Natural and Synthetic Biomedical Polymers
Natural and Synthetic Biomedical Polymers

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Summary: “Polymer scientists have made an extensive research for the development of biodegradable polymers which could find enormous applications in the area of medical science. Today, various biopolymers have been prepared and utilized in different biomedical applications. Despite the apparent proliferation of biopolymers in medical science, the Science and Technology of biopolymers is still in its early stages of development. Tremendous opportunities exist and will continue to exist for the penetration of biopolymers in every facet of medical science through intensive Research and Development. Therefore, this chapter addresses different polymerization methods and techniques employed for the preparation of biopolymers. An emphasis is given to cover the general properties of biopolymers, synthetic protocols and their biomedical applications. In order to make the useful biomedical devices from the polymers to meet the demands of medical science, various processing techniques employed for the development of devices have been discussed. Further, perspectives in this field have been highlighted and at the end arrived at the conclusions. The relevant literature was collected from different sources including Google sites, books and reviews”—Provided by publisher.

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Sangamesh G. Kumbar—To my parents (Mr. and Mrs. G. B. Kumbar), wife Swetha, and daughter Gauri.

Cato T. Laurencin—To my wife Cynthia, and my children Ti, Michaela, and Victoria.
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I am truly delighted to write the foreword for *Natural and Synthetic Biomedical Polymers* edited by well-established leaders and pioneers in the field, Professors Dr. Kumbar, Dr. Laurencin, and Dr. Deng. This book should prove extremely useful as a reference source for all those working in the fields of polymer chemistry and physics, biomaterial science, tissue engineering, drug delivery, and regenerative medicine. Polymeric materials are routinely used in clinical applications, ranging from surgical sutures to drug-eluting devices to implants. In particular, implants and drug delivery devices fabricated using biodegradable polymers provide the significant advantage of being degraded and/or resorbed after they have served their function. Yet, biomedical polymers must satisfy several design criteria, including physical, chemical, biomechanical, biological, and degradation properties when serving as an active implant material. Several natural and synthetic degradable polymers have been developed and are used clinically today. However, a wide range of new polymers, as well as modifications to existing polymers, are constantly being developed and applied to meet on-going and evolving challenges in biomedical applications. For example, polymeric nanostructures, implants, scaffolds, and drug delivery devices are allowing unprecedented manipulation of cell-biomaterial interactions, promotion of tissue regeneration, targeting of therapies, and combined diagnostic and imaging modalities.

This timely book provides a well-rounded and articulate summary of the present status of natural and synthetic biomedical polymers, their structure and property relationships, and their biomedical applications including regenerative engineering and drug delivery. Polymers that are both synthetic and natural in origin have been widely used as biomaterials for a variety of biomedical applications and greatly impacted the advancement of modern medicine. In this regard, 23 concise and comprehensive chapters are prepared by experts in their fields from different parts of the world. The chapters encompass numerous topics that appear prominently in the modern biomaterials literature and cover a wide range of traditional synthetic, natural, and semi-synthetic polymers and their applications. In my opinion, this book presents an excellent overview of the subject that will appeal to a broad audience and will serve as a valuable resource to those working in the fields of polymer science, tissue engineering, regenerative medicine, or drug delivery. I believe that this textbook will be a welcome addition to personal collections, libraries, and classrooms throughout the world.

**Kristi S. Anseth**

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16.1 INTRODUCTION

Biodegradable polymers are superior to traditional nondegradable polymers since they do not need subsequent surgical removal after being implanted in bodies. Thus, they have gained widespread application in biomedical areas in recent years, such as tissue engineering, drug delivery, gene delivery, and bioimaging [1–4]. Among biodegradable polymers, biodegradable elastomeric polymers have received increasing attention because their compliance under force can closely resemble the elastic nature of many soft tissues such as heart valves, blood vessels, tendons, cartilage, and bladder [5–7]. Elastomers are usually amorphous polymers with relatively low glass transition temperature ($T_g$). When used as an implantable material, the presence of at least one segment with a glass transition temperature ($T_g$) lower than room temperature or at least body temperature ($37^\circ$C) is necessary to make sure the polymer is in an elastic state and considerable segmental motion is possible in the temperature range used. Polyesters like poly($\varepsilon$-caprolactone) (PCL), poly(dioxanone) (PDO), and poly($\delta$-valerolactone); some poly(carbonate)s; and their copolymers synthesized by ring-opening polymerization (ROP) have low $T_g$s and can be used as elastomers. This method is restricted by the stability of cyclic monomers used, which are usually 5-, 6-, or 7-membered rings. Thus, other ROP-derived polymers such as poly(l-lactide) (PLLA), poly(glycolide) (PGA), and their copolymers (PLGA) have higher $T_g$s and are in glassy state, brittle, and stiff at the intended use (room or body) temperature [2,3,8,9]. Compared with ROP, polycondensation provides...
more options. Diacid, diol, or hydroxyalkanoate monomers used for polyester synthesis may have long aliphatic chains to ensure the softness and elasticity of the obtained polymers via polycondensation [1,7,10,11]. Among various polymerization methods used in polycondensation, such as thermal polymerization, microbial synthesis, and enzymatic polymerization, catalyst-free and solvent-free thermal polymerization are the most commonly used [1,7,10,11]. Multifunctional monomers including unsaturated monomers can be used in polycondensation, conferring the (pre) polymers with thermal or photo-cross-linkable (or curable) properties [1,2,10–12]. Among the cross-linkable elastomeric polymers, poly(polyol sebacate) [10,12–15] and citric acid-based poly(diol citrate) [2,16–27] are the two most widely researched. In this chapter, we will focus on the design strategies and applications of citrate-based biodegradable elastomeric polymers (CABEs).

Citric acid is a natural, weak organic acid that abundantly exists in many vegetables and fruits, especially citrus fruits like lemon and lime, where the citrate concentration can reach up to 8% after drying. As an intermediate in the tricarboxylic acid cycle (TCA cycle, also known as the citric acid cycle or Krebs cycle), which occurs in the metabolism of all aerobic organisms, citric acid is nontoxic and multifunctional. Thus, it is an excellent choice of a starting material for biodegradable polymer synthesis. Possessing three carboxyl groups and one hydroxyl group, citric acid has been widely used as a chelating or binding agent of various metal ions and metal oxide nanoparticles [28,29]. A majority of the body’s citrate content is located in skeletal tissues and plays a large role in metabolism, calcium chelation, hydroxyapatite (HA) formation, and regulation of the thickness of bone apatite structure [30–33]. Citrate not only functions as a calcium-solubilizing agent but is also a strong bound and integral part of the bone nanocomposite [33]. Citrate also has a unique and innate ability to induce HA formation in simulated body fluid (SBF) [34]. The rich pendent −COOH groups in CABEs, like poly(1,8-octanediol citrate) (POC) and poly(poly(ethylene glycol) maleate citrate) (PEGMC), can also chelate calcium ions. The polymers and their composites with HA have proven to be promising orthopedic biomaterials that can promote the biomineralization process and increase osteoblast adhesion and mineralization, thus enhancing osteointegration [2,35–39]. In all CABE designs, citric acid participates in prepolymer formation through polycondensation with diols, and it also preserves pendent functionalities for postpolymerization through esterification to produce a cross-linked polyester network. Cross-linking confers elasticity and mechanical stability to the polymers similar to extracellular matrix (ECM), in which collagen and elastin are also all cross-linked polymers [40]. In addition to the multifunctionality and biocompatibility of citric acid, the sodium form of citric acid, sodium citrate, is an anticoagulant often used in hospitals [17]. This implies that CABEs may also possess suitable hemocompatibility when in contact with blood, which will benefit the application of CABEs in blood-contacting applications. Because of all the advantages stated earlier, the research on CABEs is just unfolding. In this book chapter, we will discuss the design strategies and applications of previous CABEs and the outlook of their future development in biomedical engineering.

## 16.2 DESIGN STRATEGIES OF CABEs

Material design strategies are always driven by application demands. As the first polymer series of CABE family, poly(diol citrate) were initially designed for soft tissue engineering applications like blood vessels, so the chain length of diols used to react with citric acid should be long enough to guarantee the obtained polymers to be elastomeric, and 1,8-octanediol (OD) was proved to be the right diol, so was the born of POC. After that, a lot of modifications were made on POC by introducing additional diols or chain extension, to adjust the elasticity, mechanical strength, and degradation profile of the obtained polymers; bring new properties; and introduce new cross-linking mechanisms to the obtained elastomers (Figure 16.1). To obtain hydrophilic CABEs, water-soluble diol such as poly(ethyl glycol) (PEG) was also used. On the other hand, novel design strategies can also bring new application directions. The creations of biodegradable photoluminescent polymer (BPLP) [2,20,21] and injectable citrate-based mussel-inspired bioadhesives (iCMBA) [22,23] brought bioimaging and bioadhesive applications to CABE family, respectively.

The design strategies of CABEs also adapted the characteristics of the monomers used. Citric acid is a multifunctional monomer containing three carboxyl groups and one hydroxyl group; in CABEs, it not only participates in prepolymer formation by reacting with diols but also preserves pendent functionalities for postpolymerization or concurrent/postmodification with other molecules such as amine-containing molecules. In addition to citric acid, other acids were also used. By adjusting the feeding ratio of diol to citric acid, hydroxyl group-terminated CABEs were synthesized, which can be used for further chain extension by using hydroxyl groups reaction with disocyanate or initiating lactones ROP. Additional diols except OD, such as double bond-containing diols, were also introduced into CABE systems to adjust the polymer properties (Figure 16.1).

### 16.2.1 Poly(Diol Citrate) Synthesis

As mentioned earlier, CABE prepolymers are synthesized via a simple thermal polycondensation process by reacting citric acid with diol monomers (Figure 16.2 and Table 16.1). Citric acid confers CABEs with pendent functionality for postmodification or concurrent modification and cross-linking. While the elasticity of CABEs mostly depends on the chain length of the diol used, if
An increase in postpolymerization temperature and cross-networks, POC can be tuned to fit a wide range of tissue profiles, and surface energies of the cross-linked polyester diol that can dissolve in water or PBS. Drophobic diol is 1,8-octanediol (OD) as it is the longest chain length of the diol used is too short, like ethylene glycol or 1,4-butaneol, the obtained polymers are likely to be brittle and stiff. Conversely, long aliphatic chains may increase elasticity but may also slow down material degradation. Although polymers like poly(1,12-dodecanediol-co-citrate) (PDDC), synthesized by the polycondensation of citric acid and 1,12-dodecanediol, have shape-memory properties [49], the most used hydrophobic diol is 1,8-octanediol (OD) as it is the longest diol that can dissolve in water or PBS.

