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Photopolymerizable hydrogels for tissue engineering applications

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Abstract

Photopolymerized hydrogels are being investigated for a number of tissue engineering applications because of the ability to form these materials in situ in a minimally invasive manner such as by injection. In addition, hydrogels, three-dimensional networks of hydrophilic polymers that are able to swell large amounts of water, can be made to resemble the physical characteristics of soft tissues. Hydrogel materials also generally exhibit high permeability and good biocompatibility making, these materials attractive for use in cell encapsulation and tissue engineering applications. A number of hydrogel materials can be formed via photopolymerization processes mild enough to be carried out in the presence of living cells. This allows one to homogeneously seed cells throughout the scaffold material and to form hydrogels in situ. This review presents advantages of photopolymerization of hydrogels and describes the photoinitiators and materials in current use. Applications of photopolymerized hydrogels in tissue engineering that have been investigated are summarized.

Keywords: Hydrogels; Photopolymerization; Biocompatibility; Tissue engineering; Cell encapsulation; Drug delivery

1. Introduction

Hydrogels, crosslinked hydrophilic polymers, represent an important class of biomaterials in biotechnology and medicine because many hydrogels exhibit excellent biocompatibility, causing minimal inflammatory responses, thrombosis, and tissue damage [1,2]. Hydrogels can also swell large quantities of water without the dissolution of the polymer due to their hydrophilic but crosslinked structure, thus giving them physical characteristics similar to soft tissues. In addition, hydrogels have high permeability for oxygen, nutrients, and other water-soluble metabolites. Over the past three decades, a number of hydrogels differing in structure, composition, and properties have been developed. Hydrogel materials have been used extensively in medicine for applications such as contact lenses, biosensors, linings for artificial implants, and drug delivery devices [3,4].

Some types of hydrogels can be photopolymerized in vivo and in vitro in the presence of photoinitiators using visible or ultraviolet (UV) light. Photopolymerization is used to convert a liquid monomer or macromer to a hydrogel by free radical polymerization in a fast and controllable manner under ambient or physiological conditions. Photopolymerized hydrogels have been investigated for a number of biomedical applications including prevention of thrombosis [5,6]; post-operative adhesion formation [7–11]; drug delivery [10–14]; coatings for biosensors [15,16]; and for cell transplantation [17–20].

2. Photopolymerization

Visible or UV light can interact with light-sensitive compounds called photoinitiators to create free radicals that can initiate polymerization to form crosslinked hydrogels [21]. The use of light to polymerize or cure materials in vivo has been practiced extensively in dentistry to form sealant and dental restorations in situ [22,23]. Photopolymerization has also been used in electronic materials, printing materials, optical materials, membranes, polymeric materials, and coatings and surface modifications [21]. Photopolymerization has several advantages over conventional polymerization techniques. These include spatial and temporal control over polymerization, fast curing rates (less than a second

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to a few minutes) at room or physiological temperatures, and minimal heat production [24]. One major advantage of photopolymerization is that hydrogels can be created in situ from aqueous precursors using photopolymerization in a minimally invasive manner, for example, using laparascopic devices [8,9]; catheters [5,6]; or subcutaneous injection with transdermal illumination [25]. Fabrication of polymers in situ is attractive for a variety of biomedical applications because this allows one to form complex shapes that adhere and conform to tissue structures. Polymerization conditions for in vivo applications, however, are difficult since biological systems require a narrow range of acceptable temperatures and pH, as well as the absence of toxic materials such as most monomers and organic solvents. Some photopolymerization systems can overcome these limitations because the polymerization conditions are sufficiently mild (low light intensity, short irradiation time, physiological temperature, and low organic solvent levels) to be carried out in the presence of cells and tissues.

