82]. Biodegradable PUs with pendant hydroxyl groups were synthesized by Yang et al. by the introduction of benzal pentaerythritol (BPO, c in Figure 4.11(b)) into PUs followed by de-protection [83]. The pendant hydroxyl groups were used for reaction with 4-azidobenzoic acid to obtain PUs functionalized with photoactive phenyl azide groups. The PUs had the ability to immobilize proteins under UV light [84]. Clickable functional groups can also be directly introduced into PUs by the addition of click functional diols, such as 2,2-bis(prop-2-yl) propane-1,3-diol (DPPD, d in Figure 4.11(b)) [85–87], propargyl 2,2-bis(hydroxymethyl)propionate (e in Figure 4.11(b)), 2,2-bis(azidomethyl)propane-1,3-diol (f in Figure 4.11 (b)), and click functionality containing macromolecular diols [87]. Pendant vinyl groups can be obtained by the addition of double bond-containing diols such as 3-allyloxy-1,2-propanediol [87]. By adding dihydroxy-terminated poly(2-(dimethylamino)-ethyl methacrylate) ($PDEM(OH)_2$), Zhang et al. developed protein-resistant PUs containing zwitterionic side chains [88].

Overall, the incorporation of functionalities through the addition of functional diols is convenient and straightforward, especially when the desired functional groups have no obvious side reactions with isocyanate groups such as carboxyl, azide, alkyne, and vinyl groups [80–88]. The introduction of functional groups that can react with isocyanate groups, such as hydroxyl or amino groups, requires these functional groups be protected before PU formation and de-protected afterward [83].

4.4.2 Urethane/urea chemistry as a functionalization method

4.4.2.1 Introduction of functional groups into OH- or NH_2-containing polymers using functionalized monoisocyanates

As noted above, the addition of monofunctional isocyanates/alcohols in the polyadditon process of diols and diisocyanates is a way of obtaining terminally functionalized PUs [78]. The urethane/urea reactions between monofunctional isocyanates and hydroxyl or amino groups on polymers can also serve as a functionalization route for OH- or NH_2-containing polymers (Figure 4.12(a)). Among monofunctional isocyanates, ester group-containing monoisocyanate, which can be further modified by aminolysis post polymerization [80], and vinyl group functional isocyanates, such as 2-isocyanatoethyl (meth)acrylate and allyl isocyanate, are the most commonly used (Figure 4.12(a)). 2-Isocyanatoethyl methacrylate (IEM) has been used to react with the terminal OH– groups of star shaped PCL [89] or amino groups of silk protein [90,91] to obtain photo/free radical cross-linkable PCL or silk protein for gelation, precise patterning, dynamic topographical control, or microfabrication. IEM has also been used to introduce vinyl groups onto cellulose [92], or perfluoropolyether polyol macromonomer, creating a polymer with low surface energy [93]. Through the modification of 1,1,1-tri-[4-(methacryloxyethyl-aminocarbonyloxy)-phenyl]ethane with IEM, urethane-based trimethacrylate monomer has been also developed and used as a dentin adhesive [94].

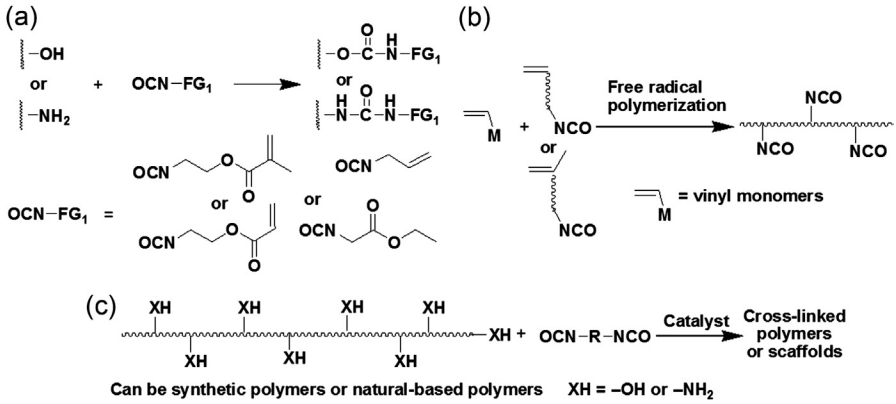

Figure 4.12 Application of urethane/urea chemistry in polymer functionalization and cross-linking: (a) introduction of functional groups using functionalized monoisocyanates; (b) introduction of isocyanates as functional groups; (c) application of urethane/urea reaction as a cross-linking method.

4.4.2.2 Introduction of isocyanates as functional groups

Vinyl group-functional isocyanates, such as IEM, can be polymerized through free radical polymerization with other vinyl monomers to give polymers with pendant isocyanate groups (Figure 4.12(b)). Polymers with pendant isocyanate groups have been used as tissue adhesives [95]. The pendant isocyanate groups can also be used to react with thiol/amino group-containing compounds for polymer surface functionalization [96].