By adjusting postpolymerization temperature and cross-linking (curing) time, the mechanical properties, degradation profiles, and surface energies of the cross-linked polyester networks, POC can be tuned to fit a wide range of tissue engineering applications (see Table 16.2) [2,16–18,35,50–56]. An increase in postpolymerization temperature and cross-linking time and the application of vacuum resulted in a network with increased mechanical strength due to the increased cross-linking densities. As shown in Table 16.2, the range of mechanical properties of POC potentially meets the needs for the engineering of various soft tissues including blood vessels, nerve, cartilage, and the bladders. The preliminary biocompatibility evaluation showed that POC supported the attachment and proliferation of human aortic smooth muscle cells (HASMC), endothelial cells (ECs), and 3T3 fibroblasts cells without any surface modifications [16,18]. Histological analysis of POC films subcutaneously implanted in Sprague-Dawley (SD) rats further confirmed that POC elicited minimal inflammatory responses. After 4-month implantation, the thickness of fibrous capsule was smaller than the reported values of the widely used commercial biodegradable polymer, PLGA [16,18].
<table>
<thead>
<tr>
<th>Monomers</th>
<th>Diol or Polyol</th>
<th>Citric Acid and Diacid</th>
<th>Pendent Modification</th>
<th>Polymer</th>
<th>Properties and Applications</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HO–CH₂–OH</td>
<td>Citric Acid and Diacid</td>
<td></td>
<td>POC</td>
<td>Hydrophobic, suitable elasticity; vascular graft, bone composite, drug delivery</td>
<td>[2,16–18,29,35]</td>
</tr>
<tr>
<td></td>
<td>PEG</td>
<td></td>
<td></td>
<td>PEGC</td>
<td>Hydrophilic, high water adsorption</td>
<td>[25–27]</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td></td>
<td></td>
<td>BPLP</td>
<td>Fluorescent; bioimaging, drug delivery, tissue engineering</td>
<td>[2,20,21]</td>
</tr>
<tr>
<td></td>
<td>PEG</td>
<td></td>
<td></td>
<td>WBPLP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEG</td>
<td></td>
<td></td>
<td>iCMBA</td>
<td>Bioadhesive, injectable; bioglue, wound closure, tissue bioadhesive</td>
<td>[22,23]</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td></td>
<td></td>
<td>cMA-POC</td>
<td>Photo-cross-linkable</td>
<td>[41]</td>
</tr>
<tr>
<td></td>
<td>MDEA</td>
<td></td>
<td></td>
<td>POCM</td>
<td>Adjust mechanical and degradation properties</td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>POC-Q(m+2)</td>
<td>Conferring antibacterial properties to PDC</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>POC-DA</td>
<td>NO-combining; vascular graft</td>
<td>[43–45]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>POC-click</td>
<td>Enhanced mechanical properties, surface conjugate—easy—vascular graft, bone composites</td>
<td>Unpublished</td>
</tr>
</tbody>
</table>
### Design Strategies and Applications of CABEs

<table>
<thead>
<tr>
<th>Pre-polymer</th>
<th>Chain Extension</th>
<th>Polymer</th>
<th>Properties and Applications</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-POC</td>
<td>HDI(^a)</td>
<td>CUPE</td>
<td>Enhanced mechanical properties; vascular graft, bone composites</td>
<td>[19]</td>
</tr>
<tr>
<td>BPLP</td>
<td>HDI(^a)</td>
<td>CUBPLP</td>
<td>Fluorescent, enhanced mechanical properties; vascular graft, bioimaging</td>
<td>[48]</td>
</tr>
<tr>
<td>Pre-POMC(^c)</td>
<td>HDI(^a)</td>
<td>CUPOMC</td>
<td>Photo-cross-linkable</td>
<td>[47]</td>
</tr>
<tr>
<td>BPLP</td>
<td>ROP of lactide</td>
<td>BPLP-LA</td>
<td>Fluorescent PLA</td>
<td>Unpublished</td>
</tr>
</tbody>
</table>

\(^{a}\) For all the hydrophobic polymers, like POC, BPLP, POCM, POC-DA, POMaC, POC-click, 1,8-octanediol, and citric acid, that composed the main chain backbone of the polymers, functional diols or polyols were used as additional monomers.

\(^{b}\) Pendent modification refers to the modification of the pendent functional groups on citrate-based prepolymers. The modification can be conducted concurrently with (BPLP, WBPLP, and iCMBA) or after (CMA-POC) the polycondensation process of diol and citric acid.

\(^{c}\) Here, polymers are the final cross-linked polymers, except for BPLP, WBPLP, and BPLP-LA. The full names of polymer abbreviations are listed as follows: POC, poly(1, 8-octanediol citrate); PEGMC, poly(poly(ethylene glycol) maleate citrate); BPLP, biodegradable photofluorescent polymer; WBPLP, water-soluble BPLP; iCMBA, injectable citrate-based mussel-inspired bioadhesive; CUPE, cross-linked urethane-doped polyester; CUBPLP, cross-linked urethane-doped BPLP.

\(^{d}\) POC-click is formed by thermo-cross-linking the mixture of pre-POC-N\(_3\) (azide-containing POC prepolymer) and pre-POC-Al (alkyne-containing POC prepolymer); the process applies synchronous binary cross-link mechanism, esterification, and thermal click reaction, and the residual azide groups on the surface of POC-click film or scaffold paved the way of surface bioconjugation through strain-promoted alkyne-azide cycloaddition (SPAAC), another copper-free click reaction.

\(^{e}\) POMaC also applies dual cross-link mechanism, thermal esterification, and photo-cross-linking of double bonds.

\(^{f}\) PEGMC was used as hydrogel at room or body temperature; thus, only double bonds serve as cross-linking functionality.

\(^{g}\) HDI: 1,6-hexamethylene diisocyanate.
<table>
<thead>
<tr>
<th>Polymer</th>
<th>Tensile Strength (MPa)</th>
<th>Modulus (MPa)</th>
<th>Elongation (%)</th>
<th>Degradation rate</th>
<th>Tested cells and Animals</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>POC</td>
<td>2.93-11.15</td>
<td>1.85-13.98</td>
<td>117-502</td>
<td>100% in 26 weeks</td>
<td>HASMCs/HAECs</td>
<td>[18]</td>
</tr>
<tr>
<td>POMaC</td>
<td>2.45-9.94</td>
<td>0.05-1.52</td>
<td>51-441</td>
<td>15-76% in 10 weeks</td>
<td>3T3 fibroblasts</td>
<td>[24]</td>
</tr>
<tr>
<td>CBPLP</td>
<td>2.2-7.6</td>
<td>2.4-8.9</td>
<td>140-272</td>
<td>100% in 31 weeks</td>
<td>3T3 fibroblasts, nude mice</td>
<td>[20]</td>
</tr>
<tr>
<td>POC-DA</td>
<td>1.49-10.71</td>
<td>5.91-32.64</td>
<td>201-290</td>
<td>20% loss in 6 weeks</td>
<td>PASMC/HASMC/HUVEC</td>
<td>[43–45]</td>
</tr>
<tr>
<td>Acrylated POC</td>
<td>2.8-15.7</td>
<td>7.4-75.9</td>
<td>86.1-260</td>
<td>27-35% in 2 months</td>
<td>–</td>
<td>[46]</td>
</tr>
<tr>
<td>POC-click</td>
<td>18.3-41.32</td>
<td>16.6-275.9</td>
<td>78-323.9</td>
<td>100% in 34 weeks</td>
<td>3T3 fibroblasts, HUVEC</td>
<td>Unpublished</td>
</tr>
<tr>
<td>CUPE</td>
<td>14-37</td>
<td>2.2-32</td>
<td>217-309</td>
<td>15% in 8 weeks</td>
<td>3T3 fibroblasts</td>
<td>[19]</td>
</tr>
<tr>
<td>CUPOMC</td>
<td>1-10.5</td>
<td>0.5-5.8</td>
<td>175-220</td>
<td></td>
<td>3T3 fibroblasts</td>
<td>[47]</td>
</tr>
<tr>
<td>CUBPLP</td>
<td>1.2-49.41</td>
<td>0.2-52</td>
<td>240-450</td>
<td>13-22 h in 0.05 M NaOH</td>
<td>3T3 fibroblasts</td>
<td>[48]</td>
</tr>
<tr>
<td>Porcine aortic heart valve (radial)</td>
<td>2.4</td>
<td>6.4</td>
<td>134.8</td>
<td>–</td>
<td>–</td>
<td>[50]</td>
</tr>
<tr>
<td>Porcine aortic heart valve (circumferential)</td>
<td>8.3</td>
<td>44.7</td>
<td>48.7</td>
<td>–</td>
<td>–</td>
<td>[50]</td>
</tr>
<tr>
<td>Ulnar peripheral nerve</td>
<td>9.8-21.6</td>
<td>–</td>
<td>8-21</td>
<td>–</td>
<td>–</td>
<td>[51]</td>
</tr>
<tr>
<td>Human coronary artery</td>
<td>1.4-11.14</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[52]</td>
</tr>
<tr>
<td>Bovine elastin</td>
<td>–</td>
<td>1.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[53]</td>
</tr>
<tr>
<td>Human ACL</td>
<td>24-112</td>
<td>–</td>
<td>–</td>
<td></td>
<td>–</td>
<td>[54]</td>
</tr>
<tr>
<td>Human cartilage</td>
<td>3.7-10.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[52]</td>
</tr>
<tr>
<td>Smooth muscle relaxed</td>
<td>–</td>
<td>0.006</td>
<td>300</td>
<td>–</td>
<td>–</td>
<td>[55]</td>
</tr>
<tr>
<td>Porcine lung</td>
<td>–</td>
<td>0.005</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[56]</td>
</tr>
</tbody>
</table>

*For POC (80 °C, 2 days), incubated in PBS (pH 7.4, 37 °C).
*For POMaC with different maleic anhydride ratios and thermo- or photocured under different conditions, incubated in PBS (pH 7.4, 37 °C).
*CBPLP refers cross-linked BPLP.
*For CBPLP-Cys0.8 (80 °C, 2 days), incubated in PBS (pH 7.4, 37 °C).
*For POC-DA with different DA ratios (80 °C, 4 days), incubated in PBS (pH 7.4, 37 °C).
*Samples with different compositions were cross-linked at 80 °C for 0.5 days, followed by 120 °C, 1 days and 120 °C, vacuum, 1 day. Degradation was conducted in PBS (pH 7.4, 37 °C).
*For POC-click3 (100 °C, 3 days), incubated in PBS (pH 7.4, 37 °C).
*For CUPE1.2 (80 °C, 2 days), incubated in PBS (pH 7.4, 37 °C).
Although POC, as a representative poly(diol citrate), is soft and elastic, it is still considered relatively weak, with a tensile strength typically no more than 10 MPa at dry state (Table 16.2). This is already much lower than that of human anterior cruciate ligament (38 MPa) and may become even lower when fabricated into porous scaffolds and/or used in vivo at wet state. To modify the material properties, functionalities, and processability of poly(diol citrates), various diols, diacids, and/or diamines were introduced to CABEs, either to adjust the material properties or to introduce a second cross-linking mechanism. Pendent group (carboxyl or hydroxyl) modification and chain extension of CABEs were also conducted to improve the mechanical properties and functionalities of CABEs [22,23,27,35-37]. This will be discussed in details in the following sections.