2.1. Photoinitiators

Photopolymerization schemes generally use a photoinitiator that has high absorption at a specific wavelength of light to produce radical initiating species. Other factors that should be considered in selecting the photoinitiator include its biocompatibility, solubility in water, stability, and cytotoxity [21,26]. Over the last decade, various photoinitiators have been investigated to achieve better photopolymerization. Three major classes of photoinitiation, depending on the mechanism involved in photolysis, include radical photopolymerization through photocleavage, hydrogen abstraction, and cationic photopolymerization [21,24,26]. Cationic photoinitiators are generally not utilized in tissue engineering applications because they generate protonic acids.

2.1.1. Radical photopolymerization by photocleavage

The photoinitiators undergo cleavage at C–C, C–Cl, C–O, or C–S bonds to form radicals when exposed to light as shown in Fig. 1A. These photoinitiators include aromatic carbonyl compounds such as benzoin derivatives, benziketals, acetophenone derivatives, and hydroxyalkylphenones. Acetophenone derivatives that contain pendant acrylic groups have been shown to substantially reduce the amount of unreacted photoinitiators with no significant loss in the initiation efficiency [21,24]. Acetophenone derivatives, such as 2,2-dimethoxy-2-phenyl acetophenone, have been used as photoinitiators to form hydrogels from acrylated polyethylene glycol (PEG) derivatives in several biomaterial studies [8,9,27–29].

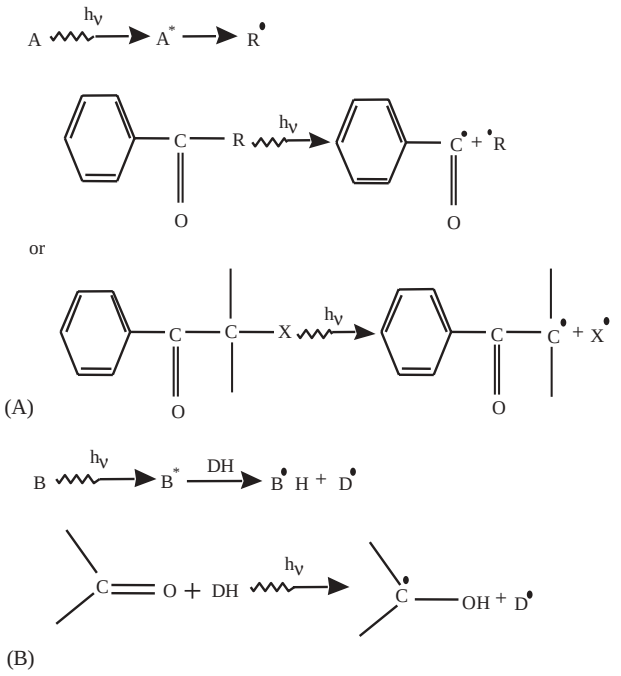

Fig. 1. Photoinitiators that promote radical photopolymerization. (A) Radical photopolymerization by photocleavage. Upon exposure to light, these photoinitiators undergo cleavage to form radicals that promote the photopolymerization reaction. (B) Radical photopolymerization by hydrogen abstraction. Upon UV irradiation, these photinitiators undergo hydrogen abstraction from the H-donor (DH) to generate radicals.

2.1.2. Radical photopolymerization by hydrogen abstraction

Upon UV irradiation, photoinitiators such as aromatic ketones (i.e., benzophenone and thioxanthone) undergo hydrogen abstraction from an H-donor molecule to generate a ketyl radical and a donor radical as shown in Fig. 1B. The initiation of photopolymerization usually occurs through the H-donor radical while the ketyl radical undergoes radical coupling with the growing macromolecular chains. The photoinitiator isopropyl thioxanthone has been shown to be cytocompatible [30].

