Review: Photopolymerizable and Degradable Biomaterials for Tissue Engineering Applications

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ABSTRACT

Photopolymerizable and degradable biomaterials are finding widespread application in the field of tissue engineering for the engineering of tissues such as bone, cartilage, and liver. The spatial and temporal control afforded by photoinitiated polymerizations has allowed for the development of injectable materials that can deliver cells and growth factors, as well as for the fabrication of scaffolding with complex structures. The materials developed for these applications range from entirely synthetic polymers (e.g., poly(ethylene glycol)) to purely natural polymers (e.g., hyaluronic acid) that are modified with photoreactive groups, with degradation based on the hydrolytic or enzymatic degradation of bonds in the polymer backbone or crosslinks. The degradation behavior also ranges from purely bulk to entirely surface degrading, based on the nature of the backbone chemistry and type of degradable units. The mechanical properties of these polymers are primarily based on factors such as the network crosslinking density and polymer concentration. As we better understand biological features necessary to control cellular behavior, smarter materials are being developed that can incorporate and mimic many of these factors.

INTRODUCTION

POLYMERIC MATERIALS ARE BEING WIDELY USED and continuously developed for a variety of biomedical applications. The past few decades have seen an increase in the development of *degradable* biomaterials for applications such as tissue engineering and delivery of drugs and molecules.[1–3] In tissue engineering, polymeric materials can provide scaffolding for the controlled development and evolution of 3-dimensional (3-D) tissues.[1,4] When the materials are designed to be degradable, the growing tissue eventually replaces them.[1,4] In molecule delivery, degradable polymers are used to entrap various molecules that are released as the polymer degrades or through diffusion mechanisms. If growth factors are delivered, this approach can lead to alterations in cellular differentiation and the type and quality of tissue that forms.[4]

Numerous clinical applications benefit from the ability to form biomaterials *in situ*. For example, poly(methyl methacrylate) (PMMA) bone cements are commonly used to secure various implant prostheses in orthopedics.[5–7] In these applications, methyl methacrylate monomer is mixed with PMMA chains to form a viscous solution that can be injected *in vivo* and polymerized via redox or thermal initiation. In dentistry, dimethacrylate monomers with ceramic fillers are polymerized in tooth caries via a photoinitiated polymerization to form composite restorations *in situ*.[8] These materials have excellent properties with respect to mechanics but are nondegradable.

With advances in synthetic chemistry, novel multifunctional monomers and macromers have been synthesized that form degradable polymers via polymerizations initiated by free radicals and can potentially be used as injectable biomaterials. Although these reactive groups can polymerize using thermal or redox initiation mechanisms, there are benefits to using photoinitiated polymerizations for polymer formation.[9] The primary advantage is the temporal and spatial control that this polymerization mechanism affords, which leads to control over polymerization exotherms and time of gelation and can be used for the fabrication of complex

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structures (via systems of lasers or masks). This review presents information on the general polymerization and degradation mechanisms and outlines the various monomers and macromers that have been synthesized for the production of photopolymerizable and degradable biomaterials for applications in tissue regeneration.

NETWORK FORMATION AND DEGRADATION

Polymerization of multifunctional monomers

In general, the polymerization of multifunctional monomers is a complex process. The reaction mechanism (i.e., initiation, propagation, and termination) for a radical chain polymerization is outlined in Figure 1.[10] Although thermal, redox, and photoinitiated mechanisms can all be used to create radicals from initiator molecules, the focus of this review is on photopolymerized networks. The rate of initiation (R_i) is dependent on parameters such as the initiator efficiency, initiator concentration, and light intensity. During polymerization, the radicals propagate through unreacted double bonds to form long kinetic chains. Chain transfer or radical termination stops the growth. The rate of termination (R_t) is a bimolecular reaction and depends on the concentration of radicals in the system, whereas the rate of polymerization (R_p) is a measure of the rate at which double bonds are consumed during the polymerization. Because the bulk of this consumption occurs in the propagation steps, R_p can be approximated as a second-order reaction that depends on the double bond concentration and the radical concentration. If one assumes pseudo-steady state on the radical concentration (i.e., $R_i = R_t$), R_p becomes a function of R_i, the monomer concentration [M], and the propagation (k_p) and termination (k_t) kinetic constants (Fig. 1). Although simple in form, the polymerization behavior is complex, because k_p and k_t are highly dependent on the conversion and evolving network structure.

A typical plot of R_p versus time for a multifunctional monomer homopolymerization is shown in Figure 2, along with the integrated rate curve, which gives double bond conversion. Changes in initiation conditions (e.g., light intensity and initiator concentration) alter the magnitude of the peak maximum and the time to reach this maximum rate.[11,12] From the onset of the reaction, the polymerization rate increases with conversion, in a region termed autoacceleration.[13,14] During this time, the 3-D crosslinked network structure is evolving, and the mobility of terminating macroradicals decreases, and consequently, the rate of termination decreases. This mobility restriction on termination leads to a build-up in the concentration of radicals in the system, and the rate of polymerization increases. In addition, at some point during the period of autoacceleration, a reaction diffusion mechanism controls termination as radicals terminate by reacting through unreacted double bonds present in the system.[15,16] After the polymerization rate reaches a maximum, autodeceleration occurs as propagating species are now diffusion controlled.[11,13] Understanding this complex interplay of reaction- and diffusion-controlled mechanisms is critical for the design of biomaterials forming *in situ*. For example, although autoacceleration helps de-
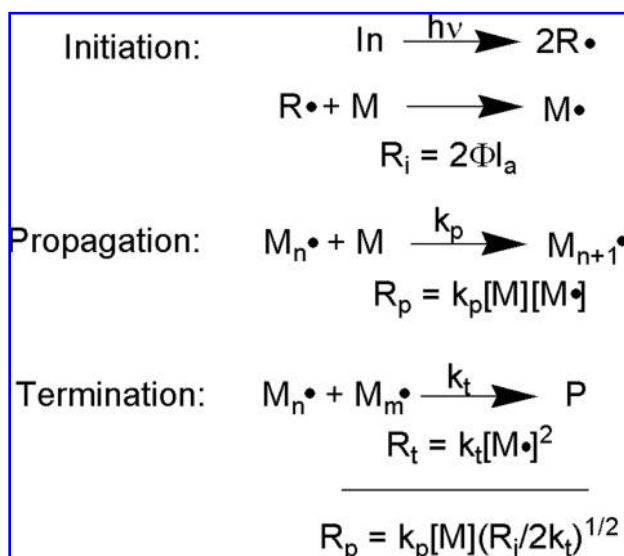