### 16.2.2 Molecular Design of CABEs

Based on poly(diol citrate), several molecular design strategies were adopted for CABE syntheses. First, the introduction of additional functionalities or additional cross-linking mechanisms using various additional diols or diacids were studied. By applying this strategy, a number of CABEs have recently been developed, including poly(1,8-octanediol-co-citrate-co-MDEA) (POCM) [18], POC with quaternary ammonium salt (POC-Q) (antibacterial POC) [42], diazeniumdiolated poly(1,8-octanediol citrate) (POC-DA) [43-45], poly(1,8-octamethylene maleate (anhydride) citrate) (POMaC) [24], poly(octamethylene maleate citrate) (POMC) [39], POC-click (unpublished), acrylated POC [46], and PEGMC [27,35,36] (Table 16.1).

Second, the modification of the pendent functionality of CABEs through reactions with amines or amino acids was developed, which can proceed concurrently or after the polycondensation of various CABE polymers, such as BPLP [2,20,21], iCMBA [22,23], and cross-linked methacyrlyated POC (cMA-POC) and cross-linked methacrylated poly(1,12-dodecanediol citrate) (cMA-PDDC) [41] (Table 16.2).

Third the chain extension through reacting with chain extenders such as 1,6-hexamethylene diisocyanate (HDI) was also developed. Such strategy has resulted in cross-linked urethane-doped polyester elastomers (CUPEs) based on POC [19], cross-linked urethane-doped BPLP (CUBPLP) [44] and cross-linked urethane-doped POMC (CUPOMC) [45]. This can also happen through initiating lactones’ ROP based on BPLP polymers to form fluorescent polylactone, BPLP-polylactone (BPLPL) (unpublished) (Table 16.2).

#### 16.2.2.1 Additional Diols

As shown in Figure 16.3, various diol or diacid monomers have been used in CABE systems to adjust material properties or to introduce additional functionalities. After introducing an amine-containing diol (N-methyldiethanolamine, MDEA) into POC, the resulting POCM showed enhanced mechanical strength and faster degradation rates (Tables 16.1 and 16.2). As reported, POCM10% and POCM5% showed mass losses of 72% and 48%, respectively, after degrading in PBS at 37 °C for 4 weeks. This is much higher than that of POC degraded in the same period (about 20%) [18]. Higher degradation rates of POCM polymers benefit from the positive charges and high water solubility of MDEA because the positive charges can neutralize the negative charges of degradation products, thus promoting the reaction balance of hydrolysis degradation to move forward.

By introducing quaternary ammonium salt diol into POC, Wynne et al. conferred antibacterial properties to the resulting POC-Q through a convenient and cost-effective thermal polycondensation process [42]. These materials have a tailored surface and strong antibacterial properties that make them good candidates as biodegradable packaging materials.

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**FIGURE 16.3** Diol and diacid monomers used in citrate-based biodegradable elastomers (CABEs) system.
In cardiovascular applications, nitric oxide (NO) released by vascular ECs has been shown to be a potent anti-thrombotic and antineointimal hyperplasia (NIH) agent by inhibiting platelet adhesion/activation and leukocyte chemotaxis, as well as smooth muscle cell (SMC) proliferation and migration. To increase the potential of CABEs in cardiovascular applications a NO-binding diol, N, N-bis(2-hydroxyethyl) ethylenediamine was introduced into POC polymer by Ameer’s Lab to form a NO-releasing diazeniumdiolated POC, called POC-D A (Table 16.1) [43–45]. POC-D A possessed similar tensile strength (1.49-10.71 MPa) to POC, a higher Young’s modulus (5.91-32.64 MPa), and an elongation at break in the range of 201-290% (Table 16.2). Cross-linked POC-D A polymer can deliver different doses of NO for 3 days by varying the amine content and the exposure time to pressurize NO gas without a significant impact on copolymer degradation rate [43]. Suitable NO-releasing dose was shown to be beneficial to the proliferation of human umbilical vein endothelial cells (HUVEC), while the proliferation of HASMC was significantly inhibited [44].

16.2.2.2 Additional Cross-Link Mechanism

The introduction of functional diols or diacids, such as double bond-containing diols or diacids and click moiety-containing diols, into CABE system, can confer the system with a second cross-link mechanism, such as free radical cross-linking of double bonds or click reaction between alkyne and azide groups (Figure 16.3). The introduction of a secondary cross-linking mechanism can adjust the mechanical properties and degradation properties of CABEs and can also confer CABEs with an additional and effective surface functionality for further bioactive molecule surface conjugation. The second cross-link mechanism is important, especially in the case of PEG-based hydrogel systems used for cell delivery or tissue bioadhesives at room or body temperature, where thermo-cross-link mechanism is not appropriate. In recent years, photo-cross-linkable biodegradable materials have attracted increased attention in tissue engineering, drug or cell delivery, and wound repair applications [57,58]. Recently, Yang Lab registered a new type of CABE referred to as poly(diol maleate citrates) (PDOMC), containing hydrophobic POMaC [24] and POMC [47] and hydrophilic PEGMC [27,36–38] (Table 16.1 and Figure 16.3) based on previous poly(diol citrate). Similar work was also done by Zhao and Ameer, but instead of introducing vinyl-containing diacid, double bond-containing diol or triol monomers (Table 16.1 and Figure 16.3) were introduced into POC to form acrylated POC [46]. Both hydrophobic and hydrophilic vinyl functional CABE systems can be quickly cross-linked into a thermoset elastomers by either thermo-cross-linking or double bond photo-redox cross-linking, or both of them, namely, dual cross-linking mechanism (DCM) [24,27,36–38,47]. The DCM allows the polymer to be quickly cross-linked by redox initiators or ultraviolet (UV) light to preserve valuable pendant carboxyl and hydroxyl groups for potential bioconjugation. PDOMC networks cross-linked by this route also show a pH-dependent swelling capability, which is useful in pH-sensitive drug delivery applications. The free radical (either photo- or redox) cross-linking method can also be combined with a thermocross-linking mechanism to further cross-link the network to fine-tune the mechanical and degradation properties in order to meet a variety of soft tissue engineering applications. As shown in Table 16.1, POMaC, POMC, and acrylated POC elastomer families have a wide range of mechanical properties (Young’s modulus of 0.05-75.9 MPa, tensile strength of 2.45-15.7 MPa, and elasticity of 51-441%) that can be modulated through adjusting monomer ratios, photoinitiator or redox initiator concentrations, and the use of DCM. Cells seeded onto the surface of POMC and POMaC films, or encapsulated in PEGMC hydrogels, exhibited normal spread morphologies. In vivo host response studies show a decline in inflammatory response and reduction in capsule thickness over a 4-week period, and no tissue necrosis was found throughout the animal studies.

The ideal bioelastomer-based implant materials not only should be soft and elastic, possess suitable mechanical properties to match with the target tissue or organ, and be biocompatible to minimize adverse biological responses but also should be amenable to surface modification with bioactive molecules such as growth factors, cell-binding peptides, or signaling molecules to positively and selectively recognize, interact with, support, and promote the appropriate cellular responses, thus accelerating the regeneration of the target tissue or organ [59–63]. Although most CABEs possess some –COOH and –OH groups on their surface [16–18], these groups are not effective enough, especially for surface bioconjugation. As one of the most effective surface/interface reactions, click chemistry [64–69], especially copper-free click chemistry [70–73] that is more applicable in biorelated systems, endows a promising way for surface conjugation. Therefore, click chemistry was introduced into CABE system and served as both an additional cross-linking mechanism and a surface bioconjugation tool. By introducing azide and alkyne functional diols in POC syntheses, azide (POC-N3) and alkyne (POC-AI)-functionalized POC prepolymers were synthesized (Table 16.1 and Figure 16.3). To fully utilize the thermal postesterification process of –COOH and –OH groups on CABE prepolymers and avoid the use of copper catalyst [74,75], POC-N3 and POC-AI prepolymers were mixed together and heated at 100°C for designated times. Accompanied with thermal esterification between –COOH and –OH groups, thermal click reactions between azide and alkyne groups proceeded simultaneously; thus, dual cross-linked (esterification and thermal click reaction) POC-click
elastomers were formed in a one-step postpolymerization process rather than a two-step process [24]. The DCM and the rigid property of triazole rings resulting from the click reaction [67] confer POC-click with significantly enhanced mechanical strength. The tensile strength of POC-click can reach as high as 40 MPa (Table 16.2), which is comparable to or even higher than that of CUPE (see Table 16.2, will be discussed in the following paragraphs), while the degradation time of POC-click has no significant increase as CUPE does when comparing with POC (Table 16.2). The degradation profile of POC-click performed a “first slow then fast” pattern, which is sometimes more favorable in bioengineering applications for the good maintenance of mechanical properties before the fulfillment of bioregeneration process and fast degradation after. Furthermore, the residual azide groups on the surface of POC-click bioelastomers paved the way for convenient and high-yield surface conjugation of bioactive molecules through strain-promoted alkyne-azide cycloaddition (SPAAC), a copper-free click reaction.

16.2.2.3 Pendent Group Modification

As a multifunctional monomer, citric acid contains three carboxyl groups and one hydroxyl group. Even after being synthesized into prepolymer with different diols, there are still some −COOH and −OH groups preserved for pendent group modifications (concurrent with or after polycondensation process) with either −NH₂ or −OH-containing molecules (react with −COOH groups) or −COOH, −COCl, or −NCO-containing molecules (react with −OH groups). When an excess amount of diol was used to react with citric acid, hydroxyl-terminated POC or other CABEs’ prepolymers were obtained that can react with diisocyanate molecules such as HDI to extend the polymer chains (such as CUPE [19], CUBPLP [47], and CUPOMC [57]). This is referred to as chain extension reaction and will be discussed in Section 16.2.2.4. In this section, we will discuss the pendent modification of poly(diol citrates) with amino acids, L-3,4-dihydroxyphenylalanine (L-DOPA) or dopamine, and other amine-containing molecules (Figure 16.3). Pendent group modification of poly(diol citrates) brought some remarkable and intriguing properties such as photoluminescent (BPLP) and bioadhesive (iCMBA) properties to the resulting polymers.

16.2.2.3.1 Development of BPLPs

Biodegradable fluorescent polymers have attracted a lot of attention in targeting drug delivery, bioimaging, and tissue engineering. The most reported fluorescent biodegradable polymers are made by either conjugating or encapsulating organic dyes or quantum dots (QDs) with biodegradable polymers [20,21,66,75–80]. However, the low photobleaching resistance of organic dyes or the unacceptable toxicity of inorganic QDs largely limited the applications of these fluorescent biodegradable polymers. Therefore, developing fully biodegradable and biocompatible fluorescent polymer is urgently needed.

