

Biomedical Applications of Biodegradable Polymers

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ABSTRACT: Utilization of polymers as biomaterials has greatly impacted the advancement of modern medicine. Specifically, polymeric biomaterials that are biodegradable provide the significant advantage of being able to be broken down and removed after they have served their function. Applications are wide ranging with degradable polymers being used clinically as surgical sutures and implants. To fit functional demand, materials with desired physical, chemical, biological, biomechanical, and degradation properties must be selected. Fortunately, a wide range of natural and synthetic degradable polymers has been investigated

for biomedical applications with novel materials constantly being developed to meet new challenges. This review summarizes the most recent advances in the field over the past 4 years, specifically highlighting new and interesting discoveries in tissue engineering and drug delivery applications. © 2011 Wiley Periodicals, Inc. *J Polym Sci Part B: Polym Phys* 49: 832–864, 2011

KEYWORDS: biodegradable; biomaterials; polyamides; polycarbonates; polyesters; polyethers; polylactide; polyphosphazenes; polysaccharides; polyurethanes

INTRODUCTION A biomaterial is defined as any natural or synthetic substance engineered to interact with biological systems to direct medical treatment.¹ Biomaterials must be biocompatible meaning that they perform their function with an appropriate host response.² To meet the needs of the biomedical community, materials composed of everything from metals and ceramics to glasses and polymers have been researched. Polymers possess significant potential because flexibility in chemistry gives rise to materials with great diversity of physical and mechanical properties. Degradable polymers are of utmost interest because these biomaterials are able to be broken down and excreted or resorbed without removal or surgical revision.

Although natural polymers such as collagen have been used biomedically for thousands of years, research into biomedical applications of synthetic degradable polymers is relatively new, starting in the 1960s.^{3,4} In the 50 years since, successes have been numerous, but grand challenges still exist in both the basic and translational elements of biomaterial design. From a basic science perspective, the capacity to modulate biomaterial chemistry to convey unique material properties is endless yet requires significant time and resources to complete the research. As biomaterials are applied in the clinical setting, numerous issues arise that cannot be adequately identified and addressed in previous *in vitro* and model *in vivo* experiments. The host response to both tissue engineering and drug delivery devices depends on the chemical,

physical, and biological properties of the biomaterials. When these materials are also biodegradable, there exists the additional issue of continuing changes in the material properties induced by degradation over time. These changes can cause long-term host responses to these biomaterials to be greatly different than the initial response. These issues are nontrivial and have contributed to the slow evolution of biodegradable polymeric biomaterials as a field of research.

To better address many issues in biomaterial design and expedite progress, biomaterials scientists have fundamentally changed their approach to the research. Especially in the last 10 years, there has been a shift in paradigm from investigators working independently on narrow research goals to collaborative teams that facilitate solving greater objectives. Researchers with expertise in chemistry, biology, materials, engineering, and clinical practices now work together to advance biomaterials research more rapidly.^{5–13}

In the design of biodegradable biomaterials, many important properties must be considered. These materials must (1) not evoke a sustained inflammatory response; (2) possess a degradation time coinciding with their function; (3) have appropriate mechanical properties for their intended use; (4) produce nontoxic degradation products that can be readily resorbed or excreted; and (5) include appropriate permeability and processability for designed application.¹⁴ These properties are greatly affected by a number of features of

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degradable polymeric biomaterials including but not limited to: material chemistry, molecular weight, hydrophobicity, surface charge, water adsorption, degradation, and erosion mechanism. Because of the wide-ranging use of polymeric biomaterials, a single, ideal polymer or polymeric family does not exist. Instead a library of materials is available to researchers that can be synthesized and engineered to best match the specifications of the material's desired biomedical function.