FIG. 1. Reaction mechanism for photoinitiated polymerizations. I_a is a function of the initiating light intensity, initiator concentration, and molar absorptivity coefficient. The polymerization rate equation shown assumes pseudo–steady state conditions.
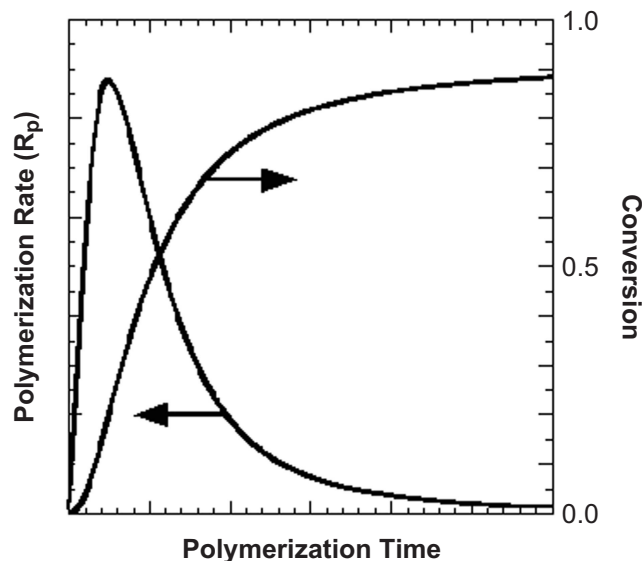

FIG. 2. General polymerization rate and conversion during the radical polymerization of multifunctional monomers.

crease total polymerization time, autodeceleration limits the maximum conversion.

In fact, with highly crosslinked glassy networks, a double bond conversion of one is almost never reached because of severe restrictions on the mobility of the reacting molecules. Unreacted monomer can have significant effects on the mechanics and biocompatibility of the resultant network, with severe implications for biological applications. For instance, low conversions can decrease the mechanical properties of the biomaterial, and unreacted and potentially toxic monomer can leach from the network and have detrimental effects on the surrounding tissue. Thus, attaining conversions approaching 100% is important and can be problematic. However, the formation of hydrogel networks in an aqueous environment can occur with high conversions because of the high mobility of reacting species during gel formation.[17]

An additional concern with radical polymerization *in vivo* is the temperature increase during polymerization. However, temporal control over the photoinitiation process can be used to minimize temperature increases during the exothermic radical polymerization. Burdick *et al.*[18] showed that, by changing initiation conditions and specifically the initiating light intensity, the temperature increase is readily controlled. For instance, when a sample was polymerized at room temperature with ultraviolet light, the surface temperature reached a maximum of approximately 46°C when polymerized with a light intensity of 100 mW/cm^2, whereas a sample polymerized with a light intensity of 25 mW/cm^2 reached a maximum temperature of only approximately 33°C. This control over the temperature increase during polymerization, which is not possible with thermal or redox initiations, could also influence the encapsulation of growth factors, because protein stability can decrease with higher temperatures. Another concern that should be addressed in using photopolymerization to form thick biomaterials is the attenuation of the initiating light source due to absorption by the initiator molecules. However, this can be overcome using systems such as photobleaching initiators, in which the initiator radicals absorb light at a different wavelength than the initiator molecules,[18] or dual initiators, in which a photoinitiation mechanism raises the sample temperature high enough to initiate thermally. This process allows for high conversions in areas where light does not reach.

Photopolymerization in the presence of cells

The delivery of cells to damaged tissues is often one of the primary goals of tissue engineering. With photopolymerization, it may be necessary to polymerize networks directly in the presence of cells. Because of the reaction conditions, potentially harmful radicals and light will be present during this polymerization process, and thus, it is necessary to determine whether cells remain viable after encapsulation. Cell encapsulation is only possible with certain types of macromers such as water-soluble macromers that form highly hydrated polymers upon polymerization.

Thus, many of the materials addressed in this review are not candidates for cell encapsulation and delivery because of their hydrophobicity and, consequently, diffusion limitations to entrapped cells.

To address toxicity during polymerization, several groups have investigated initiation conditions that lead to viable cells upon polymerization.[19,20] One specific initiating system that uses the water-soluble photoinitiator Irgacure 2959 (I2959, 2-hydroxy-1-[4-(hydroxyethoxy) phenyl]-2-methyl-1-propanone) and low-intensity ultraviolet light has been widely used for the encapsulation of multiple cell types in photopolymerizable hydrogels.[21–24]

However, there are several examples of loss of cell viability being attributed to the specific initiation system used,[19,20] and thus, it is essential to pick the appropriate conditions for cell encapsulation to promote cell viability.

General degradation behavior of crosslinked polymers

As detailed throughout this review, numerous monomers and macromers have been synthesized that are photopolymerizable into degradable networks. Several general possibilities for the formed network structures are illustrated in Figure 3. In the first example (Fig. 3A), a polymer or
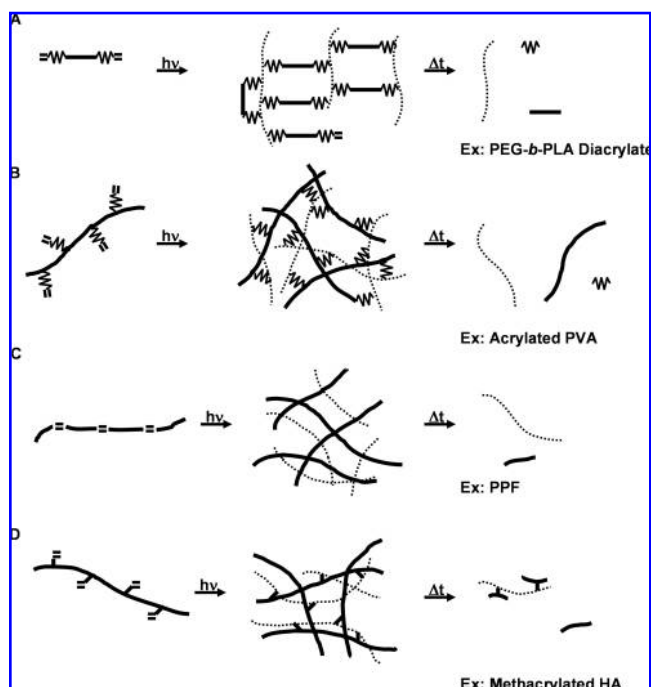

FIG. 3. Schematic of structures, network formation, and degradation for various photopolymerizable monomers and macromers. Reactive groups are represented by =, whereas hydrolytically degradable groups are represented by /\/\/\. Networks are produced using free-radical polymerizations of the reactive groups (e.g., acrylates/methacrylates) into kinetic chains (dashed lines) that are degraded via hydrolysis or enzymatic breakdown.

oligomer is end-capped first with degradable units and then photoreactive groups (e.g., acrylates or methacrylates). Upon exposure to light and in the presence of a photoinitiator, this tetrafunctional macromer forms a network with degradable units found in the crosslinks. The hydrolytically or enzymatically degradable units are then cleaved in the presence of an aqueous environment or an enzyme, respectively. This leaves degradation products of the original core molecule, the degradable units, and kinetic chains formed during the free-radical polymerization of the photoreactive groups (e.g., poly(acrylic acid) (PAA) for acrylates).