Recently, based on pure natural citric acid and all 20 essential α-amino acids as well as biocompatible aliphatic diols, Yang et al. developed a family of novel aliphatic BPLPs, referred to as BPLPs [20,21]. Unlike nondegradable aromatic fluorescent polymers or organic dyes commonly used in the lighting industry and bioimaging applications, BPLPs are aliphatic biodegradable oligomers synthesized from biocompatible and biodegradable monomers through a convenient and cost-effective thermal polycondensation process. Although whether (L-) α-amino acids contribute to the formation of BPLP backbones or not is still unclear, we conjecture that the synthesis of BPLPs is a kind of pendent modification of poly(diol citrate) concurrent with the polycondensation process (Figure 16.4). Briefly, BPLPs were synthesized by reacting one of the 20 natural (L-) α-amino acids with citric acid and diols (aliphatic diols such as OD or macrodiols such as PEG) at 140 °C for a certain time, which depends on the diol used and the feeding ratios of amino acid over other monomers.

Among BPLPs, BPLP-cysteine (BPLP-Cys, using L-cysteine) and BPLP-serine (BPLP-Ser, using L-serine) display the best fluorescent properties in terms of fluorescence intensity and quantum yield. The quantum yield of BPLP-Cys can be as high as 62.3% (Figure 16.5) [20].

![FIGURE 16.4 Pendent (concurrent with or after polycondensation process) modification of citrate-based biodegradable elastomers (CABEs).](image-url)
The fluorescence emission wavelength can be tuned from blue to red by using different amino acids in BPLP syntheses. BPLPs in different modalities (polymer solution, film, scaffold, and nanoparticles) have all shown strong fluorescence. Due to pendent −COOH and −OH groups mostly provided by citric acid, BPLPs can be further polymerized into elastomeric cross-linked BPLP (CBPLP). After cross-linking, CBPLPs exhibited improved mechanical strengths compared to POC (Table 16.2) [20].

16.2.2.3.2 Development of iCMBA

In the past two decades, bioadhesives, tissue sealants, and hemostatic agents have been widely used in clinical surgical practices for blood loss control and wound healing [81]. Although the existing tissue bioadhesives like fibrin glues, cyanoacrylate tissue adhesives, gelatin glues, and polyurethane adhesives are commercially available and have been used in many clinical applications [22,23,82–87], these bioadhesives were largely limited by their toxicity or poor mechanical and adhesive strength, especially in wet conditions. In recent years, inspired by the high underwater adhesive strength of some maritime creatures, such as blue mussel Mytilus edulis [88], researchers developed a new family of adhesives based on the catechol-containing amino acid called L-3,4-dihydroxyphenylalanine (L-DOPA), a posttranslational hydroxylation of tyrosine found in the structure of secreted mussel adhesive foot protein, which was discovered to be the reason for the strong adhesion ability of mussel in aqueous conditions [88–90]. Under oxidizing or alkaline conditions, DOPA is believed to promote cross-linking reactions through the oxidation of catechol hydroxyl groups to ortho-quinone, which subsequently triggers intermolecular cross-linking. The oxidized DOPA was found to also contribute to the strong adhesion ability to biological surfaces, through the formation of covalent bonds with available nucleophilic groups on these surfaces such as −NH₂, −SH, −OH, and −COOH groups [89,91–94].

By introducing L-DOPA or its analog dopamine into poly[poly(ethylene glycol) citrate] (PEGC), Yang et al. developed a novel family of biodegradable and strong wet-tissue adhesives, referred to as injectable citrate-based mussel-inspired tissue bioadhesives (iCMBAs) [22,23]. iCMBAs were synthesized using a facile and cost-effective polycondensation reaction of FDA-approved and inexpensive monomers including citric acid and PEG, concurrent with the pendent modification of dopamine/L-DOPA in a one-pot synthesis process (Table 16.1 and Figure 16.4) [22]. The introduction of catechol group into the structure of iCMBA prepolymer conferred them with strong adhesion to wet-tissue surfaces as well as cross-linking capacity for bulk cohesive strength. The existence of hydrolytically degradable ester bonds formed by polycondensation in the backbone of iCMBA prepolymer made this family of adhesives readily biodegradable, which makes iCMBA significantly superior over other mussel-inspired bioadhesives, such as multiaxial PEG-based ones, which are essentially nondegradable [95]. In addition, the properties of iCMBAs, such as mechanical properties as well as degradation rate, could be tuned by adjusting the molecular weight of PEG and the feeding ratio of dopamine/L-DOPA [22]. iCMBAs exhibited excellent in vitro and in vivo cytocompatibility. In vivo studies of iCMBA did not induce any significant inflammatory responses, and it was degraded and absorbed completely in rats within 28 days [22].

16.2.2.3.3 Other CABE Development

As mentioned earlier, NO-releasing POC-DA elastomers were developed in Dr. Ameer’s group. They were shown to release NO for 3 days in vitro and significantly reduce neointimal hyperplasia when implanted as a perivascular wrap in a rat carotid artery injury model [43–45]. Although promising, POC-DA still suffered from a long curing time (often more than 3 days). By introducing double bonds through post-pendent group modification
of poly(diol citrate) prepolymers with 2-aminoethyl methacrylate, Wang et al. developed a family of photo-croslinkable poly(diol citrate) (see Table 16.1 and Figure 16.3). After blending with miscible diazeniumdiolated NO donors followed by in situ and fast UV cross-linking, a long-lasting NO-releasing elastomer was formed [41]. The NO-containing polymer network could be cured within 3 min under UV light and could release NO for at least 2 weeks, which is much longer than that of previous POC-DA elastomers (released NO for only 3 days). This may be attributed to the in situ encapsulation of miscible diazeniumdiolated NO donors in the fast UV-curing process of the elastomers rather than NO-adsorbing after elastomer formation in the case of POC-DA. These materials may be very useful in cardiovascular applications.

Polyol monomer like xylitol was also used to compose biodegradable polymer poly(xylitol citrate) (PXC) with citric acid by a simple thermal polycondensation. The abundant pendent hydroxyl groups on PXC, mostly introduced by xylitol, were used to react with methacrylic anhydride to obtain double bond functional PXC (PXCma), which can be formed into a bioelastomer network by photo-cross-linking [96].

16.2.2.4 Chain Extension of CABEs

Chain extension often refers to the postmodification of one polymer by using a chain extender (such as diisocyanate) or initiating a second polymerization by the polymer itself. In CABEs, the syntheses of CUPE and BPLPL copolymers such as BPLP-PLA are classified as chain extension reactions and will be discussed in the following sections.

16.2.2.4.1 Cross-Linked Urethane-Doped Polyester

Diisocyanate is often used in the chain extension reactions of biopolymers such as PLA, PCL, and their copolymers [97–101]. The combination of hard segment and soft segment may confer the resulting polyurethanes with shape-memory property [100,101]. Polyurethane is an important type of elastomeric polymer for biomedical applications [1,9,11]. Chain extension or cross-linking by diisocyanate can be adapted to many –OH-terminated or –OH-containing polymers or prepolymers [102]. The convenience of the urethane chemistry has made it into a very popular way of polymer chain extension method in biomaterial designs.

Although a lot of CABEs, such as POC, BPLP, and POMC, have shown great potential for tissue engineering, however, they are weak in mechanical strength especially when they were molded into porous scaffolds and used in vivo at a wet state. For example, POC underwent a significant loss in peak stress from 2.93 ± 0.09 MPa (film) to 0.3 ± 0.1 MPa (scaffold) when molded into porous scaffolds [103]. To obtain stronger elastomer, Dey et al. took advantage of excellent elasticity of cross-linked polyester network and the strong mechanical strength of polyurethanes and developed a new family of CUPE based on POC [19]. CUPE prepolymers were synthesized from diluted pre-POC solution in 1,4-dioxane (3 wt%), which was reacted with various molar ratios of HDI to pre-POC (0.9, 1.2, and 1.5) at 55 °C with continuous stirring for several days, until the characteristic absorbent peak at 2267 cm⁻¹ of isocyanate (NCO) group in FTIR spectra disappeared (Figure 16.6). Similar to POC, some pendent carboxyl and hydroxyl groups originally from citric acid were preserved on CUPE prepolymers. This made them still cross-linkable by conducting a postpolymerization process. The cross-linking density between polymer chains can be adjusted by controlling the postpolymerization temperature and duration. The doped urethane bonds in the polyester served as a chain extender and enhanced hydrogen bonding within the network to produce elastomers with tensile strength as high as 41.07 ± 6.85 MPa while the elongation at break was still maintained at over 200% [19]. Amazingly, a simple urethane-doping chemical modification on POC resulted in an elastomer with almost 30 times higher tensile strength from 1.54 Ma of POC (80 °C, 4 days) to 44.98 MPa of CUPE1.2 (80 °C, 3 days).

CUPE polymers could be tuned to meet a variety of needs by varying the length of diols used in pre-POC synthesis, the feeding ratios of HDI over pre-POC, and postpolymerization conditions [104]. Preliminary cytompatibility results showed that 3T3 fibroblast and SMCs were able to adhere and proliferate on a CUPE surface with a growth rate comparable to that on a PLLA control. Unlike previous POC, the higher molecular weights and nonsticky nature of CUPE prepolymers allow the use of other scaffold fabrication techniques such as thermally induced phase separation technique (TIPS) and electrospinning [19] in addition to salt-leaching method. The soft and elastic three-dimensional porous scaffold made by TIPS technology showed a highly porous structure, and the thin scaffold sheets allowed for even seeding, growth, and distribution of 3T3 fibroblasts.
Stimulated by the success of CUPE, other urethane-doped CABEs were also developed in our Lab, including urethane-doped BPLP (UBPLP) and its cross-linked form (CUBPLP) [48], as well as photo-cross-linkable urethane-doped polyester elastomers based on POMC (CUPOMC) [47] (Table 16.1 and Figure 16.4). Based on the BPLPs, Yi et al. developed a new type of urethane-doped BPLP (UBPLP) by chain extension reaction of BPLP using HDI. Inherited from BPLPs, UBPLPs demonstrated strong fluorescence and excellent cytocompatibility. Cross-linked UBPLPs (CUBPLPs) showed soft and elastic but strong mechanical properties, in which the tensile strength can reach 49.41 ± 6.17 MPa with a corresponding elongation at break of 334.87% ± 26.31%. Even after being molded into porous triphasic vascular scaffolds, CUBPLP showed strong mechanical properties with a burst pressure of 769.33 ± 70.88 mmHg and suture retention strength of 1.79 ± 0.11N. Without cross-linking, UBPLP can be fabricated into stable and photoluminescent nanoparticles by a facile nanoprecipitation method. With a quantum yield as high as 38.65%, both CUBPLP triphasic scaffold and UBPLP nanoparticles could be noninvasively detected in vivo. UBPLPs represent another innovation in fluorescent biomaterial design and may offer great potential in advancing the field of tissue engineering and drug delivery where bioimaging has gained increasing interest. Besides UBPLPs and their cross-linked form CUBPLPs, another urethane-doped CABE based on photo-cross-linkable POMC (CUPOMC) was also developed in our lab. CUPOMC possesses tunable mechanical properties and degradation profiles. CUPOMCs could be either thermo-cross-linked or UV cross-linked providing fabrication flexibility for these polymers and fostering more convenient applications to various biomedical areas than previously developed thermal-curable biodegradable elastomers. Preliminary cell culture studies in vitro demonstrate that CUPOMCs could be good candidate materials for cell delivery carriers. The development of CUPOMCs expanded the choices of available biodegradable elastomers for broad biomedical applications like soft tissue engineering.