2.2. In situ photopolymerization

Formation of photopolymerized hydrogels in vivo can be accomplished using bulk or interfacial photopolymerization. Bulk photopolymerization is most commonly used. In this case, the photoinitiator is dissolved in the hydrogel precursor solution (monomer or macromer) and upon exposure to an appropriate light source, the precursor solution is converted to the hydrogel state. Interfacial photopolymerization is a unique technique that allows the creation of thin ($<100\,\mu m$) hydrogel linings on cells or tissues. In interfacial photopolymerization, a photoinitiator is adsorbed onto the surface of tissues or cells. Eosin photoinitiators have been commonly used for this

purpose because of their high affinity for tissues [5,6,13,18,31]. When the surface is then exposed to the hydrogel precursor solution and the appropriate wavelength of light, polymerization occurs where the hydrogel precursor is in contact with the adsorbed photoinitiator, namely at the tissue interface. Interfacially photopolymerized hydrogels have been utilized in several applications. For example, interfacial photopolymerization was used to form a thin hydrogel layer on the surface of pancreatic islets of Langerhans to provide immunoisolation while allowing rapid diffusion of nutrients and insulin [18]. Interfacial photopolymerization of thin hydrogel coatings resulted in greater cell viability and encapsulation efficiency compared to bulk photopolymerized microcapsules due to the reduced resistance to nutrient transport. Interfacial photopolymerization has also been used to form thin hydrogel coatings on arterial surfaces to prevent thrombosis and restenosis following balloon injuries [5,6] or stent deployment [32,33], as well as for intravascular drug delivery [13].

Additionally, visible or UV light can be transmitted across skin to cause photopolymerization of hydrogels [25,34]. In this case, the hydrogel precursor solution (with an appropriate photoinitiator) is injected subcutaneously and is converted to a hydrogel upon transdermal illumination. Transdermal photopolymerization has been investigated for implantation of materials for drug delivery [25] or cartilage tissue engineering [20,25,34]. These studies utilized long wavelength UV light initiation systems. While light in this wavelength regime is poorly transmitted across skin, sufficient light did penetrate to convert the precursor to a hydrogel at irradiation levels compatible with tissue. This type of procedure is likely to be more effective with visible or near infrared photoinitiators since these wavelengths exhibit better transmission across skin.

2.3. Photopolymerizable materials

Polymerization of monomers using visible or UV irradiation has been thoroughly investigated [21,24]. While such systems work well for many applications, they generally cannot be utilized in tissue engineering because most monomers are cytotoxic. As a result, photopolymerizable hydrogels for tissue engineering applications have generally been formed from macromolecular hydrogel precursors. These are water-soluble polymers with two or more reactive groups. Examples of photopolymerizable macromers include PEG acrylate derivatives [35], PEG methacrylate derivatives [20,36], polyvinyl alcohol (PVA) derivatives [37–39], and modified polysaccharides such as hyaluronic acid derivatives [40,41] and dextran methacrylate [42,43]. Chemical structures of some of the macromers that can be used to form photopolymerizable hydrogels are shown in Fig. 2.