4.4.2.3 Urethane/urea chemistry as a cross-linking method

As noted above, monofunctional isocyanates can be used to introduce functionalities onto OH- or NH_2-containing polymers. Similarly, compounds with two or more isocyanate groups can be used as cross-linkers for OH- or NH_2-containing polymers (Figure 4.12(c)). The application of PUs with preserved isocyanates as tissue adhesives is based on the cross-linking reaction between isocyanate and amino groups that are from tissue proteins or produced by water hydrolysis of isocyanate groups [19,20]. By employing the urethane reaction between 1,6-hexamethylene diisocyanate (HDI) and the pendant hydroxyl groups on PGS, Pereira et al. developed a highly tunable biocompatible biodegradable elastomer, poly(glycerol sebacate urethane), which can be cross-linked under melt conditions through solvent-based or solvent-free methods [97]. Similarly, by simply employing LDI as a cross-linker for gelatin, Neffe et al. were able to create open porous three-dimensional architecture hydrogels that can induce bone regeneration in just one step [98]. By reacting 1,2,3-triazole-rich hyperbranched polyether polyols with diisocyanate, moist-curable antimicrobial hyperbranched PU–urea coatings were developed by Kantheti et al. [51]. A DNA–lipid organogel cross-linked by IPDI has been developed by Yao et al. and reported to possess shape-memory properties [99].

4.4.2.4 *Nonisocyanate-based urethane reactions and the application of urethane-forming hydroxyl–amino coupling reactions*

In addition to the most intensively researched urethane reactions between isocyanate and hydroxyl groups (Figure 4.1(a)) that form urethane bonds, there are also nonisocyanate urethane reactions, such as the reactions between cyclic carbonate or activated carbonate/carbamate/chloroformate derivative groups and amine groups (Figure 4.1(b) and (c)) [4–6].

The ring-opening polymerization of cyclic carbonates with polyfunctional amines forms poly(hydroxyl-urethanes). The most traditional syntheses of cyclic carbonates use phosgene chemistry, which involves environmental hazard issues [100].

Another approach with cyclic carbonates is the transesterification of diols with dicarbonates [101]. The development of a green chemistry approach has eliminated the use of phosgene in cyclic carbonate syntheses. Among them, catalytic conversion of epoxides with carbon dioxide into cyclic carbonates is the most promising (Figure 4.13(a)) [4,102–104]. This chemistry opens the development of isocyanate-free bio-based green PUs from natural-based compounds, such as vegetable oils (including castor oil) [103–105]. Poly(hydroxyl-urethanes), as one type of nonisocyanate polyurethane, contain side hydroxyl groups that bring hydrophilicity and can be used as functionalities (Figure 4.13(b)). Furthermore, they do not have labile allophanate

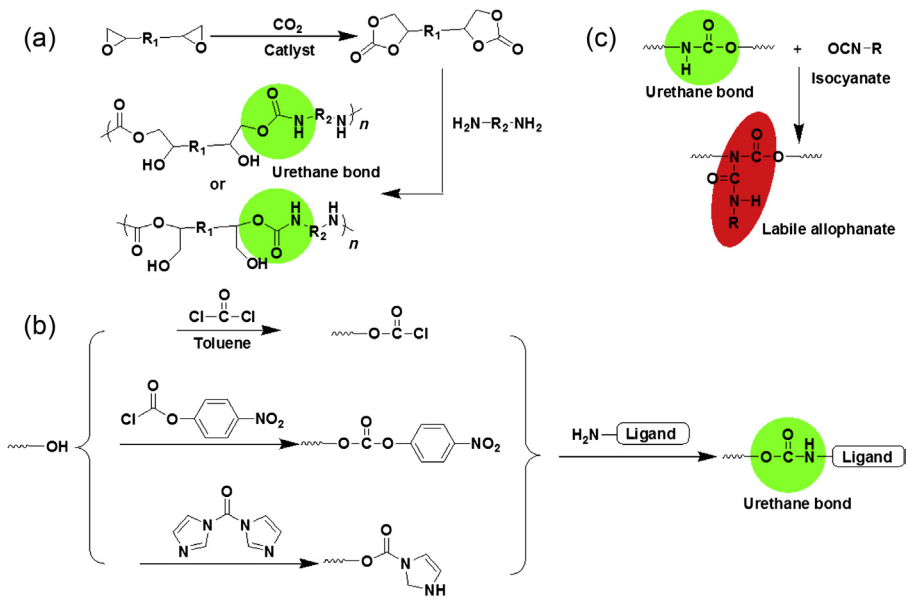

Figure 4.13 Nonisocyanate urethane reactions: (a) example of the formation of cyclic carbonate and the reaction with polyamines servers as a new polyurethane synthesis route; (b) representative coupling reactions between hydroxyl group and amino group that form a urethane bond; (c) the reaction between urethane bond and isocyanate group results in labile allophanate groups, which make traditional isocyanate-based polyurethanes less chemical resistant.

groups, side reaction products between urethane and isocyanate that make conventional isocyanate-based PU less chemical resistant (Figure 4.13(c)) [4].