16.2.2.4.2 Biodegradable Photoluminescent Polylactones

The development of BPLP not only brought new applications for CABEs, especially in bioimaging and targeting drug delivery areas, but also sparked the innovation on developing biodegradable photoluminescent aliphatic polylactone biomaterials. Fluorescence imaging has gained increasing attention in drug delivery and tissue engineering where biodegradable polymers are usually conjugated with photobleaching organic dyes or toxic QDs. Given that BPLP exhibited excellent photostability and biocompatibility, the authors’ group has started using BPLP to initiate the ROP of lactones for biodegradable photoluminescent polylactone (BPLPL) syntheses such as BPLPL-PLA. Developing biodegradable polylactone biomaterials represents new innovation on already widely used polylactone materials.

16.3 APPLICATIONS OF CABEs

16.3.1 Cardiovascular Applications

Cardiovascular disease remains the leading cause of morbidity and mortality in the world with more than 54% of the deaths in the United States [105]. For many patients, suitable vein autografts are not always available [106] necessitating the use of synthetic grafts. Although synthetic grafts such as polyethylene terephthalate (PET) grafts and expanded polytetrafluoroethylene (ePTFE) grafts have demonstrated adequate performance when replacing large blood vessels (diameter >6 mm) [107], they also reduced long-term patency compared to autografts because of thrombosis, restenosis, and calcium deposition, especially when used in small-diameter blood vessels [108, 109]. Additionally, PET and ePTFE are inert materials and nondegradable. PET and ePTFE are rigid and display mismatched compliance with the native arteries, which increases thrombosis and neointimal hyperplasia, the main causes of graft failure. Thus, biodegradable elastomers have been developed to match the soft and elastic properties of blood vessels, provide suitable biocompatibility, and allow functionalization to mediate the biological responses of native tissues [1, 2, 5, 7–12]. Among biodegradable elastomers, CABEs emerge as an important type of materials for biomedical applications. Herein, we will discuss the applications of CABEs in cardiovascular tissue engineering.

16.3.1.1 Vascular Scaffold Designs

POC has been studied for a wide range of tissue engineering applications, especially soft tissue engineering applications such as blood vessels because of the soft, elastic, and tunable mechanical properties. To address the mechanical, compartmental, and microarchitectural requirement of small blood vessels, Yang et al. developed an implantable tubular biphasic POC scaffold composed of concentric nonporous and porous layers to mimic the intimal and medial vessel layers (Figure 16.7) [18, 103, 110]. The inside nonporous phase provides a continuous surface for EC adhesion, proliferation, and differentiation, as well as mechanical strength and elasticity. The outside porous phase serves as a three-dimensional layer to facilitate the expansion and maturation of SMCs and the establishment of an appropriate ECM to constitute the media. The mechanical properties of the whole construct were comparable to that of native arteries and veins. Cell culture experiment results using human aortic ECs and SMCs, along with the minimal
foreign body response found when subcutaneously implanted in rats, supported that POC might serve as a candidate material for small-diameter blood vessel tissue engineering [18,103,110].

Although POC is biocompatible, soft, and elastic, the mechanical properties of POC are relatively weak. After chain extension using HDI, CUPE possesses much better mechanical properties with a tensile strength up to 40 MPa (for CUPE1.8 film) [19]. Even after being molded into similar tubular biphasic scaffolds as POC, the tensile strength of CUPE biphasic scaffold was still 5 MPa with an elongation still higher than 150% [111]. The burst pressure of CUPE nonporous tube were much higher than corresponding POC scaffolds polymerized under similar conditions. The burst pressure of CUPE biphasic scaffold was found to increase from about 1600 to 2600 mmHg with the thickness of nonporous CUPE phase increasing from 160 to 384 μm. This result suggested that by simply varying the thickness of the inner nonporous layer, the burst pressure of the vessels being replaced [111]. Thin (~200 μm), strong, elastic, and porous CUPE scaffold sheets that are bonded together using a layer-by-layer approach were also developed by Tran et al. [112]. CUPE thin sheets allowed for even cell distribution and can be bonded together through ECM secreted by cells in each sheet layers. The layer-by-layer technology was considered as an alternative way to construct complex tissue scaffold such as blood vessel scaffolds.

Similar to CUPE, fluorescent CUBPLPs were also used to fabricate triphasic small-diameter vascular grafts by Zhang and Yang to replicate the stratified architecture of native vessels [48]. Different to biphasic scaffolds made by POC and CUPE [18,103,111], triphasic scaffolds were composed of a rough inner lumen surface, middle layer of porous scaffold with pore size of 1-20 μm, and outer layer of porous scaffold with pore size of 150-250 μm [48]. A rough surface is more favorable for ECs [113], and pore size of 1-20 μm is preferable for the compartmentalization of ECs and SMCs simulating the elastic lamina in native vessels [103]. Pore sizes of 150-250 μm are ideal for the growth of fibroblast and the formation of ECM [114]. The burst pressure and suture retention of CUBPLP triphasic scaffold could reach 800 mmHg and 1.79 N, respectively, which meet the requirements for off-the-shelf surgical implantation. By using CUBPLP, the scaffolds also possess in vivo detectable fluorescent properties, which will be very useful for the applications where fluorescence imaging may play an important role.

Although CUPE and other urethane-doped CABEs possess much higher mechanical strengths compared to POC, the applications of them were limited by the time-consuming synthesis process, low polymer concentration due to their low solubility in some common solvents, and prolonged degradation time. To address these problems, POC-click elastomer was developed by introducing click moieties containing diols and the usage of thermal click reaction (Table 16.1 and Figure 16.3). Although the structure of POC-click elastomer contains triazole rings, which are difficult to degrade, these...
triazole rings are covalently bonded with the polymer chain backbone through hydrolyzable ester bonds just like POC. POC-click elastomers showed a “first slow then fast” degradation profile and can be totally degraded within 34 weeks, which is nearly the same rate as POC and much shorter than that of CUPE cross-linked under the same condition (100°C, 3 days) (Table 16.2). After being molded into triphasic scaffold similar to CUBPLP (112), the mechanical properties of POC-click triphasic scaffold were better than that of triphasic POC and CUPE scaffolds (data not published) for vascular applications. In addition to the superior mechanical properties of the POC-click elastomers, the residual azide groups on the surface of POC-click scaffold enabled a convenient conjugation of bioactive molecules on the polymers, which makes POC-click polymer scaffolds more amenable for biomedical applications.

16.3.1.2 Biofunctionalization of CABE Vascular Grafts

Cell-binding peptides such as cyclic RGD, RGD and their derivatives, p15, and growth factors such as REDV and VAPG have been widely used to enhance vascular graft endothelialization [59–63]. Among them, p15 is a collagen mimetic peptide that could significantly promote ECs adhesion and proliferation but are less effective for SMC adhesion and proliferation. In our recent work, p15 was conveniently conjugated onto the surface of POC-click films or scaffolds through SPAAC—a copper-free click reaction. The p15-conjugated POC-click films showed much better HUVEC adhesion and proliferation properties compared to untreated POC-click films.

As mentioned earlier, NO plays an important role in cardiovascular application in prevention of SMC proliferation and stimulation of EC proliferation. Two different kinds of NO-releasing poly(diol citrate) elastomers, NO-releasing POC- and PDDC-DA (Table 16.1, Figure 16.8a), were developed by introducing NO-binding diol into pre-poly(diol citrates) and NO treatment after thermo-cross-linking [43–45]. Long-lasting NO-releasing poly(diol citrate) elastomers were developed by blending miscible diazeniumdiolated NO donors with photo-cross-linkable poly(diol citrates) followed by photo-cross-linking (Table 16.1 and Figure 16.8b) [41]. NO-releasing POC-DA was shown to release NO for 3 days in vitro and significantly reduce neointimal hyperplasia when implanted in a rat carotid artery injury model as a perivascular wrap. By using miscible diazeniumdiolated NO donor blended with rapidly photocurable methacrylated poly(diol citrates) (MA-POC or MA-PDDC), a longer duration of NO release for at least 1 week was achieved. The NO-releasing elastomers may be useful in the prevention of restenosis and thrombosis after vascular interventions such as balloon angioplasty, stent deployment, bypass grafting, and other blood-contacting surface of implant devices.

16.3.1.3 The Use of CABEs As a Vascular Graft Coating

ePTFE have been used in large-diameter (>6 mm inner diameter) blood vessel application. Their use in small-diameter blood vessels has been limited due to early graft occlusion from thrombosis. Yang et al. has demonstrated that the modification of ePTFE vascular grafts with POC, via a simple spin-shearing method followed by in situ interfacial
 thermo-cross-linking, can improve the biocompatibility of ePTFE without affecting its graft compliance [17]. The POC interface conferred to the ePTFE grafts increased hydrophilicity, reduced thrombogenicity, facilitated graft endothelialization in vitro, and reduced macrophage infiltration in vivo. POC-coated ePTFE grafts were also implanted into the iliac artery in a porcine model. These grafts were found to dramatically inhibit platelet adhesion, aggregation, and activation compared to the ePTFE graft controls. This hemocompatibility may be explained by the anticoagulant and calcium-chelating properties of citrate, one of the components of POC, and the preservation of the fibril and node network of ePTFE. Moreover, POC supports the differentiation of peripheral progenitor cell into ECs, a model further characterized by Allen et al. [110]. Overall, POC was supported from the data to be used as a nonthrombogenic and biocompatible versatile coating, which can be widely used to improve blood-contacting devices.