In the next example (Fig. 3B), the photoreactive groups are found along the polymer backbone linked through degradable units. These pendant reactive groups then polymerize to form a network that eventually degrades into the starting polymer, the degradable units, and kinetic chains. If the number of pendant reactive groups is limited to 2, the behavior reduces to the behavior shown in Figure 3A. Additionally, the photoreactive group may be found along the polymer backbone, as shown in Figure 3C. These networks degrade into the kinetic chains and segments of the starting polymer depending on the nature and location of the degradable groups. Finally, the pendant reactive groups may be found along a polymer chain that is itself degradable (Fig. 3D). In this situation, the network cleaves along the backbone and releases kinetic chains that probably incorporate segments of the starting polymer. Although additional examples can be suggested, these comprise the majority of systems that are covered throughout the review.

As stated in these examples, one of the primary degradation products is the kinetic chains that are formed through the free-radical polymerization of the reactive groups. These kinetic chains are typically PMAA or PAA if the reactive groups are methacrylates or acrylates, respectively. Methods to understand and control the kinetic chain lengths are important for biomaterials applications because the molecular weight of water soluble polymers influences their compatibility.[25] Furthermore, the kinetic chains will influence the final polymer structure, which can influence certain material properties. As a first approximation, the kinetic chain lengths are controlled by varying the rate of polymerization relative to the rate of chain-terminating events. If one assumes that R_i is equal to R_t, then R_i (a function of the initiator concentration and initiating light intensity) can be used to control the distribution of kinetic chain lengths. Burkoth et al.[26] used matrix-assisted laser desorption and ionization time-of-flight mass spectrometry to analyze the degradation products of crosslinked polyanhydrides, and Burdick et al.[27,28] used gel permeation chromatography to assess kinetic chain lengths. These studies determined that network conversion, the rate of initiation, and sample depth heavily influence kinetic chain length distributions.[27,28]

It is difficult to predict network physical properties and degradation behavior based entirely on macromer structure (e.g., molecular weight, branching), because factors such as backbone chemistry and hydrophobicity play a role in these properties. However, an increase in the polymer crosslinking density, due to an increase in macromer concentration or a decrease in macromer molecular weight, typically leads to enhanced mechanical properties and an increase in the time for network degradation, due to a decrease in water diffusion and an increase in the number of bonds that must be cleaved to break the network into water-soluble components. Likewise, an increase in the polymer crosslinking density can be used to slow the delivery of entrapped drugs or growth factors because diffusion becomes more limited. These factors are also dependent on whether the system is a highly swollen hydrogel or a highly crosslinked network.

SYNTHETIC POLYMERS

Photopolymerizable polyanhydrides

Anseth et al.[29] originally modified polyanhydrides with crosslinkable methacrylate groups to produce polymer networks with controlled degradation and mechanics with degradation, as well as the added potential of network formation directly in the body. The general structures for selected dimethacrylated anhydride monomers are shown in Figure 4. In general, the core of the molecule consists of hydrophobic repeating units, such as sebacic acid, carboxyphenoxy propane, or carboxyphenoxy hexane but other anhydride monomers, including methacrylated tricarballylic acid (MTCA, trimethacrylated) and methacrylated pyromellitylimidoalanine (MPMA-ala, amino-acid containing) have
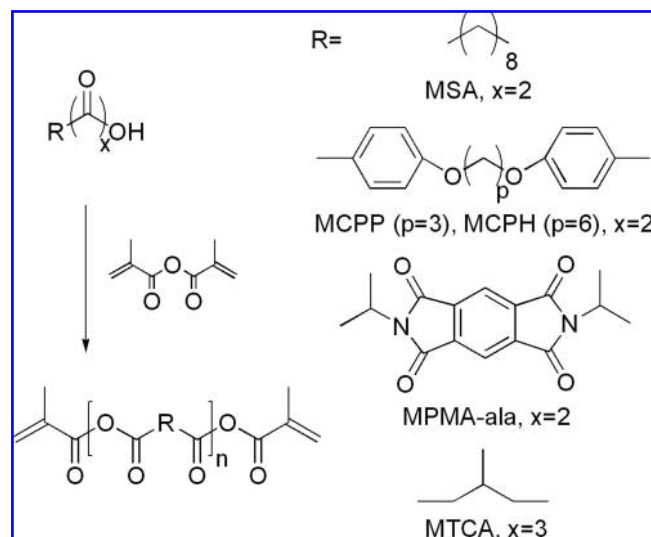

FIG. 4.   Photocrosslinkable polyanhydrides, typically synthesized via the reaction of acids with methacrylic anhydride. The "R" groups allow for tailoring of the hydrophobicity of the crosslinks and, consequently, polymer degradation.

been synthesized to impart greater crosslinking density and a biologically recognized component, respectively.[30]

Photocrosslinkable polyanhydrides have been extensively characterized with respect to reaction behavior and material properties. Even with mild initiation conditions (e.g., with 0.1 wt% initiator and $7 \, mW/cm^2$ ultraviolet light, polymerization occurs within 3 minutes), polymerization times are well within acceptable clinical time scales, allowing for network formation intra-operatively.[11] In general, the densely crosslinked networks formed from multifunctional anhydride monomers degrade via a surface erosion mechanism, with mass loss only at the surface erosion zones on the exposed areas of the polymer. These erosion zones allow only minimal penetration of water into the polymer, so hydrolysis occurs exclusively near the polymer surface and is dictated by the polymer chemistry. For example, a disk ($\sim 1.7 \, mm$ thickness) composed entirely of methacrylated sebacic acid (MSA) degrades in approximately 3 days, whereas a disk composed entirely of the more-hydrophobic methacrylated carboxyphenoxy hexane (MCPH) takes more than 1 year to completely degrade.[31] Because erosion occurs only at the polymer surface, structural integrity is maintained for longer degradation periods than in polymers that degrade throughout their bulk. For example, more than 90% of the tensile modulus of poly(MSA) and poly(MCPH) networks are maintained for up to 40% mass loss,[31] whereas in bulk-eroding systems, polymer chains are cleaved relatively homogeneously through the network, and mechanical properties can plummet even when little mass loss has occurred.[32,33]