Activated carbonate, carbamate, or chloroformate derivative groups, including (imidazolylcarbony1)oxyl (IC) derivative, carbonate derivatives of 2,4,5-trichlorophenyl and *p*-nitrophenyl, succinimidyl carbonate, and chloroformate derivative (Figure 4.1(c)), can react with amino groups under mild conditions to form urethane bonds that are very stable under physiological conditions and show little breakdown in various buffers of pH 2–11 [6]. Thus these reactions have been extensively used as the coupling reactions between hydroxyl and amino groups (Figure 4.13(c)) and applied in protein-selective modification on amino groups, drug or protein bioconjugation, and polymer modification [5–9,104]. An example of the application of urethane bond forming hydroxyl–amino group coupling reactions in drug conjugation is described below. By activating the side hydroxyl groups on biodegradable amphiphatic mPEG-b-P(LA-co-DHP) polymer with 4-nitrophenyl chloroformate (NPC), Hu et al. conjugated the amino group containing the anticancer drug doxorubicin (Dox) onto the polymer by a direct hydroxyl–amino coupling reaction with the formation of a stable urethane bond. In the same work, the acid-liable hydrazine linkage between the polymer and the Dox was also formed by reacting the NPC-activated polymer with hydrazine monohydrate followed by the reaction between the hydrazine and the ketone group on Dox [9]. The drug release profiles of these two different polymer–drug conjugate micelles were investigated [9]. Urethane bonds formed from hydroxyl–amino group coupling reactions have also been widely used in polymer modification or functionalization. By the reaction between NPC-modified PEG diols and tyramine, followed by the grafting of monotyramine-terminated NPC-activated PEG diol onto gelatin or chitosan, Park et al. [7] and Tran et al. [8] synthesized tyramine-modified gelatin or chitosan. They could be cross-linked enzymatically into bioadhesive hydrogels and used for tissue regeneration or wound healing. By modifying monohydroxyl PCL with carbonyldiimidazole, Yu el al. synthesized IC terminal PCL. It was grafted onto chitosan and formed into an amphiphilic biodegradable polymer that can be used to form micelles [5]. By activating terminal hydroxyl groups with phosgene, Wang et al. synthesized a chloroformate terminated PEO–PPO–PEO block copolymer and reacted it with propargylamine to obtain alkyne group-functionalized PEO–PPO–PEO block copolymer [106].

4.5 Conclusions and outlook

Urethane/urea chemistry has evolved and transformed to offer convenient and effective tools for the modification of biomaterials, providing them with desirable properties for biomedical applications. The efforts described above have produced an array of multifunctional urethane/urea chemistry-based biomaterials to meet the specific requirements of each application. A collection of citric acid-based PUs has been developed with tunable mechanical, degradation, photoluminescent, and biomedical properties. The CABE platform technology enables easy modulation of their unique properties by simply altering the ratios of diols, prepolymers, and other additive(s) and

the polymerization conditions. With this expandable list of CABEs, the development of more robust, elastic, soft, and biocompatible materials for biomedical applications is possible. Additionally, novel urethane/urea chemistry with isocyanate-based and nonisocyanate-based approaches was discussed in this chapter to provide insights on their potential for designing novel biomaterials. The versatility of urethane/urea chemistry in modern biomaterial designs that have been described has an impact on a broad range of applications, especially in the field of biomedical engineering.

Acknowledgments

This work was supported in part by the National Institutes of Health (NIH) Awards (NIBIB EB012575, NCI CA182670, NHLBI HL118498), and the National Science Foundation (NSF) Awards (DMR1313553, CMMI 1266116).