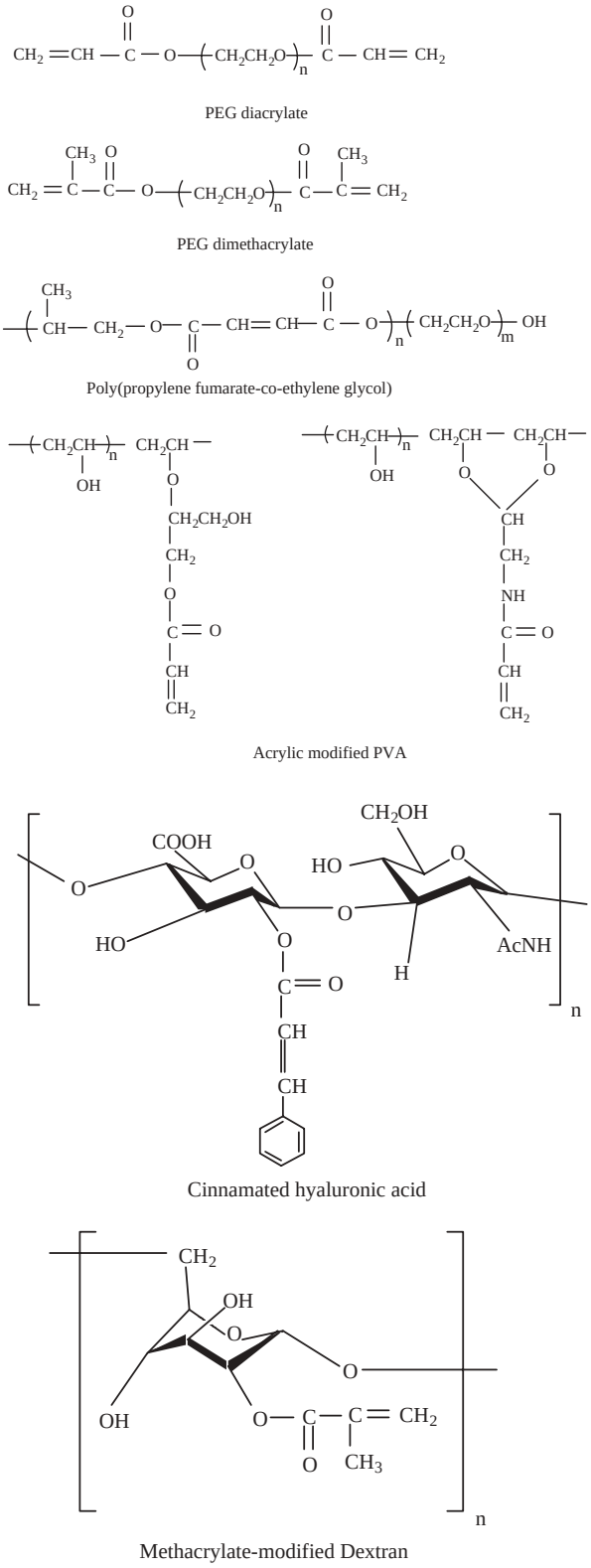

Fig. 2. Chemical structures of materials that can be photopolymerized to create crosslinked hydrogel networks: (A) PEG diacrylate, methacrylate, and propylene fumarate derivatives, (B) Crosslinkable PVA derivatives, (C) Hyaluronic acid derivatives, (D) Dextran-methacrylate.

In many applications, biodegradable or bioerodible photopolymerized hydrogels are required. Sawhney et al. developed photopolymerizable, bioerodible hydrogels based on PEG-co-poly(α-hydroxy acid) diacrylate macromers [35]. The synthesis, photopolymerization, and biodegradation of these types of hydrogels are shown in Fig. 3. In this system, degradation rates could be widely varied by changing the length and composition of the α-hydroxy acid segments of the block copolymers. The permeability and mechanical properties of the hydrogels depend on the length of the PEG segment and the concentration of macromers in the hydrogel precursor solution. Suggs et al. have synthesized a similar photopolymerizable and bioerodible material, poly(propylene fumarate-co-ethylene glycol) [44,45]. Since propylene fumarate is a linear unsaturated molecule, these copolymers also have many points of unsaturation along the polymer backbone for photocrosslinking. Additionally, photopolymerizable hyaluronic acid derivatives are intrinsically biodegradable [40,41,46]. Hyaluronidase, an endohexosaminidase, cleaves hyaluronic acid into polysaccharide fragments.

Proteolytically degradable photopolymerized hydrogels have also been developed for tissue engineering applications. Proteolytically degradable peptides that are cleaved by enzymes involved in cell migration, such as collagenase and plasmin, were co-polymerized with PEG as a BAB block copolymer, then terminated with acrylate groups. The resultant polymers were photopolymerizable macromers used to form hydrogels that were found to rapidly degrade in the presence of the targeted protease in a dose-dependent manner, but remained stable in the presence of other proteases [27]. Furthermore, cells were able to degrade these materials during migration [28]. This scheme may target material degradation to tissue formation.