Photocrosslinkable polyanhydrides have been explored for several applications. Because they are injectable, they can be formed directly in a bone defect through a photo-initiated polymerization and, with time, degrade as new bone fills the defect and replaces the degrading polymer. Histological sections shown in Figure 5 illustrate the dramatic difference in the filling of defects between a prepolymerized polymer implant and an implant forming *in situ*. In Figure 5A, good contact between the polymer implant and the surrounding bone is seen; however, in Figure 5B, the presence of a large gap in the medullary canal of the rat tibia indicates a lack of complete defect filling by the polymer plug. This may be one of the most important benefits of the photocurable polyanhydrides, because good contact between the biomaterial and bone tissue is essential in tissue regeneration and in maintaining good mechanical properties with the polymer implant. Several studies have also shown that polyanhydrides are biocompatible when degraded *in vivo*.[34–37] The controlled degradation and polymerization behavior also make crosslinked polyanhydrides excellent candidates as drug-releasing materials.[34] Owens *et al.*[38,39] developed a compressed antisolvent precipitation and photopolymerization process, which enables photopolymerization of multifunctional monomers to form degradable crosslinked particles and is applicable to forming microparticles from photocrosslinkable polyanhydrides.
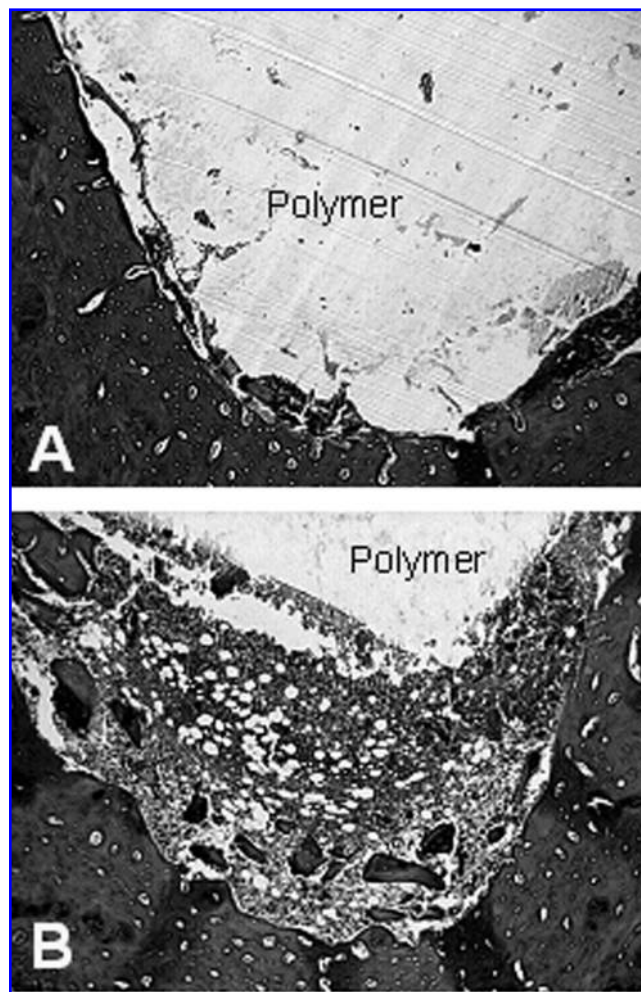

FIG. 5. Histological sections of *in vivo* photopolymerized (**A**) and prefabricated (**B**) polyanhydride implants in a tibial defect in rats. These images illustrate the filling of the defect that is possible with injectable and photopolymerizable materials.

Photocrosslinkable poly(ethylene glycol)

Poly(ethylene glycol) (PEG), a water-soluble polymer, has a long history of use in biomaterials. This is primarily because of the extreme hydrophilicity of PEG, which decreases the adsorption of proteins and can be used to alter the interaction between materials and tissues and cells. Additionally, the end groups on PEG are easily modified through a variety of synthetic reactions. For instance, the reaction of PEG with acryloyl chloride or methacryloyl chloride in the presence of triethylamine is a simple technique for adding photoreactive vinyl groups.[40] Photopolymerizable PEG hydrogels have been used for numerous applications, including as membranes for the encapsulation of islets of Langerhans,[40–42] as barriers to reduce intimal thickening after balloon angioplasty,[43] as matrices for chondrocyte encapsulation in cartilage regeneration,[44–48] for osteoblast encapsulation in bone

regeneration,[21] for the encapsulation of mesenchymal stem cells,[49] and for the delivery of nitric oxide to reduce platelet adhesion and smooth muscle cell proliferation.[50] Additionally, Elbert and Hubbell[51] used diacrylated PEG macromers to fabricate hydrogels incorporating various peptides by first reacting the macromer with a cysteine-containing peptide via a conjugate addition reaction and subsequent photopolymerization into a network.

Sawhney et al.[52] added oligomers of α-hydroxy acids between the PEG and photoreactive groups to produce degradable macromers. The general synthesis scheme for this reaction is illustrated in Figure 6. PEG was first mixed with dl-lactide (or glycolide) in the presence of stannous octoate and reacted under vacuum. In the second step, the intermediate product was redissolved in dichloromethane and reacted on ice with triethylamine and acryloyl chloride. The final product was obtained by filtration and subsequent precipitation in dry diethyl ether. Metters et al.[53] followed up this study by characterizing the swelling and mechanical behavior of the PEG-b-poly(lactic acid) (PEG-b-PLA) hydrogels with degradation. They showed that the volumetric swelling ratio of the networks exponentially increased and the compressive modulus exponentially decreased with degradation. Altering the crosslinking density (i.e., initial macromer concentration) of the hydrogels modulated the timing of this behavior. A statistical kinetic model predicting the degradation behavior of these hydrogels was also developed[54,55] that accurately predicts the cleavage of crosslinks in the PEG-b-PLA networks. A second-generation model incorporating network non-idealities was also introduced.[56]

For tissue-engineering applications, the acrylated PEG-b-PLA macromers have been primarily explored for the regeneration of musculoskeletal tissues. For cartilage regeneration,[57–60] hydrogels were fabricated from non-degradable PEG macromers, degradable PEG-b-PLA macromers, and copolymers of these two macromers. The overall conclusion of the work is that the copolymers support the most ideal cartilaginous tissue formation. Specifically, the neocartilage formed in the non-degrading hydrogels was not as spatially distributed as the cartilage formed in the copolymer gels and did not maintain the proper phenotype. Additionally, the crosslinking density of the hydrogels influenced the amount, type, and distribution of cartilage tissue that was engineered. The histological images in Figure 6 show the distribution of one extracellular matrix component (collagen) produced by osteoblasts photoencapsulated in degradable PEG hydrogels fabricated from macromers with various ratios of lactic acid and caprolactone as the degradable component (unpublished data). The lactic acid crosslinks are more rapidly hydrolyzed from the networks than the caprolactone crosslinks, and thus, can be used to temporally control the network degradation. After 12 weeks of implantation subcutaneously in the dorsum of nude mice, the histology indicates that the initial hydrogel chemistry plays a large role in controlling extracellular matrix distribution. For the hydrogel composed entirely of the more slowly degrading macromer, there is little distribution of collagen, whereas for the 50:50 ratio of macromers, there is even distribution of collagen matrix throughout the construct.

Degradable PEG hydrogels have also been extensively investigated as matrices for drug-delivery applications. West and Hubbell[61,62] photoencapsulated model drugs of various molecular weights in the hydrogels and showed that release rofiles were altered by changing the drug molecular weight, the number of degradable units in the macromer, and the PEG molecular weight. Burdick et al.[63] and Piantino et al.[64] used PEG hydrogels for the delivery of osteoinductive growth factors and neurotrophic factors to stimulate mineralized tissue formation and neurite outgrowth, respectively. This work illustrated the activity of growth factors released from the hydrogels through the stimulation of ectopic bone formation subcutaneously and in behavioral and anatomical outcomes in spinal cord injuries. Finally, Quick and Anseth[65–67] photoencapsulated deoxyribonucleic acid (DNA) in PEG hydrogels and used several techniques to preserve the integrity of the DNA during the encapsulation process. Various models[68,69] have been developed that theoretically predict release behavior from the photopolymerizable and degradable PEG hydrogels.