Biomaterial applications of biodegradable polymers have already been extensively reviewed in the past, so no attempt will be made to provide a further exhaustive review. Instead, the reader is referred to comprehensive articles in *Advances in Biochemical Engineering/Biotechnology*¹⁵ and *Progress in Polymer Science*,¹⁶ which include research prior to and including 2006. This review will focus on the numerous advancements made in the development of hydrolytically and enzymatically degradable polymers over the past 4 years.

HYDROLYTICALLY DEGRADABLE POLYMERS

Hydrolytically degradable polymers are materials that possess hydrolytically labile chemical bonds in their backbone and can be broken down without secondary influence as shown in Figure 1. The broken bond yields two species with one product gaining a hydrogen atom and the other gaining a hydroxyl group. A number of degradable polymers possess

bonds that are susceptible to hydrolysis including esters, anhydrides, acetals, carbonates, amides, urethanes, and phosphates. One of the major features that conveys significant impact on the capacity of these polymeric families to function as biomaterials is their relative degradation rates and erosion mechanisms. An extensive investigation into a number of different degradable polymeric families showed that the degradation rates (Table 1) can vary 12-fold from very hydrolytically unstable (polyphosphazenes) to extremely hydrolytically stable (polyamides).¹⁷ It should be noted with certain families' (polyphosphazenes and polyanhydrides) degradation rate can be greatly modulated based on polymer chemistry conveying significant flexibility in material properties for these families. Degradation rates are incorporated with other factors such as water diffusion, monomer solubility and diffusion, and device geometry and size, to determine how a degradable polymeric biomaterial will erode. Erosion

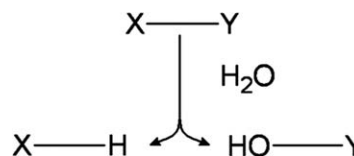


FIGURE 1 The hydrolytically sensitive bond X–Y is cleaved by a water molecule yielding the products of X–H and HO–Y.

TABLE 1 Summary of Different Polymeric Families' Applications, Advantages, Disadvantages, Degradation Rate, and Structure

Polymer	Applications	Advantages	Disadvantages	λ , Degradation Rate Constant (s^{-1})	Structure
Polyphosphazenes	Tissue Engineering; Vaccine Adjuvant	Synthetic Flexibility; Controllable Mechanical Properties	Complex Synthesis	$4.5 \times 10^{-2} - 1.4 \times 10^{-7}$ (refs. 13 and 776)	$\left(\begin{array}{c} R_1 \\ \\ P=N \\ \\ R_2 \end{array} \right)_n$
Polyanhydrides	Drug Delivery; Tissue Engineering	Significant Monomer Flexibility; Controllable Degradation Rates	Low-molecular Weights; Weak Mechanical Properties	$1.9 \times 10^{-3} - 9.4 \times 10^{-9}$ (refs. 17 and 777)	$\left(\begin{array}{c} O \\ \\ C-R-C-O \\ \\ O \end{array} \right)_n$
Polyacetals	Drug Delivery	Mild pH Degradation Products; pH Sensitive Degradation	Low Molecular Weights; Complex Synthesis	6.4×10^{-5} (ref. 17)	$\left(-R_1-O-\begin{array}{c} R_2 \\ \\ C \\ \\ R_3 \end{array}-O- \right)_n$
Poly(ortho esters)	Drug Delivery	Controllable Degradation Rates; pH Sensitive Degradation	Weak Mechanical Properties; Complex Synthesis	4.8×10^{-5} (ref. 17)	$\left(-R_1-O-\begin{array}{c} R_2 \\ \\ C \\ \\ O \\ \\ R_3 \end{array}-O- \right)_n$
Polyphosphoesters	Drug Delivery; Tissue Engineering	Biomolecule Compatibility; Highly Biocompatible Degradation Products	Complex Synthesis	1.4×10^{-6} (refs. 778 and 779)	$\left(-R_1-O-\begin{array}{c} O \\ \\ P \\ \\ R_2 \end{array}-O- \right)_n$
Polycaprolactone	Tissue Engineering	Highly Processable; Many Commercial Vendors Available	Limited Degradation	3.5×10^{-8} (ref. 27)	$\left(-O-(CH_2)_5-\begin{array}{c} O \\ \\ C \end{array}- \right)_n$
Polyurethanes	Prostheses; Tissue Engineering	Mechanically Strong; Handle Physical Stresses Well	Limited Degradation; Require Copolymerization with Other Polymers	8.3×10^{-9} (ref. 780)	$\left(-R-N-\begin{array}{c} O \\ \\ C \\ \\ H \end{array}-O- \right)_n$
Poly lactide	Tissue Engineering; Drug Delivery	Highly Processable; Many Commercial Vendors Available	Limited Degradation; Highly Acidic Degradation Products	6.6×10^{-9} (ref. 17)	$\left(-O-\begin{array}{c} H \\ \\ C \\ \\ CH_3 \end{array}-\begin{array}{c} O \\ \\ C \end{array}- \right)_n$
Polycarbonates	Drug Delivery; Tissue Engineering; Fixators	Chemistry-Dependent Mechanical Properties; Surface Eroding	Limited Degradation; Require Copolymerization with Other Polymers	4.1×10^{-10} (ref. 285)	$\left(-R-O-\begin{array}{c} O \\ \\ C \\ \\ O \end{array}-O- \right)_n$
Polyamides	Drug Delivery	Conjugatable Side Group; Highly Biocompatible Degradation Products	Very Limited Degradation; Charge Induced Toxicity	2.6×10^{-13} (ref. 17)	$\left(-R-N-\begin{array}{c} O \\ \\ C \\ \\ H \end{array}- \right)_n$