References

[1] Q.Z. Chen, S.L. Liang, G.A. Thouas, Elastomeric biomaterials for tissue engineering, Prog. Polym. Sci. 38 (March–April 2013) 584–671.
[2] H.W. Engels, H.G. Pirkl, R. Albers, R.W. Albach, J. Krause, A. Hoffmann, et al., Polyurethanes: versatile materials and sustainable problem solvers for today's challenges, Angew. Chem. Int. Ed. 52 (September 2, 2013) 9422–9441.
[3] Q.Y. Liu, L. Jiang, R. Shi, L.Q. Zhang, Synthesis, preparation, in vitro degradation, and application of novel degradable bioelastomers – a review, Prog. Polym. Sci. 37 (May 2012) 715–765.
[4] M. Fleischer, H. Blattmann, R. Mulhaupt, Glycerol-, pentaerythritol- and trimethylolpropane-based polyurethanes and their cellulose carbonate composites prepared via the non-isocyanate route with catalytic carbon dioxide fixation, Green Chem. 15 (2013) 934–942.
[5] H.J. Yu, W.S. Wang, X.S. Chen, C. Deng, X.B. Jing, Synthesis and characterization of the biodegradable polycaprolactone-graft-chitosan amphiphilic copolymers, Biopolymers 83 (October 15, 2006) 233–242.
[6] S. Zalipsky, Functionalized poly(ethylene glycol) for preparation of biologically relevant conjugates, Bioconjug. Chem. 6 (March–April 1995) 150–165.
[7] K.M. Park, K.S. Ko, Y.K. Joung, H. Shin, K.D. Park, In situ cross-linkable gelatin-poly(ethylene glycol)-tyramine hydrogel via enzyme-mediated reaction for tissue regenerative medicine, J. Mater. Chem. 21 (2011) 13180–13187.
[8] N.Q. Tran, Y.K. Joung, E. Lih, K.D. Park, In situ forming and rutin-releasing chitosan hydrogels as injectable dressings for dermal wound healing, Biomacromolecules 12 (August 2011) 2872–2880.
[9] X.L. Hu, S. Liu, Y.B. Huang, X.S. Chen, X.B. Jing, Biodegradable block copolymer-doxorubicin conjugates via different linkages: preparation, characterization, and in vitro evaluation, Biomacromolecules 11 (August 2010) 2094–2102.
[10] R.S. Bezwada, S.P. Nukavarapu, D.L. Dorcemus, N. Srivasthava, R.J. Armentano, Novel absorbable polyurethane biomaterials and scaffolds for tissue engineering, MRS Proc. 1621 (2014) 93–99.

[11] P. Alves, P. Ferreira, M.H. Gil, Biomedical Polyurethane-Based Materials, in: Polyurethane: Properties, Structure and Applications, Nova Publishers, New York, 2012. ISBN: 978-1-61942-453-1.
[12] R.J. Zdrahala, I.J. Zdrahala, Biomedical applications of polyurethanes: a review of past promises, present realities, and a vibrant future, J. Biomater. Appl. 14 (July 1999) 67–90.
[13] J. Dey, H. Xu, K.T. Nguyen, J.A. Yang, Crosslinked urethane doped polyester biphasic scaffolds: potential for in vivo vascular tissue engineering, J. Biomed. Mater. Res. Part A 95A (November 2010) 361–370.
[14] J.S. Guo, D.Y. Nguyen, R.T. Tran, Z.W. Xie, X.C. Bai, J. Yang, Design strategies and applications of citrate-based biodegradable elastomeric polymers, in: Natural and Synthetic Biomedical Polymers, 2014, pp. 259–285.
[15] Y. Zhang, R.T. Tran, I.S. Qattan, Y.T. Tsai, L.P. Tang, C. Liu, et al., Fluorescence imaging enabled urethane-doped citrate-based biodegradable elastomers, Biomaterials 34 (May 2013) 4048–4056.
[16] J. Dey, H. Xu, J.H. Shen, P. Thevenot, S.R. Gondi, K.T. Nguyen, et al., Development of biodegradable crosslinked urethane-doped polyester elastomers, Biomaterials 29 (December 2008) 4637–4649.
[17] R.T. Tran, W.M. Choy, H. Cao, I. Qattan, J.C. Chiao, W.Y. Ip, et al., Fabrication and characterization of biomimetic multichanneled crosslinked-urethane-doped polyester tissue engineered nerve guides, J. Biomed. Mater. Res. A 102 (August 2014) 2793–2804.
[18] R.T. Tran, L. Wang, C. Zhang, M.J. Huang, W.J. Tang, C. Zhang, et al., Synthesis and characterization of biomimetic citrate-based biodegradable composites, J. Biomed. Mater. Res. Part A 102 (August 2014) 2521–2532.
[19] P. Ferreira, R. Pereira, J.F.J. Coelho, A.F.M. Silva, M.H. Gil, Modification of the biopolymer castor oil with free isocyanate groups to be applied as bioadhesive, Int. J. Biol. Macromol. 40 (January 30, 2007) 144–152.
[20] M. Mehdizadeh, J. Yang, Design strategies and applications of tissue bioadhesives, Macromol. Biosci. 13 (March 2013) 271–288.
[21] P. Ping, W.S. Wang, X.S. Chen, X.B. Jing, Poly(ε-caprolactone) polyurethane and its shape-memory property, Biomacromolecules 6 (March–April 2005) 587–592.
[22] W.S. Wang, P. Ping, X.S. Chen, X.B. Jing, Polylactide-based polyurethane and its shape-memory behavior, Eur. Polym. J. 42 (June 2006) 1240–1249.
[23] W.S. Wang, P. Ping, H.J. Yu, X.S. Chen, X.B. Jing, Synthesis and characterization of a novel biodegradable, thermoplastic polyurethane elastomer, J. Polym. Sci. A Polym. Chem. 44 (October 1, 2006) 5505–5512.
[24] J. Guo, Z. Xie, R.T. Tran, D. Xie, D. Jin, X. Bai, et al., Click chemistry plays a dual role in biodegradable polymer design, Adv. Mater. 26 (March 26, 2014) 1906–1911.
[25] Y. Zhang, R.T. Tran, D. Gyawali, J. Yang, Development of photocrosslinkable urethane-doped polyester elastomers for soft tissue engineering, Int. J. Biomater. Res. Eng. 1 (January 2011) 18–31.
[26] J. Yang, A.R. Webb, G.A. Ameer, Novel citric acid-based biodegradable elastomers for tissue engineering, Adv. Mater. 16 (6) (2004) 511–516.
[27] D. Motlagh, J. Yang, K.Y. Lui, A.R. Webb, G.A. Ameer, Hernocompatibility evaluation of poly(glycerol-sebacate) in vitro for vascular tissue engineering, Biomaterials 27 (August 2006) 4315–4324.
[28] J. Yang, D. Motlagh, A.R. Webb, G.A. Ameer, Novel biphasic elastomeric scaffold for small-diameter blood vessel tissue engineering, Tissue Eng. 11 (11–12) (2005) 1876–1886.
[29] R.T. Tran, Y. Zhang, D. Gyawali, J. Yang, Recent developments on citric acid derived biodegradable elastomers, Recent Pat. Biomed. Eng. 2 (2009) 216–227.