Other PEG-based synthetic macromers have also been developed. Wang et al.[70] synthesized PEG hydrogels that contain phosphate groups. The PEG-di-[ethylphosphatidyl (ethylene glycol) methacrylate] macromers were water soluble and formed hydrogels upon exposure to ultraviolet light in the presence of a photoinitiator. The hydrogels lost mass continuously over a 9-week period and supported the
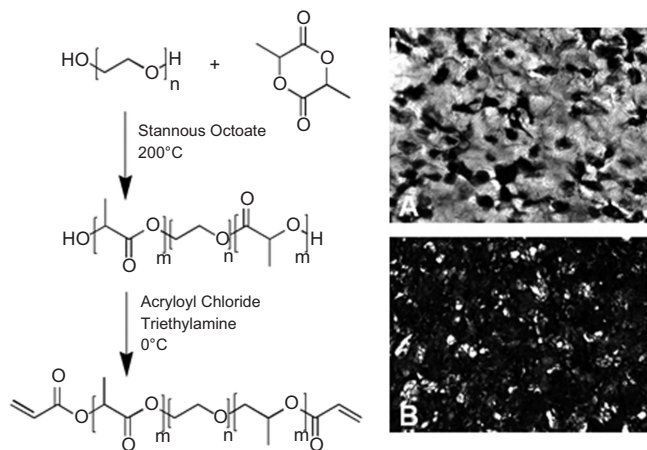

FIG. 6. Left. Synthesis of photopolymerizable and hydrolytically degradable poly(ethylene glycol) (PEG) macromers. Right. Collagen staining for osteoblasts photoencapsulated in degradable PEG hydrogels, in which the degradable unit is a slowly degrading caprolactone (A) or a 50:50 mixture of macromers containing either caprolactone or lactic acid (B). These alterations in degradation can be used to control the distribution of extracellular matrix by entrapped cells.

encapsulation of viable human mesenchymal stem cells. Finally, Li *et al.*[71] synthesized a new biodegradable and photocrosslinkable macromer with a polyphosphoester backbone containing PEG spacers followed by acrylate groups. Properties such as the swelling ratio and mass loss were found to decrease as the amount of macromer increased. No cytotoxicity was observed when bone marrow stem cells isolated from goat (GMSCs) were cultured in media containing macromer up to concentrations of 10 mg/mL. Furthermore, it was shown that GMSCs retained their viability when encapsulated in these photopolymerized gels.[71]

As an alternative to hydrolytically degradable hydrogels, West and Hubbell[72] developed networks that were proteolytically degradable by enzymes present near a cell surface during cell migration. The hydrogels were collagenase or plasmin sensitive, depending on the peptide incorporated. The synthesized hydrogels degraded specifically in the presence of the various proteases. Mann *et al.*[73] used an alternate procedure to synthesize proteolytically degradable hydrogels. Adhesive peptides were grafted to the hydrogels, and the hydrogels supported the viability, proliferation, and production of extracellular matrix components by encapsulated smooth muscle cells. Gobin and West[74] continued this work to control the migration of fibroblasts through collagenase and plasmin degradable hydrogels. Their work illustrated the importance of the hydrogel design (i.e., tethered ligand density) on cell migration and showed that proteolytically degradable sites and adhesive tethers were necessary for cell migration.

Finally, PEG-based macromers have been used to fabricate complex 3-D structures, taking advantage of the spatial resolution that is afforded during photoinitiated polymerizations. Although non-degradable PEG was used, Tsang *et al.*[75] and Arcaute *et al.*[76] developed systems of photopatterning and sterolithography to fabricate complex structures that incorporate living cells. These techniques are useful in the development of multicellular scaffolds with complex architectures for the engineering of a variety of tissues.

Photocrosslinkable poly(propylene fumarates)

Poly(propylene fumarate)s (PPFs) are linear polyesters consisting of repeat units with multiple ester groups and unsaturated carbon–carbon double bonds. The general structures of PPFs are shown in Figure 7. Networks are formed using covalent crosslinking through the carbon–carbon double bonds using thermal- or photoinitiators and hydrolyzed into primarily fumaric acid and propylene glycol, which are cleared from the body via metabolic pathways.[77–86] Fisher *et al.*[80] were the first to investigate the photoinitiated crosslinking mechanism of PPF networks with variations in initiator concentrations. This work demonstrates the importance of initiator type and concentration on network properties such as sol fraction and tensile modulus.[80] Timmer *et al.*[87] also investigated the importance of
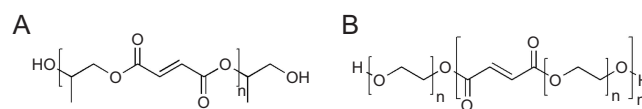
FIG. 7. Examples of photocrosslinkable poly(propylene fumarates) for generating highly crosslinked networks (**A**) and hydrogels (**B**).

initiator type by comparing the mechanical properties and average molecular weight between crosslinks of PPF-based networks formed via thermal- and photoinitiation. In general, networks formed using photoinitiation had greater compressive moduli and strength, reaction conversions, and crosslinking densities than networks formed using thermal initiation.[87]

PPF-based networks are attractive for orthopedic applications because of their high compressive strengths.[87,88] Various techniques such as polymerization in silicone molds,[88] stereolithography,[89] and porogen leaching[78,79,81,84,86] have been used to develop PPF scaffolds for implantation. Scaffolds implanted into rabbit cranial defects demonstrated bone ingrowth,[81,84] especially when the scaffolds were coated with transforming growth factor-β_1.[84] Various copolymers containing PPF-based macromers have also been developed. For example, Jo *et al.*[90,91] and Temenoff *et al.*[92] developed oligo(poly(ethylene glycol) fumarate) (OPF) macromers containing alternating blocks of fumaric acid and PEG (Fig. 7). Photocrosslinked hydrogels based on these macromers exhibit a range of bulk properties, such as mesh size and percentage elongation at fracture, depending on the molecular weight of the PEG block.[92] Further functionalization of these networks was demonstrated using OPFs modified with the addition of glycine-arginine-glycine-aspartic acid groups and crosslinked with PPF to form biodegradable scaffolds.[90] In addition, networks with compressive and diametrical tensile strengths ranging from 1.8 to 146.0 MPa and 2.5 to 9.3 MPa, respectively, have been prepared using the crosslinking of methacrylated propylene fumarate and acrylated poly(ε-caprolactone) (PCL) oligomers.[93] Moreover, Wang *et al.*[85,94] have developed multiblock copolymers consisting of PPF and PCL, as well as PPF, PCL, and PEG, for tissue engineering applications.