In addition, bioactive derivatives of photopolymerizable macromers have been investigated as a means to control cell–material interactions for tissue engineering. Such materials may foster tissue regeneration or direct

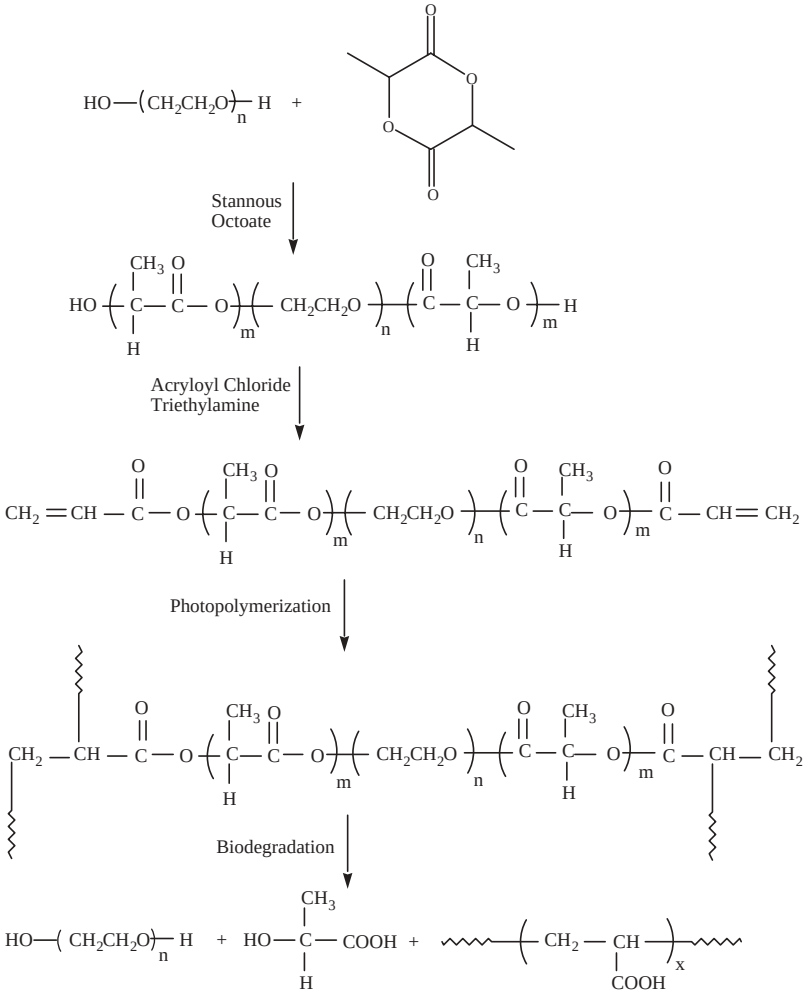

Fig. 3. The synthesis, photopolymerization, and degradation of bioerodible hydrogels, poly(ethylene glycol)-co-poly(α-hydroxy acid) diacrylate macromers. Adapted from Sawhney et al. [55].

the formation of organ specific tissue [47]. Covalent immobilization of peptides containing the adhesion domains of extracellular matrix proteins has been investigated to promote biospecific cell adhesion. For example, biomaterials have been modified with a variety of cell adhesion ligands such as RGD, a ubiquitous intergrin-binding peptide, a fibronectin-derived peptide KQAGDV, or a laminin-derived peptide YIGSR to enhance cell adhesion [48–51]. In some cases, materials can be designed to preferentially allow adhesion of a particular cell type provided that the base material is intrinsically cell non-adhesive, as is the case with many hydrogels. The fibronectin-derived peptide REDV, for instance, allows the adhesion of endothelial cells, but not adhesion of fibroblasts, smooth muscle cells, and platelets [48]. Peptides have been incorporated into photopolymerized PEG-diacrylate hydrogels by functionalizing the amine terminus of the peptide with an acrylate moiety as shown in Fig. 4 [28,50]. Growth factors can also be covalently incorporated into biomaterials to regulate cell behaviors such as proliferation, migration, and differentiation. Epidermal growth factor, for instance, has been conjugated to polyethylene glycol surfaces; the tethered growth factor was shown to direct hepatocytes to maintain their liver-specific morphology and function [52]. In addition, transforming growth factor-β (TGF-β1) has been covalently grafted to photopolymerized PEG-diacrylate hydrogels and shown to significantly increase extracellular matrix production by vascular smooth muscle cells growing within the hydrogel scaffold compared to soluble TGF-β1 at the same concentration [53].