[30] M. Schappacher, T. Fabre, A.F. Mingotaud, A. Soum, Study of a (trimethylenecarbonate-co-ε-caprolactone) polymer part 1: preparation of a new nerve guide through controlled random copolymerization using rare earth catalysts, Biomaterials 22 (November 2001) 2849–2855.
[31] A.P. Pego, C.L. Vleggeert-Lankamp, M. Deenen, E.A. Lakke, D.W. Grijpma, A.A. Poot, et al., Adhesion and growth of human Schwann cells on trimethylene carbonate (co)polymers, J. Biomed. Mater. Res. A 67 (December 1, 2003) 876–885.
[32] C.A. Sundback, J.Y. Shyu, Y.D. Wang, W.C. Faquin, R.S. Langer, J.P. Vacanti, et al., Biocompatibility analysis of poly(glycerol sebacate) as a nerve guide material, Biomaterials 26 (September 2005) 5454–5464.
[33] J. Yang, D. Motlagh, A.R. Webb, G.A. Ameer, Novel biphasic elastomeric scaffold for small-diameter blood vessel tissue engineering, Tissue Eng. 11 (November–December 2005) 1876–1886.
[34] F.R. Noyes, E.S. Grood, The strength of the anterior cruciate ligament in humans and Rhesus monkeys, J. Bone Joint Surg. Am. 58 (December 1976) 1074–1082.
[35] J. Yang, A.R. Webb, S.J. Pickerill, G. Hageman, G.A. Ameer, Synthesis and evaluation of poly(diol citrate) biodegradable elastomers, Biomaterials 27 (March 2006) 1889–1898.
[36] G.A. Skarja, K.A. Woodhouse, Synthesis and characterization of degradable polyurethane elastomers containing an amino acid-based chain extender, J. Biomater. Sci. Polym. Ed. 9 (1998) 271–295.
[37] J. Kylma, J.V. Seppala, Synthesis and characterization of a biodegradable thermoplastic poly(ester-urethane) elastomer, Macromolecules 30 (May 19, 1997) 2876–2882.
[38] L. Tatai, T.G. Moore, R. Adhikari, F. Malherbe, R. Jayasekara, I. Griffiths, et al., Thermoplastic biodegradable polyurethanes: the effect of chain extender structure on properties and in-vitro degradation, Biomaterials 28 (December 2007) 5407–5417.
[39] C.R. Lee, S. Grad, K. Gorna, S. Gogolewski, A. Goessl, M. Alini, Fibrin-polyurethane composites for articular cartilage tissue engineering: a preliminary analysis, Tissue Eng. 11 (September 2005) 1562–1573.
[40] S. Grad, L. Kupcsik, K. Gorna, S. Gogolewski, M. Alini, The use of biodegradable polyurethane scaffolds for cartilage tissue engineering: potential and limitations, Biomaterials 24 (December 2003) 5163–5171.
[41] S.L. Chia, K. Gorna, S. Gogolewski, M. Alini, Biodegradable elastomeric polyurethane membranes as chondrocyte carriers for cartilage repair, Tissue Eng. 12 (July 2006) 1945–1953.
[42] J. Yang, J. Dey, in: Bio-polymer and Scaffold-Sheet Method for Tissue Engineering, Google Patents, 2009.
[43] J. Dey, R.T. Tran, J.H. Shen, L.P. Tang, J. Yang, Development and long-term in vivo evaluation of a biodegradable urethane-doped polyester elastomer, Macromol. Mater. Eng. 296 (December 12, 2011) 1149–1157.
[44] D. Gyawali, R.T. Tran, K.J. Guleserian, L.P. Tang, J.A. Yang, Citric-acid-derived photo-cross-linked biodegradable elastomers, J. Biomater. Sci. Polym. Ed. 21 (2010) 1761–1782.
[45] S.H. Kim, J.H. Lee, H. Hyun, Y. Ashitate, G. Park, K. Robichaud, et al., Near-infrared fluorescence imaging for noninvasive trafficking of scaffold degradation, Sci. Rep. 3 (2013) 1198.
[46] K.M. Bratlie, T.T. Dang, S. Lyle, M. Nahrendorf, R. Weissleder, R. Langer, et al., Rapid biocompatibility analysis of materials via in vivo fluorescence imaging of mouse models, PLoS One 5 (2010) e10032.