Photocrosslinkable poly(α-hydroxy esters)

Poly(α-hydroxy esters), such as PLA, PGA, and PCL are among the most thoroughly investigated synthetic biomaterials.[52,95–101] However, poly(α-hydroxy esters) are highly crystalline polyesters that lack modifiable side groups, which could be used to facilitate better material–cell interactions.[96–101] Several investigators have combined degradable PLA and photopolymerization technology to manipulate the backbone with amino acids to allow for further functionalization.[100,101] PLA films have also been surface grafted

with PAA and poly(acrylamide) using photopolymerization in an attempt to generate a bioactive surface with rapid degradation.[99]

Various copolymers containing blocks of poly(α-hydroxy esters) and other synthetic polymers have been prepared. For example, PCL-b-PEG-b-PCL networks have been synthesized and exhibit a greater compressive modulus and degradation rate than PCL alone.[102] Networks based on adipic acid, 4-hydroxycinnamic acid, and PCL diols with elastomeric properties have also been prepared.[103,104] PCL has also been combined with trimethylene carbonate, and the reaction behavior and bulk properties have been characterized.[105–113] Furthermore, star-PCL-b-PLA macromers have been synthesized.[114,115] These networks show dependence in physical properties and degradation on the length of the copolymer block.[114,115] Han and Hubbel[96,97] and Ju et al.[98] prepared lactide-based PEG networks emanating from glycerol centers. The ratio of the lactide and PEG incorporated controlled the degradation rates of these networks.[96,98]

Diethylene glycol has also been used as an initiator for the ring-opening polymerization of d,l-lactide and ε-caprolactone, which were subsequently methacrylated to allow for crosslinking.[12,116–118] Alterations in the oligomer chemistry led to changes in mechanical properties and degradation behavior. In particular, a decrease in loss of bulk-eroding mass, as well as an increase in protein adsorption, osteoblast viability, and other indications of bone formation, corresponded to an increase in network hydrophobicity.[12,116–118] Porous scaffolds of one of the more hydrophobic oligomers were prepared using salt leaching and implanted into critical-sized cranial defects in a murine model, which demonstrated the potential of this material as an *in situ* synthetic graft for large bone defects.[119] Similar triblock polymers were synthesized and prepared as scaffolds using micro-patterning.[120]

Photocrosslinkable poly(vinyl alcohol)

Poly(vinyl alcohol) (PVA) has been used in a variety of biomedical applications, such as contact lenses, tendon repair, and drug delivery and as scaffolds for a wide variety of tissue-engineering applications, including bone, cartilage, and heart valves.[121,122] Hydrogels prepared from this synthetic polymer are of particular interest because of its biocompatibility, high water content, tissue-like elasticity, and ease of fabrication and sterilization.[17,122–125] Perhaps the most attractive feature of using PVA is the abundance of pendant hydroxy groups along the backbone which allow for various chemical modifications such as the introduction of methacrylate groups or biological molecules like fibronectin.[17,121–129]

Previously, PVA hydrogels have been crosslinked using chemical means such as aldehydes[128] and physical mechanisms such as repeated freeze–thaw cycles to induce crystallinity.[125,128] Limitations to these methods include toxicity of the aldehydes and stability of physical crosslinks. Muhlebach et al.[130] were the first to use photopolymerization to crosslink PVA by modification of the aforementioned pendant hydroxy groups with acrylic acid and methacrylic acid for contact lens applications.[125,130] Several other groups have been successful in introducing various functional groups for photopolymerization by reaction with various reagents such as glycidyl acrylate,[127] methacrylamidoacetaldehyde dimethyl acetal,[121] and 2-isocyanatoethyl methacrylate.[17] A wide range of mechanical properties and degradation times are obtainable by varying the concentration of reactive groups and number and type of degradable groups.[121,123,128] These hydrogels degrade via hydrolysis of ester bonds until reverse gelation occurs when there is no longer an infinite network present but only branched, soluble chains.[124] Nuttelman et al.[125] engineered a hydrogel scaffold by preparing PLA capped with hydroxyethyl methacrylate, which was subsequently grafted onto PVA. This copolymer demonstrated control over degradation and greater cell adhesion based on the number of lactide repeat units per side chain.[125] Copolymers of PVA and PEG, as well as PVA and chondroitin sulfate (CS), have been created and used to encapsulate chondrocytes for cartilage tissue engineering applications.[17,129]

Photocrosslinkable poly(β-amino ester)s

Poly(β-amino ester)s are a class of materials that were originally developed for such biomedical applications as nonviral gene delivery vehicles, because of lower toxicity than other cationic polymers used for the same application.[131,132] Anderson et al.[133] synthesized and characterized a large library of poly(β-amino ester)s with acrylate end groups using various amines and diacrylates and a simple synthetic process with no byproducts. The general structure of these macromers is shown in Figure 8. The various reagents were chosen to introduce chemical diversity and variations in hydrophobicity within the macromer library, and an excess of diacrylates (i.e., diacrylate:amine >1) was used to ensure reactive end groups. The macromers can be photopolymerized into networks with hydrolysis resulting in small molecule bis(β-amino acid)s, diols, and PAA kinetic chains as degradation products.[133] The macromers formed polymers that exhibited a wide range of degradation behaviors and times (an example of one time point is shown in Fig. 8), and it was observed that mass loss was slower when more hydrophobic amines were incorporated into the macromers. In addition, a wide range of mechanical properties ($E = 4$-350 MPa) was obtained through variations in macromers. The stiffness of these materials did not necessarily correlate to degradation time. Therefore, materials exhibiting the optimal mechanical properties and degradation rates can be prepared for a variety of tissue engineering applications.[133] Brey et al.[134] further illustrated the ability to use macromer molecular weight to control the network properties and cellular interactions.
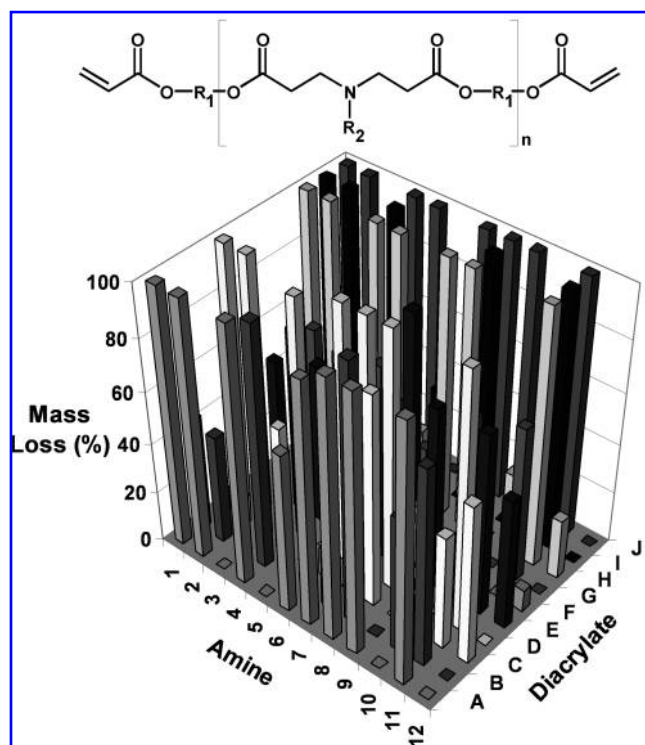
FIG. 8. The general chemical structure of poly(β-amino ester)s and an example of mass loss at one time point (99 days); R_1 depends on the diacrylate (A–J) used, and R_2 depends on the amine (1–12) used. These results illustrate the diversity available in the macromer library.