16.3.2 Orthopedic Applications

16.3.2.1 Bone Tissue Engineering

Bone is a distinctive and dynamic tissue of the skeletal system that continually undergoes a coupled remodeling process defined by osteoclast bone resorption followed by new bone formation produced by osteoblasts [115]. Despite the capacity of the human skeletal system to rejuvenate itself, over 2.2 million bone-grafting procedures are performed annually worldwide to treat orthopedic pathological conditions such as fractures, tumor resections, and osteoporosis [116]. In fact, the bone has become the second most transplanted tissue in the world, and over 28 billion dollars per year was spent in total orthopedic medical costs, which are projected to significantly increase for the next decades with the demands of an aging population [117]. Autografts and allografts remain the gold standard for graft materials, but are unable to fulfill the increasing clinical demands for an effective off-the-shelf bone graft due to their limited availability, complications from donor site morbidity, and possible risk of pathogen transmission [118–120]. Synthetic counterparts are not impeded by these issues but are limited by their inability to provide mechanical compliance and mimic the native composition of bone tissue, which is composed of a 70% carbonated HA embedded in a type I collagen matrix [121]. While the incorporation of ceramic particles has been shown to improve the mechanical properties of and bone formation onto synthetic polymers, a limit in the amount of total ceramic that can be incorporated into the composite, significant inflammatory responses, long degradation times, and poor bone integration is a major roadblock for these materials [122–125]. For example, PLA-hydroxyapatite (PLLA-HA) composites can only incorporate a maximum of up to 30 wt% HA to avoid brittleness and can take up to 5 years to fully degrade, which leads to insufficient bone regeneration, significant inflammation, and poor mechanical integration. Therefore, the search for a suitable bone tissue-engineered substitute that can match the native composition of bone, provide adequate mechanical properties, minimize inflammatory responses, quickly induce bone regeneration, and fully integrate with the surrounding tissue within a year of implantation remains a significant challenge.

Citrate is traditionally known as an intermediate of the Krebs cycle (TCA cycle) for eukaryotic energy production. Previous studies have shown that a majority of the body’s citrate content is located in skeletal tissues, and plays a large role in metabolism, calcium chelation, HA formation, and regulation of the thickness of bone apatite structure [30–33]. More recently, a careful solid-state nuclear magnetic resonance (NMR) study revealed that the surface of apatite nanocrystals is abundantly studded with strongly bound citrate molecules [33]. Citrate not only functions as a dissolved calcium-solubilizing agent but also is a strongly bound and integral part of the bone nanocomposite. Citrate also has a unique and innate ability to induce HA formation in SBF [34]. Surprisingly, the role of citrate is rarely mentioned in the literature related to bone development in the past 30 years including those on bone tissue engineering. The natural existence of citrate in bone and its importance in bone physiology hints that citrate should be considered in orthopedic biomaterial and scaffold design.

16.3.2.1.1 Prefabricated Implantable Bone CABE/HA Composites

In 2006, Qiu et al. first reported the development of a bioceramic-elastomer composite based on the citrate-based POC and HA (POC-HA) [35]. It was believed that the pendant carboxyl groups of POC could potentially aid in calcium chelation to facilitate polymer/HA interaction [34, 37, 126, 127]. This improved calcium chelation resulting in POC-HA’s ability to incorporate up to 65 wt% HA in POC-HA composites, which is not possible for traditional biodegradable lactide-based polymers (≤30 wt% HA). The enhanced amount of incorporated bioactive ceramic maximized the osteointegration of the material while maintaining suitable degradability [35]. The POC-HA composite successfully induced surface mineralization after 15 days of incubation in SBF and displayed favorable primary human osteoblast cell adhesion in vitro. POC-HA disks implanted into rat medial femoral condyles displayed no chronic inflammation and were well integrated with the surrounding cartilage along with mineralized chondrocytes located immediately adjacent to the implant after 6 weeks of implantation, which suggests healthy and normal bone remodeling. The composites also displayed good processability, giving them the potential to be machined and molded into bone screws for bone fixation applications [35].
Although POC-HA displayed excellent biocompatibility, osteoconductivity, and osteointegration in vivo, none of the investigated formulations containing other polymer/HA composites could provide sufficient mechanical strength to match that of human cortical bone [123–125,128]. To improve upon the mechanical strength of the previously reported POC-HA composites, we have recently developed a new generation of citrate-based polymer blend HA composite (CBPBHA) based on POC, CUPE [19,129], and HA. Both CUPE and POC are citrate-based cross-linkable polyester elastomers where CUPE is a urethane-doped version of POC. Although the urethane (urea)-doping chemistry sacrifices available –OH and –COOH groups in the final polymers due to the reactions between diisocyanates (like HDI) with –OH and that with –COOH, CUPE is almost 30 times stronger than POC [19,129]. We initially expected to make stronger bone composite materials using CUPE alone with HA compared to POC-HA; however, the reduced available free –COOH and –OH in CUPE may affect the polymer’s ability to chelate with calcium-containing HA particles, thus influencing the material mechanical properties [37]. Therefore, our strategy for improving the mechanical strength of POC-HA was to fabricate polymer blend HA composites by blending the –COOH-rich POC with the mechanically strong CUPE to composite with HA in hopes of achieving optimal polymer/HA interactions and enhanced mechanical properties.

CBPBHA networks composed of 90% CUPE and 10% POC produced materials with a compressive strength of 116.23 ± 5.37 MPa, which falls within the range of human cortical bone (100–230 MPa) and is a significant improvement over POC-HA composites. CBPBHA produced in vitro mineralization and increased C2C12 osteosarcoma (OSX) gene and alkaline phosphatase (ALP) gene expression in vitro. After 6-week implantation in a rabbit lateral femoral condyle defect model, CBPBHA composites elicited minimal fibrous tissue encapsulation and were well integrated with the surrounding bone tissues. The promising results in the preceding text prompted an investigation on the role of citrate supplementation in culture medium for stem cell and osteoblast culture. The results showed that citrate media supplementation in vitro accelerated both mesenchymal stem cell and MG-63 osteoblast phenotype progression and promoted calcified matrix formation by bone marrow stromal cells. Future studies will focus on further understanding the role of citrate in culture medium for bone stem cell differentiation and optimize the citrate contents in polymer/HA composites for orthopedic applications. CBPBHA composites represent a new generation of bone biomaterials that address the critical issues such as inflammation, osteoconductivity, and osteointegration.

16.3.2.1.2 Injectable Bone Composites

To expand the application of CABEs to bone tissue engineering, Gyawali et al. set out to develop an injectable, porous, and strong citric acid-based composite [38], which could be used as a delivery vehicle for cells and drugs in bone tissue engineering applications. PEGMC was combined with various percentages of HA to create PEGMC-HA composites with the help of PEG diacrylate (PEGDA) as an additional cross-linker and bicarbonates that can react with the pendent carboxylic acid groups on PEGMC to form CO₂ gas, which then forms pores to create an injectable porous bone material. The degradation profiles for PEGMC-HA networks showed increasing mass loss with lower concentrations of incorporated HA. The mechanical compressive tests showed that the PEGMC-HA networks were elastic and achieved complete recovery without any permanent deformation under cyclic load in both hydrated and dry conditions. Human fetal osteoblasts (hFOB 1.19) encapsulated in PEGMC-HA hydrogel composites were viable and functional over a 21-day culture. ECM production was measured by the total ALP and calcium content. The results show that both increased after 3 weeks of culture. Scanning electron microscopy (SEM) and energy dispersive X-ray analysis of the constructs showed that the PEGMC-HA films were covered with small cauliflower-shaped mineralized structures after 7 days of incubation in SBF. The presence of pendent groups in the PEGMC polymer allows for easy modification through the bioconjugation of biological molecules such as type I bovine collagen and resulted in enhanced cellular attachment and proliferation at the end of day 7 of subculture. An ex vivo study on a porcine femoral head demonstrated that PEGMC-HA is a potentially promising injectable biodegradable bone material for the treatment of osteonecrosis of the femoral head. Unlike many injectable systems, PEGMC-HA composites could also be fabricated into highly porous architectures from gas-foaming techniques in situ after injection into the implant site and can also be used to deliver therapeutics, as shown in the controlled release profiles using bovine serum albumin (BSA) as a model drug. Thus, unlike previous injectable materials, PEGMC-HA composites show great potential as an injectable, porous, and strong cell/drug delivery system for orthopedic applications.

16.3.2.2 Cartilage Tissue Engineering

Osteoarthritis is a joint disease that affects more than 20 million people in the United States and is characterized by articular cartilage degeneration, which ultimately leads to complete loss of cartilage tissue at the joint surface. For professional athletes and those over the age of 65, osteoarthritis is one of the most frequent causes of physical disability [130]. Due to the very limited capacity for cartilage
regeneration and the varying success of techniques to repair damaged cartilage such as mosaicplasty and autologous chondrocyte implantation, the treatment of osteoarthritis and cartilage injuries has been a major challenge to orthopedic research [131–133]. Recent efforts in tissue engineering have focused on creating cartilaginous tissues in vitro for subsequent transplantation. However, cells grown in vitro under static conditions may not display the normal physiological function as cells located in the dynamic in vivo environment. In attempts to increase the quality of engineered constructs, cell-seeded scaffolds are often subjected to external mechanical stimuli in the form of cyclic compression and shear forces to mimic natural joint movement, which have been shown to be important in maintaining the homeostasis of cartilage glycosaminoglycan (GAG) and collagen formation [134,135]. Unfortunately, currently used materials for scaffolds in chondrocyte mechanical regimens have limited strength and elasticity and are prone to elastic deformation after cyclic compressive strains [136–138].

In 2006, Kang et al. published a study to address the limitations of the previous materials and assessed whether POC would be a suitable material to engineer elastomeric scaffolds for cartilage tissue engineering [139]. In this study, the authors fabricated porous POC scaffolds via a salt-leaching technique and characterized the POC scaffolds’ ability to support chondrocyte attachment, proliferation, matrix synthesis, and cell differentiation. POC scaffolds were compared to 2% agarose, 4% alginate, nonwoven PGA, and nonwoven PLGA meshes in terms of recovery ratio. Of all the materials tested, only POC was able to display a 100% recovery ratio. The GAG and collagen content of chondrocytes cultured after 28 days on POC scaffolds was 36% and 26%, respectively, of those values found in bovine knee cartilage explants. Histology and immunohistochemistry evaluations confirmed that chondrocytes were able to attach to the pore walls within the scaffold, maintain their cell phenotype, and form a cartilaginous tissue during the 28 days of culture [139]. In summary, POC’s elastomeric qualities showed potential as a biodegradable scaffold, which long-term cyclic and shear strains can be applied to in vitro to increase the GAG and collagen content of tissue-engineered cartilage. In addition, the elastomeric properties of POC constructs may be better suited to appropriately transfer local compression and shearing forces produced by joint mobilization to enhance in vivo cartilage regeneration.