[47] J. Yang, Y. Zhang, S. Gautam, L. Liu, J. Dey, W. Chen, et al., Development of aliphatic biodegradable photoluminescent polymers, Proc. Natl. Acad. Sci. U.S.A. 106 (June 23, 2009) 10086–10091.
[48] Z. Xie, Y. Zhang, L. Liu, H. Weng, R.P. Mason, L. Tang, et al., Development of intrinsically photoluminescent and photostable polylactones, Adv. Mater. 26 (26) (March 26, 2014) 4491–4496.
[49] M.D. Best, Click chemistry and bioorthogonal reactions: unprecedented selectivity in the labeling of biological molecules, Biochemistry 48 (July 21, 2009) 6571–6584.
[50] C.S. McKay, M.G. Finn, Click chemistry in complex mixtures: bioorthogonal bioconjugation, Chem. Biol. 21 (September 18, 2014) 1075–1101.
[51] S. Kantheti, R. Narayan, K.V.S.N. Raju, Click chemistry engineered hyperbranched polyurethane-urea for functional coating applications, Ind. Eng. Chem. Res. 53 (May 21, 2014) 8357–8365.
[52] S.H. Rhee, J. Tanaka, Effect of citric acid on the nucleation of hydroxyapatite in a simulated body fluid, Biomaterials 20 (November 1999) 2155–2160.
[53] S. Gogoi, N. Karak, Biobased biodegradable waterborne hyperbranched polyurethane as an ecofriendly sustainable material, ACS Sustain. Chem. Eng. 2 (2014) 2730–2738.
[54] F.M.B. Coutinho, M.C. Delpech, Waterborne anionic polyurethanes and poly (urethane-urea)s- influence of the chain extender on mechanical and adhesive properties, Polym. Test. 19 (2000) 939–952.
[55] B.K. Kim, Aqueous polyurethane dispersions, Colloid Polym. Sci. 274 (1996) 599–611.
[56] M.G. Lu, J.Y. Lee, M.J. Shim, S.W. Kim, Synthesis and properties of anionic aqueous polyurethane dispersions, J. Appl. Polym. Sci. 86 (2002) 3461–3465.
[57] M.A.R. Meier, J.O. Metzger, U.S. Schubert, Plant oil renewable resources as green alternatives in polymer science, Chem. Soc. Rev. 36 (2007) 1788.
[58] T. Gurunathan, S. Mohanty, S.K. Nayak, Effect of reactive organoclay on physicochemical properties of vegetable oil-based waterborne polyurethane nanocomposites, RSC Adv. 5 (2015) 11524–11533.
[59] Y. Xia, R.C. Larock, Vegetable oil-based polymeric materials: synthesis, properties, and applications, Green Chem. 12 (2010) 1893.
[60] I. Vroman, L. Tighzert, Biodegradable polymers, Materials 2 (2009) 307–344.
[61] Y. Lu, R.C. Larock, Soybean-oil-based waterborne polyurethane dispersions: effects of polyol functionality and hard segment content on properties, Biomacromolecules 9 (2008) 3332–3340.
[62] N.M.K. Lamba, K.A. Woodhouse, S.L. Cooper, Polyurethanes in Biomedical Applications, CRC Press, New York, 1998, pp. 205–241.
[63] D. Xu, Z. Meng, M. Han, K. Xi, X. Jia, X. Yu, et al., Novel blood-compatible waterborne polyurethane using chitosan as an extender, J. Appl. Polym. Sci. 109 (2008) 240–246.
[64] T.J. Lee, S.H. Kwon, B.K. Kim, Biodegradable sol-gel coatings of waterborne polyurethane/gelatin chemical hybrids, Prog. Org. Coat. 77 (2014) 1111–1116.
[65] W. Wang, P. Ping, X. Chen, X. Jing, Shape memory effect of poly(L-lactide)- based polyurethanes with different hard segments, Polym. Int. 56 (2007) 840–846.
[66] S.A. Dai, C.-W. Chen, Y.-S. Chen, S.-H. Hsu, Biodegradable and biocompatible waterborne polyurethane, Patent US 20120108742 (October 25, 2011).
[67] H. Chen, X. Jiang, L. He, T. Zhang, M. Xu, X. Yu, Novel biocompatible waterborne polyurethane using L-lysine as an extender, J. Appl. Polym. Sci. 84 (2002) 2474–2480.
[68] X. Jiang, F. Yu, Z. Wang, J. Li, H. Tan, M. Ding, et al., Fabrication and characterization of waterborne biodegradable polyurethanes 3-dimensional porous scaffolds for vascular tissue engineering, J. Biomater. Sci. Polym. Ed. 21 (2010) 1637–1652.