Other synthetic and photocrosslinkable polymers

Other systems of synthetic polymers have been prepared using various modifications and processing techniques. For example, Carnahan et al.,[135] Grinstaff et al.,[136] Luman et al.[137] and Sontjens et al.[138] synthesized photocrosslinkable dendrimers based on PEG, glycerol, and succinic acid. These systems have been applied as scaffolds for cartilage tissue engineering and corneal tissue repair.[135,136,138] Thiol-acrylate photopolymers, which are capable of photopolymerization with or without the addition of photoinitiators, have been polymerized using a mixed-mode chain and step-growth mechanism between the diacrylate (e.g., PEG-PLA) monomer and a multifunctional thiol (e.g., pentaerythritol tetrakis (3-mercaptopropionate)). A wide range of bulk properties[139] and degradation rates are offered through the versatility of the chemistry involved in this system.[139–141] Furthermore, one significant benefit of these networks is that curing depths may exceed 10 cm with initiator-free systems.[139]

NATURAL POLYMERS

Photocrosslinkable collagen and gelatin

Gelatin, or denatured collagen, has several desirable properties for use as a biomaterial, including its biological interaction capabilities and numerous side groups for modification.[142] Previously, chemical crosslinking was initiated using various bifunctional reagents such as glutaraldehyde, but these gels resulted in cases of local cytotoxicity and calicification.[142,143] Van Den Bulcke et al.[142] derivatized gelatin by reacting it with methacrylic anhydride to introduce photocrosslinkable moieties. They noted that the degree of substitution of the gelatin and the storage conditions controlled the overall strength of the gel.[142] Brinkman et al.[144] also used methacrylic anhydride to incorporate an acrylate moiety onto the lysine and hydroxylysine residues of the collagen backbone (Fig. 9). Photocrosslinking of the macromer using visible light irradiation and in the presence of rat aortic smooth muscle cells was used to prepare gels.[144] A significant increase in the mechanical integrity of the construct was observed, although it was still sufficiently less than the tensile strength required for *in vivo* applications, such as vascular grafts. They showed that the triple helical conformation, as well as cell viability, were maintained during the crosslinking process.[144]

In addition to reaction with methacrylic anhydride, collagen has been derivatized using an 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide/N-hydroxysuccinimide (EDC/NHS) conjugation method to add photosensitive cinnamate moieties.[143] This method produced photocrosslinked gels with mechanical properties comparable with those crosslinked using glutaraldehyde.[143] Moreover, collagen and gelatin have been reacted with other reagents to facilitate light-induced chemical crosslinking. For example, gelatin has been modified with benzophenone and xanthene dyes and has been reacted in the presence of PEG diacrylate for the production of tissue adhesives.[145] Gelatin has also been modified with styrene groups by reaction with 4-vinylbenzoic acid. This modified gelatin has also been reacted with PEG diacrylate and investigated as a tissue adhesive glue for arterial repair.[146] The release rate of albumin from these gels is indirectly related to the gelatin concentration and degree of modification, and the adhesivity of the gel was greater than that of fibrin glue.[147] Styrene-derivatized gelatin has also been investigated for applications such as delivery vehicles,[148–150] nerve guides,[151,152] and cell carriers for chondrocyte transplantation.[153]

Photocrosslinkable polysaccharides

Hyaluronic acid. Hyaluronic acid (HA) is a naturally derived nonimmunogenic, nonadhesive glycosaminoglycan composed of D-glucuronic acid and *N*-acetyl-D-glucosamine and is found in many connective tissues.[154–162] HA undergoes enzymatic degradation[154,156–160,162,163] and plays roles in the promotion of cell motility and proliferation,[154,156,160,163] wound healing,[154,157,158,163] angiogenesis,[157–159] and the reduction of long-term inflammation.[154,157–159] It is attractive for biomaterial applications because it can be modified with various functional groups such that covalent crosslinking reactions are possible.[154–169] Smeds et al.[162] modified HA
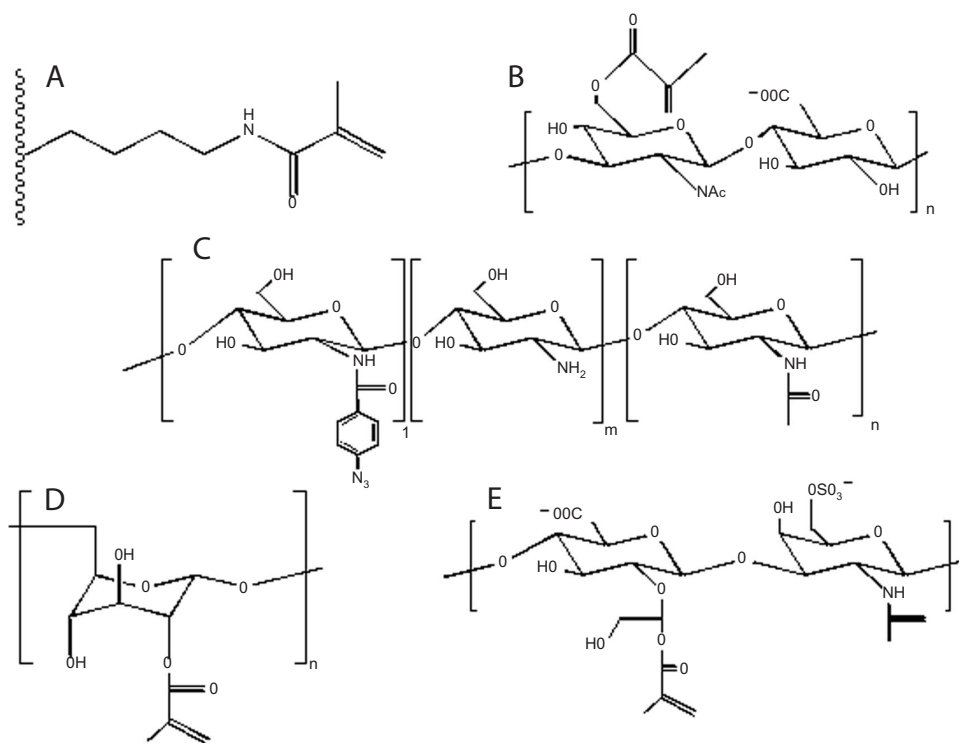
FIG. 9. Examples of various photopolymerizable natural polymers including (**A**) collagen, (**B**) hyaluronic acid, (**C**) chitosan, (**D**) dextran, and (**E**) chondroitin sulfate.