is typically categorized as surface erosion, bulk erosion, or a combination of the two.¹⁸ Surface erosion is characterized by the rate of polymer degradation and mass relief at the water-device interface being much greater than the rate at which water diffuses into the bulk of the material leading to a device that degrades almost entirely at its surface. Bulk erosion is characterized by the reverse in which water diffusion is much faster than degradation leading to degradation and subsequent mass loss occurring throughout the bulk of the material. These categorizations are extremely important in determining which material is best for a desired application. For example, in sustained drug delivery a material that

can undergo surface erosion may be desired because stable, near zeroth-order release can be maintained and payload release kinetics can be more easily tailored,¹⁹ whereas for applications requiring a permeable membrane like in tissue engineering, bulk eroding materials would allow for necessary hydrolytic diffusion.²⁰ The following sections discuss a number of hydrolytically sensitive polymers and their biomedical applications.

Poly(α -esters)

Poly(α -esters) are a class of polymers that contain an aliphatic ester bond in their backbone. Although a number of

polyesters are commercially available and all are theoretically degradable, the hydrolytically stable nature of the ester bond (Table 1) means only polyesters with reasonably short aliphatic chains can be utilized as degradable polymers for biomedical applications. Although these polymers are often mildly hydrophobic, ester bond stability causes them to undergo bulk erosion.²¹ Because of the relative ease of their synthesis (via ring-opening or condensation polymerization) and commercial availability, poly(α -esters) have been the most heavily researched degradable biomaterials to date.²²

Polyglycolide

Polyglycolide or poly(glycolic acid) (PGA) was one of the very first degradable polymers ever investigated for biomedical use. With a melting point (T_m) greater than 200 °C, a glass transition temperature (T_g) of 35–40 °C, and very high tensile strength (12.5 GPa),²³ PGA found favor as the degradable suture DEXON[®], which has been actively used since 1970.²⁴ From 1984 to 1996, PGA was marketed as an internal bone pin under the name Biofix[®], but since 1996 Biofix has been converted to a poly(L-lactide) base for better long-term stability.^{25,26}