In 2010, Jeong et al. published a study to compare the performance of chondrocyte-seeded scaffolds made of similar architectures to determine the influence of material on in vitro cartilage regeneration [140]. Three-dimensional scaffolds of the same design were fabricated using PCL, poly(glycerol sebacate) (PGS), or POC, and tissue regeneration was characterized by cell phenotype, cellular proliferation and differentiation, and matrix production. The studies showed that PGS was the least favorable material for cartilage regeneration as determined by the high dedifferentiation (Col11), hypertrophic mRNA expression (Col10), and high matrix degradation (MMP13 and MMP3) results. Although a majority of the cells seeded on PCL remained on the scaffold periphery, the PCL scaffolds showed moderate cellular activity but still caused dedifferentiation (Col1) of chondrocytes within the scaffold. Interestingly, POC provided the best support for cartilage regeneration with the highest tissue ingrowth (cell penetration), matrix production, relative mRNA expressions for chondrocyte differentiation (Col2/Col1), and DNA and sGAG content after 4 weeks of culture. This study demonstrates that POC can outperform other biodegradable elastomers for cartilage tissue engineering and warrants further in vivo studies.

### 16.3.3 Bioimaging and Drug Delivery

BPLPs are the first aliphatic BPLPs reported, which was developed in Dr. Yang’s Lab based on biocompatible monomers, including citric acid and amino acids [20]. The BPLPs were synthesized simply by a polycondensation reaction of diol, citric acid, and α-amino acid [20,48]. The synthesis route is very versatile, as both organic solvent-soluble and water-soluble BPLPs (WBPLP) could be prepared by using OD and PEG, respectively. All the 20 natural amino acids and some unnatural amino acids have been used to create completely degradable polymers with intrinsic and tunable fluorescence. The backbone of BPLPs consists of ester bonds, which can be hydrolyzed in physiological conditions, and both BPLP and its degradation products are biocompatible since all the three monomers are natural or FDA-approved. The unique characteristics of BPLPs eliminated the long-term concern of fluorescent dyes and inorganic QDs, as well as their conjugation difficulties [21].

Most notably, BPLPs exhibited extraordinary fluorescence properties [20,141]. First, using different amino acids, BPLPs can emit fluorescent light from blue to near-infrared range (up to 825 nm for BPLP with α-methyl serine). Thus, BPLPs are available for both in vitro and in vivo imaging applications. Second, unlike traditional organic dyes, such as rhodamine B, BPLPs displayed less photobleaching behavior. After 3 h continuous UV excitation, BPLP-Cys only lost less than 2% of fluorescence intensity, which is significantly less than that of rhodamine B (10% loss). Third, the quantum yield of BPLPs is exceptional high. For instance, BPLP-Cys has a quantum yield of 62.3%, which is much higher than that of CdTe/ZnS QDs (20%) [142] and even higher than that of most organic dyes [143] and green fluorescent protein (GFP) [144]. These advantages of BPLPs probably result from a unique fluorescence mechanism, although it has yet to be fully understood. As Zhang et al. suggested [21], a six-member ring on the side of citrate...
backbone is the possible fluorophore of BPLPs. The long polymer chain makes the six-member ring into a planar conformation, resulting in photoluminescence without a large conjugated structure.

With the versatility of their molecular design, BPLPs have been fabricated into films, porous scaffolds, nanoparticles, micelles, and nanogels [20,21,141]. After thermocross-linking, BPLPs can be cross-linked into elastic films, which can be applied as medical implants. Porous tissue engineering scaffolds have also been prepared simply by salt-leaching after thermo-cross-linking. Subcutaneously implanted BPLP films and scaffolds can be observed by in vivo fluorescent imaging system (Figure 16.9). Recently, the fluorescence emission is a new candidate to monitor the scaffolds in vivo noninvasively [145]. BPLPs could help patients and doctors to locate the material better and later envision the erosion and performance simply by fluorescent imaging. Moreover, BPLP nanoparticles have been easily fabricated by nanoprecipitation or single/double emulsion approaches. Intratumor and intravenously injected BPLP nanoparticles were captured by in vivo fluorescent imaging system (Figure 16.9), indicating that these nanoparticles are potentially available for cancer diagnostics [141]. By adding maleic acid into the chain of WBPLP, photo-cross-linked WBPLP nanogels were also created [146]. BPLP nanoparticles and WBPLP nanogels do not need further fluorescent dye coating or conjugating to perform theranostic nanomedicine since they can emit intrinsic fluorescence and encapsulate drugs. In addition, multimodal imaging is an emerging area, since it could lead to a faster, higher-resolution, and deeper visualization by using several imaging approaches at the same time [147]. Wadajkar et al. utilized both oil-soluble BPLPs and WBPLPs to coat magnetic nanoparticles via double emulsion methods [148], the resulting core-shell nanoparticles showed dual-imaging (fluorescent imaging and MRI) capabilities after uptake by prostate cancer cells. It is also interesting that different cancer cells (PC3 and LNCaP cells) exhibited selective uptake behavior based on hydrophilicity/hydrophobicity of the particle surface.

Recently, our lab extended the BPLP class by doping the polymer with urethane segments [48]. The newly developed urethane-doped biodegradable photoluminescent polymers (UBPLPs) possess soft but strong mechanical properties that are suitable for off-the-shelf vascular grafts. Inherited from BPLPs, UBPLPs also showed strong manageable fluorescence. Unlike BPLPs, the chain-extended UBPLPs had controlled drug release profiles and better mechanical performance due to the modified polymer structure.

Overall, citrate-based photoluminescent biodegradable polymers are a novel class of polymers that are biocompatible, biodegradable, and promising for in vivo fluorescent imaging applications. BPLPs have the potential to conquer current challenges of biomedical materials in tissue engineering, drug delivery, and molecular imaging areas. Current and future research will be focused on further exploring the fluorescent mechanism and developing new polymers with better fluorescent and biological properties to meet clinical requirements. In addition, expanding the family with copolymerization, for instance, with polylactide, and creating polymer/inorganic hybrid materials for more medical applications will be another direction for the promising future of BPLPs.

16.3.4 Tissue Bioadhesive

Employing catechol chemistry, a novel family of biodegradable and strong wet-tissue adhesives, iCMBAs, was developed in our lab by introducing dopamine into the pendant groups of PEGC [22,23]. iCMBAs are superior to

![FIGURE 16.9](a) Fluorescent image of BPLP-Ser nanoparticles injected subcutaneously in a nude mouse; (b) fluorescent image of BPLP-Ser porous scaffold implanted subcutaneously in a nude mouse [21].
other PEG-based mussel-inspired bioadhesives in terms of cost-effective synthesis process and readily biodegradable properties [22]. Exhibiting excellent in vitro and in vivo cytocompatibility, iCMBAs also showed 2.5-8.0-fold stronger wet-tissue adhesion strength over clinically used fibrin glue, tunable degradability, and tissue-like elastomeric mechanical properties. Otherwise, iCMBAs were able to stop bleeding instantly and suturelessly and close the wound models (2 cm long and 0.5 cm deep) created on the backs of SD rats, which are impossible using the existing gold standard, fibrin glue, due to its weak tissue adhesion strength. Equally important, iCMBA bioadhesives facilitate wound healing and are totally biodegradable and absorbable without eliciting significant inflammatory response. All the results support that iCMBA is highly translational and could have broad impact on surgeries where surgical tissue adhesives, sealants, and hemostasis are needed.

16.3.5 Other Applications

16.3.5.1 Cell and Drug Delivery

Many tissue engineering designs using injectable, in situ forming systems have been reported with many advantages over previous methods. Unlike tissue engineering approaches that utilize prefabricated scaffolds, injectable systems have gained increasing interest as a unique method for delivering biomaterials into difficult to reach areas of the body using minimally invasive procedures. They also show the ability to fill and conform to any shape irrespective of the defect geometry. Furthermore, injectable systems can be used as fillers to reinforce the mechanical properties of diseased/injured tissue and as a competent carrier of cells and therapeutic agents such as drugs and growth factors [149–151]. Unfortunately, previous citrate-based composite designs required the use of organic solvents for material processing and harsh processing temperatures (>80°C) for network formation, rendering them unable to be used in injectable strategies.

To overcome this limitation, Gyawali et al. recently developed a new family of in situ cross-linkable citrate-based polymers that can be dissolved in water and cross-linked through free radical polymerization methods based on double bond-containing PEGMC to avoid the use of harsh processing conditions required by the previous designs. Free radical cross-linking allowed for the preservation of valuable carboxyl and hydroxyl groups derived from citric acid, which could later be used to conjugate bioactive molecules into the bulk material to control cell behavior [20]. To ensure that cells and sensitive drugs/factors could be incorporated and delivered to the injury site, PEGDA and/or acrylic acid monomer was introduced into the system to create a cross-linked network with PEGMC [27]. These new citrate-based polymers could easily be injected and cross-linked through free radical polymerization. Cyclic conditioning tests showed that PEGMC networks possess a maximum tensile strength of 638 kPa with a corresponding elongation at break of 723%. In addition, PEGMC hydrogels could be compressed up to 75% strain without permanent deformation and with negligible hysteresis. PEGMC hydrogels also supported the encapsulation and proliferation of NIH 3T3 and human dermal fibroblasts. The cytotoxicity of the degradation products was comparable to the PEGDA [27]. The pH-sensitive and controlled drug release using BSA as a drug model demonstrated that PEGMC hydrogel has the potential to be used as a suitable drug delivery vehicle. In addition, PEGMC hydrogels caused minimal inflammation and were fully degraded without chronic inflammation or changes in histology within 30 days in a rodent subcutaneous model. In conclusion, PEGMC materials were synthesized in a convenient, one-pot reaction and demonstrated excellent injectability, in situ cross-linking, adequate functionalities, elastic mechanical properties, and controlled degradability. Collectively, the development of these platform biomaterials for injectable tissue engineering adds new members of CABE family and presents unique opportunities for many biomedical applications such as drug delivery and orthopedic tissue engineering.

16.3.5.2 Endoscopic Mucosal Resection

Gastrointestinal (GI) cancers frequently occur in industrialized countries with new cases of esophageal, gastric, and colorectal cancers affecting 3.60%, 11.4%, and 30.1%, respectively, of the developed world’s population in 2008. The early stages of GI cancers (mucosal dysplasias or cancers) exhibit nonspecific symptoms, making them difficult to diagnose. This usually results in the majority of cases being diagnosed at advanced stages when bleeding, pain, or obstructions have already occurred resulting in 5-year survival rates below 30% [152,153]. Endoscopic mucosal resection (EMR) is a minimally invasive endoscopic procedure developed to remove dysplastic and malignant lesions limited to the mucosa and top part of the submucosal layer of the GI tract. Originally, EMR was accomplished by mechanical separation of the mucosal layer from the underlying muscle. However, perforation, bleeding, and damage to the muscle layer remained common occurrences. The current clinical approach to minimize EMR-associated complications is to inject a solution within the submucosal layer, which physically separates the diseased mucosal strata and provides a “safety cushion” for the subsequent underlying muscle layers [154].