for photopolymerization with the addition of a methacrylate group by reaction with methacrylic anhydride (Fig. 9).[162] They investigated the influence of the degree of methacrylation on bulk mechanical properties such as swelling, compression, and creep compliance. It was demonstrated that the hydrogels prepared from methacrylated HA (HA-MA) are capable of swelling up to 14 times their dry weight and are stronger and more resilient than corresponding alginate gels.[161]

Because of its role in cardiac morphogenesis, HA-MA has been studied as a scaffold for heart valve tissue engineering.[163,167] Masters *et al.*[163] investigated the spreading and proliferation of valvular interstitial cells (VICs) on HA-MA–based gels. VICs encapsulated within the gels remained viable, and the scaffold degradation products increased VIC proliferation.[163] Burdick *et al.*[22] systematically studied the effect of HA molecular weight, degree of methacrylation, and macromer concentration on the bulk properties of the resulting HA-MA gels. Volumetric swelling ratios varied from approximately 8 to 42, and the compressive modulus ranged from approximately 2 to more than 100 kPa when the macromer concentration was varied from 2% to 20%. The viability of fibroblasts seeded within these gels decreased as the macromer concentration increased. Neocartilage was observed in gels seeded with swine auricular chondrocytes.[154] Further study of this system for cartilage-engineering applications demonstrated optimal neocartilage

production in hydrogels fabricated with 2 wt% of 50 kDa HA-MA macromer and early passaged chondrocytes.[164,165] HA-MA has also been investigated for corneal regeneration[168] and for micromolding of cellular microarrays.[156,166]

HA was also modified with *N*-3-aminopropyl methacrylamide[160] and glycidyl methacrylate (GMHA). [155,157–159] GMHA was further modified with acrylated forms of PEG, and EDC/NHS was used to conjugate the model peptide hexaglycine to GMHA.[157] Stable hydrogels with high peptide conjugation efficiencies (≤80%) and defined physiochemical properties were formed by controlling the reactant ratios.[157] GMHA was also partially oxidized to reduce chain rigidity and was examined for vocal fold regeneration.[155] Moreover, protein release from GMHA scaffolds has been investigated in an effort to create a combinatorial scaffold and delivery device.[159]

Dextran. Dextran is a biodegradable bacterial polysaccharide consisting of α-1,6 D-glucopyranosyl residues with approximately 5% to 10% α-1,3 linked side chains.[170–172] It has previously been studied for delivery of pharmaceutical drugs, peptides, and proteins.[170,172,173] Repeat units in dextran have 3 free hydroxy groups that allow for further functionalization with various reactive moieties and allow for covalent crosslinking.[171–173] For example, dextran has been modified by reaction with methacrylic anhydride to incorporate an acrylate functional group onto one of the

hydroxy groups (Fig. 9).[170,174] A wide range of swelling properties can be obtained by altering the degree of methacrylate substitution. Hydrogels based on this system were loaded with different drugs, such as doxorubicin, and their release profiles were investigated. It was observed that a higher degree of substitution led to a delay in drug release time; the quantity of drug released also decreased as the molecular weight of the drug increased.[174] Hydrolytic degradation of dextran-based hydrogels was induced by the addition of PLA subunits onto the backbone.[172,173,175] This system was further modified by reacting dextran with allyl isocyanate and PLA such that a wider range of physical properties could be obtained because of the greater degree of substitution.[172,175] Drug release from these gels was found to be dependent on the rate and formulation of the 3-D porous scaffold in the gel, the hydrolytic degradation of PLA, and the hydrophobic interaction between PLA and the drug.[175]

Chitosan. Chitosan is a partially deacetylated form of chitin, a natural linear homopolymer of β-1,4-linked N-acetyl-D-glucosamine.[176–178] Useful advantages of chitosan include its hemostatic activity,[176] immunological activity, and ability to accelerate wound healing.[176,178] It has been modified by reaction with N,N,N',N'-tetramethylethylenediamine, EDC, and 4-O-β-D-galactopyranosyl-(1,4)-D-gluconic acid to introduce azide and lactose moieties for photocrosslinking (Fig. 9). This modified chitosan (AZ-CH-LA) has primarily been investigated as a tissue adhesive,[176,178,179] and it has been shown that AZ-CH-LA demonstrates binding strengths stronger than fibrin glue and is effective at sealing punctures in thoracic aorta and lungs in rabbit models.[179] Azide-modified chitosans have also been investigated as matrices for drug delivery[177,180] and as a cell-seeded material for micromolding[181] and photolithography.[182] Moreover, chitosan has also been modified by reaction with 4-vinylbenzoic acid, which has further been used to create tubular structures upon irradiation with visible light.[183]

Chondroitin sulfate. Chondroitin sulfate is an enzymatically degradable proteoglycan composed of repeating units of glucuronic acid and N-acetylgalactosamine with a sulfate and carboxyl group located on each disaccharide unit.[184–186] It is one of the major components of native cartilage tissue aggrecans, is capable of absorbing large quantities of water, and is thus regarded as being responsible for the great compressive strength of the tissue.[186] Chondroitin sulfate has been modified for photocrosslinking (Fig. 9) by reaction with glycidyl methacrylate to form glycidyl methacrylate (GMA)-CS,[184,186] and an inversely proportional relationship between degree of methacrylate substitution, as well as crosslinking density and water content, was found.[186] GMA-CS was combined with polyethylene oxide diacrylate to form hydrogels, which had a greater water content than hydrogels composed of polyethylene oxide diacrylate alone. The viability of chondrocytes loaded into these gels was also maintained.[184] Similar results were obtained with CS modified with methacrylic anhydride and copolymerized with PEG[185] and PVA.[17]

SUMMARY AND FUTURE DIRECTIONS

In summary, a wide range of different precursor molecules are being developed that form networks via photoinitiated polymerizations for tissue-engineering and molecule-delivery applications. The diversity in polymer properties, ranging from highly crosslinked, hydrophobic networks to loosely crosslinked, swollen hydrophilic hydrogels, expands the applicability of these biomaterials. As more knowledge and understanding of biological events such as tissue healing and cell–material interactions becomes available, the materials used in these applications will become smarter and more complex. Particularly, there is great interest in designing biological function into polymers, such as enzymatically degrading crosslinks and adhesion sites, to better control the interactions between cells and materials. Also, as advances are made in the area of polymer synthesis, it is becoming easier to tailor polymer properties and structure as desired. Novel materials may be able to open up avenues for unique material behavior such as externally triggered properties (e.g., temperature induced), shape-memory polymers, and the patterning of structures 3-dimensionally. The next decade is bound to produce previously unimaginable biomaterials that use photopolymerization technology and can help to overcome our shortage of tissue available for transplantation to patients.

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