3. Photopolymerized hydrogels in tissue engineering

Photopolymerized hydrogels have been used in a wide range of biomedical applications as described above. In tissue engineering, photopolymerized hydrogels have been used to alter and improve tissue function, for instance, by functioning as tissue barriers or local drug delivery depots, and have also been investigated for use as cell carrier materials for tissue replacement strategies.

Hydrogels as barriers. Photopolymerized hydrogels have been investigated for use as barriers following tissue injury in order to improve the healing response. These applications have included the prevention of thrombosis and restenosis following vascular injury [5,6] and post-operative adhesion formation [7–10]. Barriers were formed from degradable poly(ethylene glycol-co-lactic acid) diacrylate macromers as coatings on the tissue surfaces. These barriers were highly resistant to protein adsorption and diffusion as well as to cell adhesion. For prevention of thrombosis and restenosis, thin hydrogel layers were formed intravascularly via interfacial photopolymerization following vascular injury. These materials prevented thrombosis and significantly reduced intimal thickening (a measure of restenosis) in rat and rabbit models [5,6] as well as porcine models [32,33]. Restenosis was reduced due to the prevention of contact with platelets, coagulation factors, and plasma proteins that stimulate smooth muscle cell proliferation, migration, and matrix synthesis following injury. For prevention of post-operative adhesion formation, hydrogel barriers were formed on intraperitoneal surfaces by bulk photopolymerization of poly(ethylene glycol-co-lactic acid) diacrylate. These

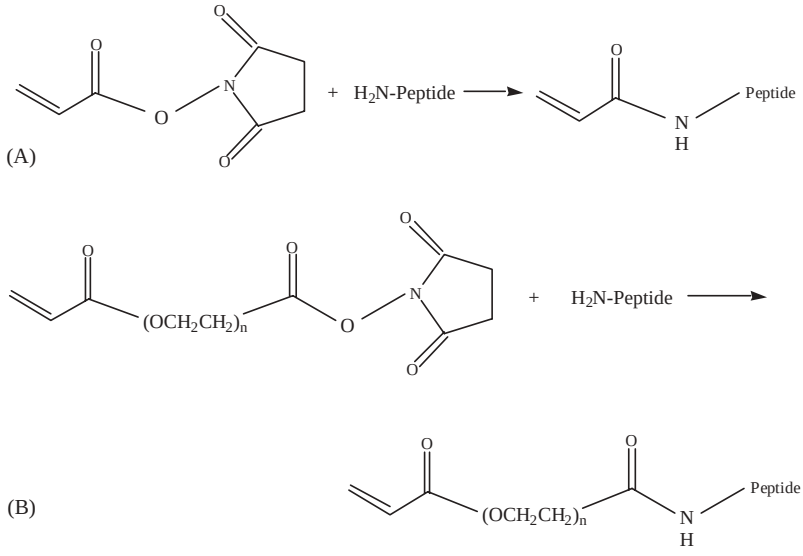

Fig. 4. Incorporation of peptides without (A) and with (B) a PEG spacer arm. *N*-hydroxysuccinimidyl-activated esters were used to couple the N-terminal amine of the peptide to an acrylate moiety. These compounds can be mixed with macromolecular hydrogel precursors. Following photopolymerization, the peptide is covalently grafted into the hydrogel network. Adapted from Hern and Hubbell [50].

barrier materials were found to effectively reduce adhesion formation in several rat and rabbit models [7–10]. The reduction in adhesion formation was due to the prevention of fibrin deposition and fibroblast attachment to the tissue surface.