Because of PGA's rapid degradation and insolubility in many common solvents, limited research has been conducted with PGA-based drug delivery devices. Instead, most recent research has focused on short-term tissue engineering scaffolds and the utilization of PGA as a filler material coupled with other degradable polymer networks. PGA is often fabricated into a mesh network and has been used as a scaffold for bone,^{27–30} cartilage,^{31–33} tendon,^{34,35} tooth,³⁶ vaginal,³⁷ intestinal,³⁸ lymphatic,³⁹ and spinal regeneration.⁴⁰ Although there has been research conducted into a wide range of applications, there exists significant issues with PGA. Rapid degradation leads to the loss of mechanical strength and significant local production of glycolic acid. Although glycolic acid is bioresorbable by cells via the citric acid cycle,⁴¹ high level of glycolic acid have been linked to a strong, undesired inflammatory response.^{42–44} In addition, PGA has mechanically failed as a biomaterial when used to facilitate colonic anastomosis formation³⁸ and prevent intrapericardial adhesions.⁴⁵

Polylactide

As polylactide (PLA) possesses chiral molecules, PLAs come in four forms: poly(L-lactic acid) (PLLA), poly(D-lactic acid) (PDLA), poly(D,L-lactic acid) (PDLLA)—a racemic mixture of PLLA and PDLA, and meso-poly(lactic acid). As far as use in biomedical research, only PLLA and PDLLA have shown promise and have been extensively studied.

PLLA has a T_g of 60–65 °C, a melting temperature of around 175 °C and a mechanical strength of 4.8 GPa.⁴⁶ The additional methyl group in PLA causes the polymer to be much more hydrophobic and stable against hydrolysis than PGA. High molecular weight PLLA has been shown to take greater than 5 years to be completely resorbed *in vivo*.⁴⁷ Because of the slow degradation time, limited research has been recently conducted into drug delivery by PLLA systems alone.^{48–51} To reduce degradation time, investigators have

either developed modification techniques or have blended or copolymerized PLLA with other degradable polymers. One interesting modification technique has been through the use of radiation.^{52,53} This process works by creating radicals in the ester alpha carbon, which upon rearrangement shortens the polymer backbone through the removal of an ester bond and the release of carbon dioxide. Recombination of carbon radicals induces branching and crosslinking causing a decrease in crystallinity due to the modified polymers possessing unique molecular architectures. Shortening of the polymer and decrease in crystallinity work in concert to facilitate more rapid device degradation. Although this process is very predictable, allowing for fine tuning of PLLA degradation behavior, even heavily irradiated PLLA is not completely absorbed until months after being delivered *in vivo*. This holds promise for drug eluting depots (i.e., birth control delivery devices), but further research must be completed in order for PLLA to be more widely used for short-term controlled delivery applications. Under the product name Fixsorb[®], PLLA has been used as a bone fixator.⁵⁴ PLLA has also been extensively utilized in tissue engineering applications ranging from scaffolds for bone,^{55–58} cartilage,^{59,60} tendon,⁶¹ neural,^{62,63} and vascular⁶⁴ regeneration. Specifically, Dr. Peter Ma's group has produced some very exciting research on the design of PLLA-based patient specific scaffolds (Fig. 2).⁶⁵ A CT image of a digit was converted to a three-dimensional (3D) structured wax mold through layer-by-layer (LBL) printing. By utilizing a solvent-extraction process and paraffin spheres, a 3D PLLA scaffold that matched the structure of the digit was manufactured. The authors were able to uniquely control the nanostructure, microstructure, and macrostructure of the scaffold. This promising technique has the potential to be used for a number of different degradable polymers and parameters could be optimized for a wide-range of applications. Composite materials include PLLA combined with PDLLA,⁶⁶ poly(lactide-co-glycolide) (PLGA),⁶⁷ poly(caprolactone),^{68,69} poly(ethylene glycol) (PEG),⁷⁰ collagen,⁷¹ and chitosan.⁷²

PDLLA is an amorphous polymer due to the random positions of its two isomeric monomers within the polymer chain yielding a slightly lower T_g of 55–60 °C and lower mechanical strength of 1.9 GPa.²³ Although possessing more desirable degradation properties than PLLA, PDLLA still takes over a year to properly erode which has kept it from being researched as a particle-based delivery vehicle. Instead PDLLA has been commonly used as a drug delivery film for inorganic implants,^{73–76} or as a tissue engineering scaffold.^{77–79} Like PLLA, PDLLA has been often combined with other degradable polymers such as PLGA,⁸⁰ PEG,^{81,82} and chitosan⁸³ to create composites with desirable material properties.