Despite the recent advancements in the field, EMR has been historically limited by the available injection solution materials, which have been constrained by two design
avenues: the osmolarity and viscosity of a solution are responsible for the lifting properties of EMR materials [155]. Saline is the most commonly used in clinic and is considered the “gold standard” due to its biocompatibility, low cost, and ease of use. However, it suffers from quick dissipation and requires repeated injections resulting in surgical difficulties. In order to achieve greater lift heights with longer lift durations, higher viscosity compounds such as sodium hyaluronate and fibrinogen have been employed. Sodium hyaluronate is currently being studied as a standard for comparing new compounds owing to its relative ease of injection and high viscosity, which results in better submucosal lift. However, the high cost of naturally derived solutions such as sodium hyaluronate and fibrinogen has prevented their large-scale use [155].

Albeit significant inroads have been made in viscous EMR solutions, a paradigm shift has been made toward the development of solutions, which rely on gel formation to create improved tissue elevation heights with extended lift durations. For example, photo-cross-linkable chitosan and thermoresponsive polymers have been recently reported for EMR with great enthusiasm [156,157]. Although these materials are widely available and have shown promise in creating adequate submucosal elevation heights and prolonged lift durations, there are inherent limitations to these approaches such as complex preparatory requirements and administration difficulties. Material transformation from a liquid to a gel state using photoinitiated free radical polymerization methods requires the use of an ultraviolet light, which may be difficult in hard-to-reach areas and is not widely applicable in conjunction with the current clinically used endoscopic tools. Thermoresponsive polymers utilize a liquid to gel transition when the temperature of the system is raised toward body temperature. Although this gel formation does not require the use of an ultraviolet light, the potential for clogging inside long delivery tools is common.

To address all the concerns of the current EMR solutions, Tran and Yang reported the use of a citrate-based injectable material to aid in EMR procedures and deliver therapeutics to the resected tissue [158]. This was the first injectable drug-eluting elastomeric polymer (iDEEP) system based on PEGMC and therapeutic rebamipide, which is a mucosal protective and ulcer-healing drug that stimulates prostaglandin generation and improves the speed of ulcer healing to aid in the management of EMR-induced damages [159]. PEGMC formulations used in this study demonstrated a tunable transition from a viscous flowable liquid into a cross-linked soft biodegradable hydrogel within 5 min. iDEEP-A component (composed by dissolving PEGMC, PEGDA, and tetramethylthelyenediamine [TEMED, catalyst] in water), which is more viscous than saline, remained a viscous liquid until combined with the water-soluble iDEEP-B component (ammonium persulfate [redox initiator] in water) to produce a soft biodegradable hydrogel. Dividing the system into two separate components offers a huge advantage over previous designs in that the surgeon can precisely control the gel setting location and time, which avoids premature gelling inside the delivery tools. In addition, the utilization of a redox-initiated cross-linking mechanism does not require the use of additional equipment such as a UV light for the gel formation to occur.

The in vitro drug release profile studies of iDEEP hydrogels using rebamipide displayed an initial burst release followed by a sustained release for up to 2 weeks and could be controlled through polymer/monomer ratios. To characterize ex vivo submucosal lift, the upper third portions of porcine stomachs were injected with saline, sodium hyaluronate, and iDEEP; the results showed that all submucosal cushions created with iDEEP were more durable than those performed with saline and sodium hyaluronate at all time points. No significant changes in iDEEP cushion height were observed after 5 min due to gel formation. To evaluate the efficacy of iDEEP, standard EMR procedures were performed in vivo using a live porcine stomach model. iDEEP-A was easily injected using standard delivery tools and was able to create an adequate submucosal cushion. Using the same injection needle, an iDEEP-B solution was then injected into the same location without any clogging inside the delivery tool. After 5 min of iDEEP-B injection, the en bloc resection of the elevated mucosa revealed a soft biodegradable gel underneath the mucosa to provide protection for the underlying muscle layer from electrocautery damage. Although the iDEEP gel cannot be removed entirely following the EMR procedure, the remaining material can be used to deliver therapeutics. In addition, previous small animal studies have shown complete biodegradation of the hydrogel, excellent tissue compatibility, and minimal inflammation in vivo [27,158].

In conclusion, iDEEP is a cost-effective, readily available, and easily injectable two-component solution, which allows for biodegradable gel formation under the submucosal space without complex administration difficulties and can potentially aid in mucosal regeneration through controlled therapeutic delivery. These results suggest that iDEEP may provide a significant step toward the realization of an ideal injection material for EMR. Future studies will be dedicated to comparative long-term evaluations in living animals with pathological review to confirm the efficacy, depth of resection ability, and submucosal regeneration of the iDEEP system.

16.3.5.3 Nerve Tissue Engineering

Peripheral nerve injury remains a difficult and challenging problem in reconstructive surgery [160]. When the nerve defect or “gap” size is smaller than a few millimeters, the damaged proximal axonal stump is able to regenerate axonal sprouts toward the distal segment to reestablish motor
and sensory function [161]. However, this form of neural regeneration does not always result in full functional recovery due to misdirection of the regenerating axons or inappropriate target reinnervation [162]. To complicate matters, without the presence of specific guidance, nerve ends separated by a gap size greater than 1 cm in length generally result in the backward growth of axons into the proximal nerve stump forming neuromas [163]. To increase the prospects of axonal regeneration and functional recovery, the current clinical “gold standard” for large gap repair involves the use of nerve autografts, which rely on the premise that viable Schwann cells (SC) located in the basal lamina tubes release a synergistic combination of growth factors and cell adhesion molecules to support and direct oriented axonal regeneration [164,165]. Unfortunately, autologous grafting is frequently associated with limitations including the need for multiple surgeries, donor site morbidity, distal donor site denervation, neuroma formation, and the limited availability of suitable grafts for harvesting [166].

To address the aforementioned limitations, several laboratories are actively pursuing the development of synthetic alternatives to replace nerve autografts in bridging the gap between transected nerve ends. Tissue-engineered nerve guides (TENGs) are a promising option for large gap nerve repair in that they can provide a biodegradable conduit for the delivery of therapeutic cell types, mechanical support, and chemical stimulation for axonal growth and nerve regeneration [167,168]. A variety of materials such as collagen [169], PLA [170], polyamide [171], poly(phosphoesters) [172], and poly(ethylene) [173] have been used with numerous processing strategies including TIPS and injection molding [174] techniques to fabricate synthetic alternatives to bridge neural defects. Recent years have witnessed the development of TENG with increasingly sophisticated and intricate internal structures based upon mechanisms of contact guidance and basement membrane microtube theory for nerve regeneration, which hypothesize that axon elongation requires guidance by contact with the appropriate substrate through topographical control [175,176]. By creating longitudinally oriented channels to fill the interior of the conduit, novel TENG has been produced to support the systems’ natural pattern of growth [176]. The multichanneled designs are advantageous in that they provide better nerve target reinnervation, a greater surface area for cell growth, the topography necessary to direct the growth of regenerating nerve fibers (bands of Büngner), and internal support to prevent conduit collapse [162,166–168,177,178].

Our lab has recently developed a novel CUPE-multichanneled TENG. CUPE is a highly strong, soft, and biodegradable elastomer developed in our lab, which has shown excellent biocompatibility and hemocompatibility [19]. It is expected that a TENG fabricated using CUPE will have adequate strength and elasticity to withstand tension and retain sutures and will be suited for immediate implantation. In order to better recreate the native parallel channels of nerve basal lamina tubes, we have proposed the fabrication of novel porous multichanneled nerve guides with the following rationale: (1) a parallel multichannel design can better mimic the native architecture of nerve basal lamina tubes and promote nerve cell alignment through contact guidance; (2) the introduction of microporosity (<10 μm) between the channels can minimize fibrous tissue infiltration, increase permeability for cell-to-cell communication, and limit cell dispersion to enhance nerve target reinnervation; and (3) an outer sheath of the nerve guide conduit can provide the necessary mechanical strength for surgical implantation.

Porous and elastic CUPE scaffolds were developed for peripheral nerve regeneration based on the basement membrane microtube theory and designed with multiple internal longitudinally oriented channels as well as an external non-porous sheath to mimic the native endoneurial microtubular structure and epineurium, respectively. This fabrication technique allows for great flexibility in the scaffold channel geometry, porosity, and mechanical properties. CUPE-multichanneled scaffolds displayed an ultimate peak stress of 2.83 ± 0.24 MPa with corresponding elongations at break of 259.60 ± 21.49 %, which are in the range of native nerve mechanical properties. CUPE-multichanneled scaffolds were also evaluated in vivo for the repair of 1 cm rat sciatic nerve defects. After 8 weeks of implantation, CUPE-multichanneled scaffolds compared favorably with nerve autograft in terms of fiber density and population.

In conclusion, a novel CUPE TENG consisting of longitudinally oriented parallel microchannels was fabricated using particulate-leaching techniques and evaluated mechanically and in vivo for potential use in peripheral nerve tissue engineering. The scaffolds were made from CUPE, a new type of strong, soft, and hemocompatible biodegradable polyester elastomer. These studies represent the first step toward the investigation of the role of scaffold architecture on the resulting tensile, suture retention, and in vivo performance. Using this design, TENG can be produced with tunable strength and architecture to fit the needs of a particular application. CUPE TENG performed as well as nerve autografts in the in vivo evaluation studies.

16.3.5.4 Gene Delivery

In addition to providing a physical substrate for cellular growth, tissue-engineered scaffolds should also facilitate the delivery of cell-signaling factors in order to repair and/or integrate with the diseased tissues in the body [179]. The delivery of these factors should allow for both short- and long-term delivery while allowing control over dosing without compromising the biological activity of the factor. Traditionally, the physical adsorption of a protein onto a scaffold followed by the protein release during scaffold
16.4 CONCLUSIONS

Since the creation of the first and initial citrate-based biodegradable elastomers (CABEs), poly(diol citrate) by Yang et al. in 2004, benefited from the facile and cost-effective synthesis process, available choices of diol comonomers (from small diol molecules to macrodiols, from hydrophobic diols to hydrophilic ones, and from saturated diols to unsaturated diols), and the multifunctionality of citric acid, CABEs have stood out and become an intensively studied and used biomaterial among the family of biodegradable polymers.

CABEs have become an important branch of biodegradable polymers. To meet the diversified needs in biological and biomedical applications, the innovation of CABEs will continue with focus on addressing some limitations on mechanical properties, degradation, and biofunctionalities required by specific applications. For example, wet mechanical strengths including adhesion strength (specifically for iCMBA) of CABEs should be improved for tissue engineering applications or orthopedic fixation device applications. Further understanding is needed on the mechanism of citrate signals for tissue development, which should be instrumental for the design of CABEs that may present dynamic citrate signals in response to tissue development such as bone regeneration. There is still much to do in the design of biodegradable polylactone biomaterials, which should constitute the next wave of innovations for CABE polymer. Confering intriguing fluorescent properties to polylactones can give a new life to the mature polylactone syntheses/technology and will generate significant impacts on the fields that have largely benefited from the use of biodegradable polylactone materials such as drug delivery, biosensing, bioimaging, cancer nanotechnology, and tissue engineering.

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REFERENCES


Chapter 16 Design Strategies and Applications of CABEs


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