[69] D. Cohn, A.H. Salomon, Designing biodegradable multiblock PCL/PLA thermoplastic elastomers, Biomaterials 26 (May 2005) 2297–2305.
[70] J.S. Nowick, N.A. Powell, T.M. Nguyen, G. Noronha, An improved method for the synthesis of enantiomerically pure amino acid ester isocyanates, J. Org. Chem. 57 (1992) 7364–7366.
[71] F. Liang, B. Qin, Y. Yang, M. Jia, Study on the synthesis and properties of biodegradable waterborne polyurethane, Adv. Mater. Res. 554-556 (2012) 130–135.
[72] F. Xu, Y. Wang, X. Jiang, H. Tan, H. Li, K.J. Wang, Effects of different biomaterials: comparing the bladder smooth muscle cells on waterborne polyurethane or poly-lactic-co-glycolic acid membranes, Kaohsiung J. Med. Sci. 28 (January 2012) 10–15.
[73] G.R. da Silva, A. da Silva-Cunha, F. Behar-Cohen, E. Ayres, R.L. Oréfice, Biodegradable polyurethane nanocomposites containing dexamethasone for ocular route, Mater. Sci. Eng. C 31 (2011) 414–422.
[74] A.Y. Khosroushahi, H. Naderi-Manesh, H. Yeganeh, J. Barar, Y. Omidi, Novel water-soluble polyurethane nanomicelles for cancer chemotherapy: physicochemical characterization and cellular activities, J. Nanobiotechnol. 10 (2012) 2.
[75] H.J. Yoo, H.D. Kim, Synthesis and properties of waterborne polyurethane hydrogels for wound healing dressings, J. Biomed. Mater. Res. B Appl. Biomater. 85 (May 2008) 326–333.
[76] S.H. Hsu, H.J. Tseng, Y.C. Lin, The biocompatibility and antibacterial properties of waterborne polyurethane-silver nanocomposites, Biomaterials 31 (September 2010) 6796–6808.
[77] S.-H. Hsu, K.-C. Hung, Y.-Y. Lin, C.-H. Su, H.-Y. Yeh, U.S. Jeng, et al., Water-based synthesis and processing of novel biodegradable elastomers for medical applications, J. Mater. Chem. B 2 (2014) 5083.
[78] Y.H. Lin, K.H. Liao, N.K. Chou, S.S. Wang, S.H. Chu, K.H. Hsieh, UV-curable low-surface-energy fluorinated poly(urethane-acrylate)s for biomedical applications, Eur. Polym. J. 44 (September 2008) 2927–2937.
[79] T.F. Yang, W. Chin, J. Cherng, M. Shau, Synthesis of novel biodegradable cationic polymer: N,N-diethylethylenediamine polyurethane as a gene carrier, Biomacromolecules 5 (September–October 2004) 1926–1932.
[80] X.Y. Liu, W.Y. Ho, W.J. Hung, M.D. Shau, The characteristics and transfection efficiency of cationic poly (ester-co-urethane) – short chain PEI conjugates self-assembled with DNA, Biomaterials 30 (December 2009) 6665–6673.
[81] S.A. Madbouly, J.U. Otaigbe, A.K. Nanda, D.A. Wicks, Rheological behavior of aqueous polyurethane dispersions: effects of solid content, degree of neutralization, chain extension, and temperature, Macromolecules 38 (May 3, 2005) 4014–4023.
[82] L. Billiet, O. Gok, A.P. Dove, A. Sanyal, L.T.T. Nguyen, F.E. Du Prez, Metal-free functionalization of linear polyurethanes by thiol-maleimide coupling reactions, Macromolecules 44 (October 25, 2011) 7874–7878.
[83] L.X. Yang, J.Z. Wei, L.S. Yan, Y.B. Huang, X.B. Jing, Synthesis of OH-group-containing, biodegradable polyurethane and protein fixation on its surface, Biomacromolecules 12 (June 2011) 2032–2038.
[84] D. Fournier, F. Du Prez, "Click" chemistry as a promising tool for side-chain functionalization of polyurethanes, Macromolecules 41 (July 8, 2008) 4622–4630.
[85] C. Ott, C.D. Easton, T.R. Gengenbach, S.L. McArthur, P.A. Gunatillake, Applying "click" chemistry to polyurethanes: a straightforward approach for glycopolymer synthesis, Polym. Chem. 2 (2011) 2782–2784.