Poly(lactide-co-glycolide)

Random copolymerization of PLA (both L- and D,L-lactide forms) and PGA, known as PLGA, is the most investigated degradable polymer for biomedical applications and has been used in sutures, drug delivery devices, and tissue engineering scaffolds. With a number of commercial

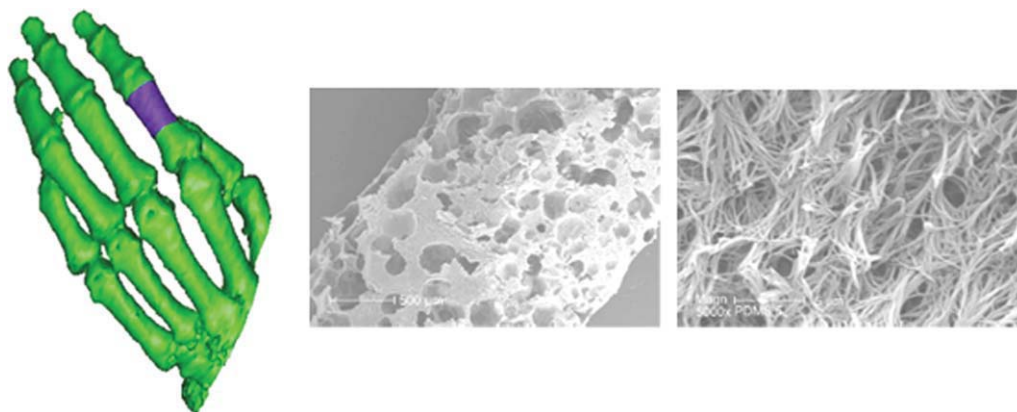


FIGURE 2 Conversion of CT images into microstructure- and nanostructure-controlled PLA scaffolds. A CT image of a hand (left) with a nontraditional defect (shown in purple) is converted into a wax mold which can be filled with PLA to create a scaffold with controllable pore size on the micro scale (center) and fiber size on the nano scale (right). (Reproduced from ref. 65, with permission from Elsevier.)

manufacturers and easy polymer processability, researchers do not have to be polymer synthesis experts to utilize PLGA in their work. One particular advantage is that because PLA and PGA have significantly different properties, careful choice of copolymer composition allows for the optimization of PLGA for intended applications. Property modulation is even more significant for PLGA copolymers because with 25–75% lactide composition, PLGA forms amorphous polymers, which are very hydrolytically unstable compared with the more stable homopolymers.^{41,84} This is evident in the degradation times of 50:50 PLGA, 75:25 PLGA, and 85:15 PLGA being 1–2 months, 4–5 months, and 5–6 months, respectively.⁸⁵

PLGA has been used as a suture material since 1974⁸⁶ under the product name Vicryl[®] (Ethicon), a 10:90 PLGA braided construct. More recently a modified version, Vicryl Rapide[®], has come to market. Vicryl Rapide[®] degrades much more quickly than traditional Vicryl[®], because it is irradiated during production. Panacryl[®] (Ethicon) is another product which has a higher LA/GA ratio (90:10) than Vicryl[®] causing it to undergo more rapid degradation. Unfortunately, Panacryl[®] has seen a significant drop in recent use due to public concern that it induces significant inflammation after implantation even though a recent report refutes this argument.⁸⁷ Although Ethicon produces the most widely used PLGA sutures, Polysorb[®] (Syneture) and Purasorb[®] (Purac Biomaterials) are also commonly used suture materials composed of PLGA.