Drug delivery systems. Photopolymerized hydrogels have also been employed as localized drug delivery depots [11,13,14]. Hydrogels are attractive for use as drug carriers because of their compatibility with hydrophilic, macromolecular drugs such as proteins or oligonucleotides, good biocompatibility, and the ease of regulating drug release by controlling swelling, crosslink density, and degradation. Photopolymerized hydrogels are attractive for localized drug delivery because the hydrogel can be formed in situ and thus will adhere and conform to the targeted tissue. Photopolymerized hydrogels have been used for local delivery of various agents to prevent post-operative adhesion formation; in this case, the use of localized drug delivery was intended to act synergistically with the barrier effect also provided by the photopolymerized hydrogel. Tissue plasminogen activator [10], urokinase plasminogen activator [10], and ancrod [11] locally released from biodegradable photopolymerized hydrogels formed on intraperitoneal tissues have been shown to significantly reduce adhesion formation compared to either hydrogel barriers alone or intraperitoneal injection of these agents in a rat model.

In addition, photopolymerized hydrogels have been investigated for intravascular drug delivery. Hydrogels containing protein or oligonucleotide drugs can be formed on the inner surface of blood vessels via interfacial photopolymerization [13]. Bilayer hydrogels can be formed with the luminal (innermost) layer less permeable than the intimal (near the vessel wall) layer by using a lower molecular weight precursor for the luminal layer. This type of hydrogel structure was shown to enhance delivery of the released protein into the arterial media rather than into the blood stream. An example of a bilayer intravascular hydrogel is shown in Fig. 5.

Similarly, photopolymerization of hydrogels has also been investigated to create layered matrix devices to release drugs in non-uniform concentration profiles [14,54]. In these multilaminated matrix devices, each layer was sequentially photopolymerized with a different drug concentration to achieve the optimized release behavior. Non-uniform drug release could also be achieved by varying the thickness and the solute diffusion coefficient of each layer [14,54].

Hydrogels for cell encapsulation. The use of photopolymerized hydrogels for cell transplantation, where the hydrogel material provides immunoisolation but allows facile diffusion of oxygen, nutrients, and metabolic products, has also been investigated. Photopolymerized PEG diacrylate hydrogels have been explored for the transplantation of islets of Langerhans for development of a bioartificial endocrine pancreas [17,18,55]. PEG-based microspheres were formed with entrapped islets by photopolymerization of PEG diacrylate prepolymer solution that was atomized with a suspension of islets. These capsules provided immunoisolation, but the success of the grafted tissue was limited, presumably by diffusion of nutrients to the entrapped cells. Interfacially photopolymerized hydrogels for the encapsulation of islets were then investigated to reduce the diffusional limitations by reducing the thickness of the hydrogel capsule [18,55,56]. These studies found that encapsulated islets not only remained viable for prolonged periods but were also glucose responsive. These interfacially encapsulated islets were free of fibrous tissue after implantation. PEG diacrylate-encapsulated porcine islets were found to be viable and contain insulin after 30 days implantation in Sprague-Dawley rats [18].

Fig. 5. Rat artery treated with a bilayer polymer hydrogel adherent to the arterial intima. The intimal layer (labeled by incorporation of fluorescein-containing 1 μm beads, green color) was formed by interfacially photopolymerizing a PEG-diacrylate solution atop the arterial intima. Drugs can be incorporated into this layer. The luminal layer (labeled by incorporation of rhodamine-containing 1 μm beads, red color) was formed by interfacially photopolymerizing a lower molecular weight PEG-diacrylate solution atop the intimal layer. By making the luminal layer less permeable than the intimal layer (using a lower molecular weight precursor for the luminal layer), it was possible to drive more of the released protein into the arterial media by limiting loss into the lumen.