[86] L. Billiet, D. Fournier, F. Du Prez, Step-growth polymerization and 'click' chemistry: the oldest polymers rejuvenated, Polymer 50 (July 31, 2009) 3877–3886.
[87] M. Basko, M. Bednarek, L. Billiet, P. Kubisa, E. Goethals, F. Du Prez, Combining cationic ring-opening polymerization and click chemistry for the design of functionalized polyurethanes, J. Polym. Sci. Part A Polym. Chem. 49 (April 1, 2011) 1597–1604.
[88] C.F. Ma, H. Zhou, B. Wu, G.Z. Zhang, Preparation of polyurethane with zwitterionic side chains and their protein resistance, ACS Appl. Mater. Interfaces 3 (February 2011) 455–461.
[89] D.M. Le, K. Kulangara, A.F. Adler, K.W. Leong, V.S. Ashby, Dynamic topographical control of mesenchymal stem cells by culture on responsive poly(ε-caprolactone) surfaces, Adv. Mater. 23 (August 2, 2011) 3278–3283.
[90] N.E. Kurland, T. Dey, S.C. Kundu, V.K. Yadavalli, Precise patterning of silk microstructures using photolithography, Adv. Mater. 25 (November 20, 2013) 6207–6212.
[91] N.E. Kurland, T. Dey, C.Z. Wang, S.C. Kundu, V.K. Yadavalli, Silk protein lithography as a route to fabricate sericin microarchitectures, Adv. Mater. 26 (July 9, 2014) 4431–4437.
[92] K.S. Halake, S.Y. Choi, S.M. Hong, S.Y. Seo, J. Lee, Regioselective substitution of 2-isocyanatoethylmethacrylate onto cellulose, J. Appl. Polym. Sci. 128 (May 5, 2013) 2056–2062.
[93] Z.K. Hu, L.M. Pitet, M.A. Hillmyer, J.M. DeSimone, High modulus, low surface energy, photochemically cured materials from liquid precursors, Macromolecules 43 (December 28, 2010) 10397–10405.
[94] J.G. Park, Q. Ye, E.M. Topp, P. Spencer, Enzyme-catalyzed hydrolysis of dentin adhesives containing a new urethane-based trimethacrylate monomer, J. Biomed. Mater. Res. Part B Appl. Biomater. 91B (November 2009) 562–571.
[95] G.M. Brauer, C.H. Lee, Oligomers with pendant isocyanate groups as tissue adhesives. 2. Adhesion to bone and other tissues, J. Biomed. Mater. Res. 23 (July 1989) 753–763.
[96] R.M. Hensarling, S.B. Rahane, A.P. LeBlanc, B.J. Sparks, E.M. White, J. Locklin, et al., Thiol-isocyanate "click" reactions: rapid development of functional polymeric surfaces, Polym. Chem. 2 (2011) 88–90.
[97] M.J.N. Pereira, B. Ouyang, C.A. Sundback, N. Lang, I. Friehs, S. Mureli, et al., A highly tunable biocompatible and multifunctional biodegradable elastomer, Adv. Mater. 25 (February 25, 2013) 1209–1215.
[98] A.T. Neffe, B.F. Pierce, G. Tronci, N. Ma, E. Pittermann, T. Gebauer, et al., One step creation of multifunctional 3D architectured hydrogels inducing bone regeneration, Adv. Mater. 27 (10) (January 20, 2015) 1738–1744.
[99] W.G. Liu, J.R. Zhang, K.D. Yao, DNA/lipid complex organogel with shape-memory behavior, J. Appl. Polym. Sci. 86 (October 3, 2002) 259–263.
[100] S.A. Barker, H.C. Tun, S.H. Doss, C.J. Gray, J.F. Kennedy, Preparation of cellulose carbonate, Carbohydr. Res. 17 (1971) 471–474.
[101] K.M. Tomczyk, P.A. Gunka, P.G. Parzuchowski, J. Zachara, G. Rokicki, Intramolecular etherification of five-membered cyclic carbonates bearing hydroxyalkyl groups, Green Chem. 14 (2012) 1749–1758.
[102] J.H. Clements, Reactive applications of cyclic alkylene carbonates, Ind. Eng. Chem. Res. 42 (February 19, 2003) 663–674.
[103] H. Blattmann, M. Fleischer, M. Bahr, R. Mulhaupt, Isocyanate- and phosgene-free routes to polyfunctional cyclic carbonates and green polyurethanes by fixation of carbon dioxide, Macromol. Rapid Commun. 35 (July 2014) 1238–1254.

[104] B. Nohra, L. Candy, J.F. Blanco, C. Guerin, Y. Raoul, Z. Mouloungui, From petrochemical polyurethanes to biobased polyhydroxyurethanes, Macromolecules 46 (May 28, 2013) 3771–3792.
[105] C. Carre, L. Bonnet, L. Averous, Original biobased nonisocyanate polyurethanes: solvent- and catalyst-free synthesis, thermal properties and rheological behaviour, RSC Adv. 4 (2014) 54018–54025.
[106] W.J. Wang, T. Li, T. Yu, F.M. Zhu, Synthesis of multiblock copolymers by coupling reaction based on self-assembly and click chemistry, Macromolecules 41 (December 23, 2008) 9750–9754.