With rapid degradation compared to other polyesters, PLGA has been utilized extensively in drug delivery applications. PLGA has been used to deliver chemotherapeutics,^{88,89} proteins,^{90–92} vaccines,^{93–95} antibiotics,^{96–98} analgesics,^{99,100} anti-inflammatory drugs,^{101,102} and siRNA.^{103–105} Most often PLGA is fabricated into microspheres,^{90–95,97,98,101} microcapsules,^{106–108} nanospheres,^{88,89,95,96,100} or nanofibers^{109,110} to facilitate controlled delivery of encapsulated or adsorbed payloads. Depending on the composition of the PLGA used and the interactions between payload and polymer, drug or

protein release profiles can vary.⁵⁴ Unfortunately, bulk erosion of the polymer prevents significant modulation of the release rate. Water diffusion in, payload dissolution and subsequent diffusion out is not controlled by polymer degradation rate and often PLGA delivery devices have a significant bolus release of their payload. Additionally, hydration of the entire matrix can often damage or deactivate hydrolytically sensitive encapsulated materials through constant water exposure and the high acidity of PLGA degradation products.^{111,112} The use of surface eroding polymers is better for zeroth-order and controlled release kinetics as well as payload protection.

PLGA demonstrates great cell adhesion and proliferation properties making it an excellent candidate for application in tissue engineering. PLGA has been fabricated into scaffolds by a number of different techniques including gas foaming,^{113,114} microsphere sintering,^{115–117} porogen leaching,^{118–120} electrospinning,^{121–124} polymer printing,^{125,126} or a combination of these techniques^{80,127,128} to create unique nanostructured and microstructured materials that can facilitate tissue development. Polymer printing in particular is a novel technique that holds great promise in the design of tissue engineering scaffolds. Dr. James Dunn's group has demonstrated the capacity of 3D printing with PLGA.^{126,129} As shown in Figure 3, very complex designs with controllable features can be generated to mimic structured tissue like villi for smooth muscle tissue engineering.¹²⁶ The ability to utilize this technology with other degradable polymers holds promise in allowing for the design of organ-like structures that until now have been impossible to replicate. PLGA scaffolds have been used in the engineering of bone,^{10,79,115,116} cartilage,^{60,92,117} tendon,^{117,123,130,131} skin,^{108,122,132} liver,^{133–135} and nerve tissue.^{136–138}

Polyhydroxyalkanoates

Polyhydroxyalkanoates are biodegradable polyesters that can be produced by both bacterial and synthetic routes. The most common polymer in this family is poly(3-hydroxybutyrate) (PHB), a semicrystalline isotactic polymer that

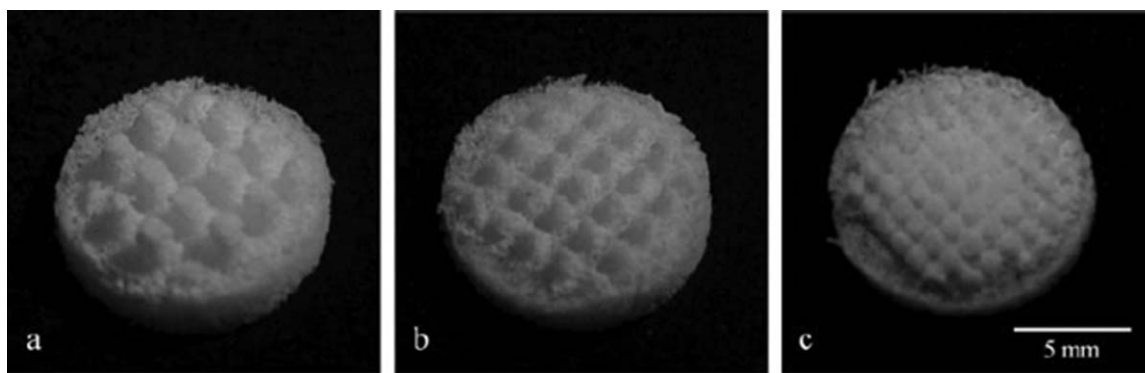


FIGURE 3 PLGA scaffolds with villi architecture generated by indirect three-dimensional printing with villus diameter, height and intervillus spacing of (a) 0.5, 1, and 0.5, mm; (b) 0.5, 1, and 1 mm; (c) 1, 1, and 1 mm, respectively. (Reproduced from ref. 126, with permission from Wiley.)