Scaffold materials. Because the mechanical properties of many hydrogels can be tailored to match those of many soft tissues, these materials may be attractive scaffolds for development or regeneration of soft tissues. For example, photopolymerized hydrogels have been investigated for use as scaffolds for cartilage regeneration [20,25,34]. Photopolymerization was used to encapsulate bovine and ovine chondrocytes in semi-interpenetrating networks of poly(ethylene glycol)-dimethacrylate and poly(ethylene glycol) [20]. Cells were found to be dispersed evenly through the scaffold material and remained viable after photopolymerization and 2 weeks of culture; however, the cell content of scaffolds decreased significantly over time, presumably due to the non-degradable nature of these scaffolds. Extracellular matrix production (sulfated glycosaminoglycan and collagen) was increased over the 14 days of

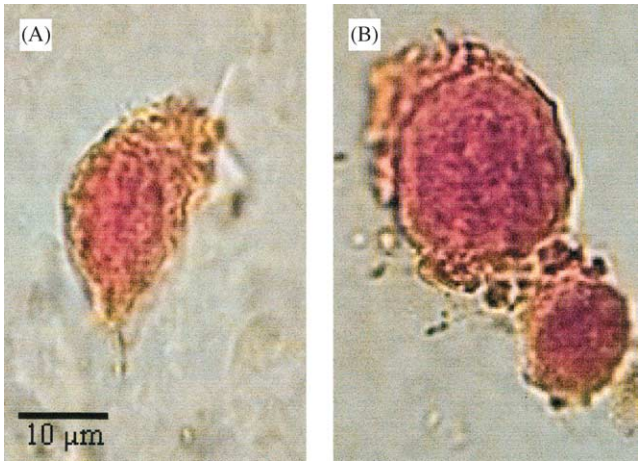

Fig. 6. Human aortic smooth muscle cells growing in PEG hydrogels and stained with Biebrich's Scarlet Acid Fuschin: (A) in biodegradable-derivative PEG hydrogels; (B) in non-degradable PEG-diacrylate hydrogels.

culture. Equilibrium moduli, dynamic stiffness, and streaming potentials of these tissues were also found to increase with culture time. These results indicate promise for photopolymerized hydrogels for scaffolds for cartilage regeneration and replacement, but suggest that biodegradable materials will ultimately be required.

Photopolymerizable hydrogels have also been utilized as scaffolds for vascular cell growth. Endothelial cells in biodegradable poly(propylene fumarate-co-ethylene glycol) scaffolds were implanted subcutaneously in rats [19]. Cell proliferation, as shown by ^{3}H-thymidine incorporation, was observed in these hydrogels following implantation. Histological sections of the hydrogels showed that cells were distributed evenly throughout hydrogels. In addition, Mann et al. [28] have utilized photopolymerized hydrogels as scaffolds for vascular smooth muscle cells. These materials were PEG-diacrylate derivatives with grafted RGD-peptides. The cells were homogeneously distributed within the scaffolds and remained viable with subsequent proliferation and matrix protein production. In proteolytically degradable scaffolds, cells were able to spread and migrate, while in non-degradable hydrogels, cells were round and formed clusters. Additionally, cell proliferation and extracellular matrix production reached higher levels in proteolytically degradable hydrogels than in similar non-degradable PEG-diacrylate scaffolds. Histological sections of smooth muscle cells growing in degradable and non-degradable PEG-diacrylate hydrogels are shown in Fig. 6.

4. Conclusions

Due to their biocompatibility, permeability, and physical characteristics, hydrogels are good candidates as biomaterials for use in many medical applications, including tissue engineering. Hydrogels may be useful for manipulation of tissue function or for scaffolds for tissue regeneration or replacement. The use of photopolymerization in the preparation of hydrogels is advantageous in comparison with conventional crosslinking methods because liquid hydrogel precursors can be delivered and crosslinked to form hydrogels in situ in a minimally invasive manner. This process also gives one spatial and temporal control over the conversion of a liquid to a gel, so that complex shapes can be fabricated. Hydrogels can be formed with varying polymer formulations in three-dimensional patterns since sequentially polymerized layers will firmly adhere to one another. Photopolymerized hydrogels can be designed to degrade via hydrolytic or enzymatic processes and can be modified with biofunctional moieties within their structure to manipulate cell behavior and to generate organ-specific tissue formation. These photopolymerizable hydrogels have been used as barriers, localized drug delivery depots, cell encapsulation materials, and scaffold materials.

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