undergoes surface erosion due to the hydrophobicity of its backbone and its crystallinity.¹³⁹ PHB has a T_g around 5 °C and a melting temperature from 160 to 180 °C.¹⁴⁰ Hydrolytic degradation of PHB results in the formation of D-(–)-3-hydroxybutyric acid, a normal blood constituent.¹⁴¹ The biocompatibility, processibility, and degradability of PHB make it an excellent candidate for use in long-term tissue engineering applications.^{142–147} Unfortunately, the stability of PHB makes it a poor candidate for controlled delivery applications.

To widen the applicability of PHB as a biomaterial, most commonly PHB is copolymerized with 3-hydroxyvalerate to create poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV). PHBV is less crystalline than PHB with a lower melting temperature of 80–160 °C and a T_g in the range of –5 to 20 °C depending on HV content.¹⁴⁸ PHBV has been used in tissue engineering of bone,^{147,149,150} cartilage,¹⁵¹ tendon,¹⁵² skin,^{143,153} and nerves.^{143,147} Although the addition of HV content improves the biomaterial potential of PHB, degradation is still too slow for other biomedical applications. Significant research is underway to speed degradation rates through copolymerizing or blending PHB or PHBV with PLLA,¹⁵³ PDLLA,^{154,155} PLGA,^{114,156–158} poly(dioxanone),¹⁵⁹ poly(caprolactone),^{160–162} and polyethers.^{163–165}

Polycaprolactone

Polycaprolactone (PCL) is a semicrystalline polyester with great organic solvent solubility, a melting temperature of 55–60 °C and $T_g = -54$ °C.¹⁶⁶ Because of PCL's very low *in vivo* degradation rate and high drug permeability, it has found favor as a long-term implant delivery device. Capronor[®] is a commercial contraceptive PCL product that is able to deliver levonorgestrel *in vivo* for over a year and has been on the market for over 25 years.¹⁶⁷ Current research is being conducted into the development of microsized and nanosized drug delivery vehicles, but the degradation rate (2–3 years) is a significant issue for pure PCL products to be FDA approved for this use. Instead PCL is often blended or copolymerized with other polymers such as PLLA,^{68,168,169} PDLLA,^{170,171} PLGA,^{104,172,173} and polyethers^{174–176} to expedite overall polymer erosion.

Although somewhat limited in drug delivery applications, tissue engineering implications of PCL are numerous. PCL has low tensile strength (~23 MPa), but very high elongation at breakage (4700%) making it a very good elastic biomaterial.⁴¹ PCL's processability allows for the formation of scaffolds composed of adhered microspheres,^{177,178} electrospun fibers,^{179–181} or through porous networks created by porogen leaching.^{182–184} PCL and PCL composites have been used as tissue engineering scaffolds for the regeneration of bone,^{182,185,186} ligament,^{187,188} cartilage,^{133,189} skin,^{177,181,190} nerve,^{184,191,192} and vascular tissues.^{183,193,194} A recent advancement using PCL hybrid scaffolds has been used in interfacial tissue engineering. Lee and co-workers have shown that if distinct scaffold regions are seeded with appropriate cells harvested from cartilage or ligament sources (Fig. 4), complex tissue interfaces like the bone-ligament interface can be regenerated.¹⁹⁵

Poly(propylene fumarate)

Poly(propylene fumarate) (PPF) is a high-strength polymeric biomaterial that while technically a polyester, possesses the unique ability to be crosslinked through the unsaturated bonds in its backbone. As PPF can be crosslinked, polymer degradation is dependent on molecular weight, crosslinker, and crosslinking density.¹⁹⁶ PPF is a liquid injectable, which

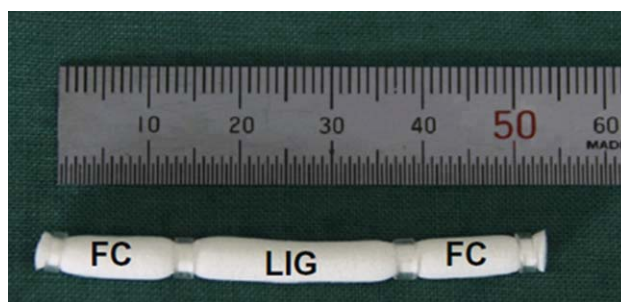


FIGURE 4 Cylindrical porous poly(L-lactide-co-caprolactone) scaffold loaded with fibrochondrocytes (fibrocartilage sections) on either end with fibroblasts (ligament section) in the center in order to mimic the ligament-bone interfacial tissues. (Reproduced from ref. 195, with permission from Elsevier.)

becomes solid during crosslinking; therefore, it has found favor in biomedical applications such as filling bone defects^{197–199} and the depot, long-term delivery of ocular drugs.^{200–202} For osteogenic tissue engineering, PPF is often mixed with ceramics such as hydroxyapatite^{203–205} or alumoxane^{206–208} to create stronger, more-bioactive scaffolds. Recent research has focused on the use of PPF to fill irregular shaped bone defects such as ear ossicle²⁰⁹ or mandibular defects.²¹⁰ In both circumstances, PPF-based scaffolds allow the design of structures that may not be attainable from noncrosslinkable degradable polymers.

Polyanhydrides

Polyanhydrides are a class of surface eroding polymers that contain two carbonyl groups bound together by an ether bond and have been almost exclusively studied for biomedical applications. While originally developed as textile fibers in the 1930s, their hydrolytic instability precluded their wide-spread usage.²¹¹ Beginning in the 1980s, polyanhydrides were investigated for the biomaterial potential,²¹² eventually leading to their FDA approval as drug delivery vehicles in 1996.²¹³ One particularly unique property of polyanhydrides is that the degradation of the anhydride bond is highly dependent on polymer backbone chemistry. In fact degradation rate can vary by over six orders of magnitude based on monomer chemistry (Table 1). Surface erosion and control over degradation rate allow for precision tuning of payload release rate which is why polyanhydrides have found significant favor in drug delivery applications. Polyanhydrides have been used for the delivery of chemotherapeutics,^{214,215} antibiotics,^{216,217} vaccines,^{218–221} and proteins.^{106,222,223} Polyanhydrides are often fabricated into microparticles^{106,218,220,222} or nanoparticles^{214,215,219,221,223} to allow for injectable, oral, or aerosol delivery. Aliphatic homo-polyanhydrides, such as poly(sebacic anhydride) (poly(SA)) have been found to have limited applications due to their rapid degradation. To retard polymer degradation and extend payload delivery, aliphatic diacid monomers have been copolymerized with hydrophobic aromatic diacid monomers^{218,222,224–226} or aliphatic fatty acid dimers.^{227,228} By varying aromatic monomer, (1,3-bis-*p*-(carboxyphenoxy)hexane) (CPH), content, Determan and coworkers have fabricated polyanhydride particles that release their payload over a few days to a couple of years, as shown in Figure 5.¹⁹ Additional research in polyanhydrides has focused on novel monomer development to allow for the replacement of SA due to its high acidity in solution (pH = 4.2).²²⁹ A monomer of interest is 1,8-bis-(*p*-carboxyphenoxy)-3,6-dioxaoctane, which is an aromatic diacid monomer that contains a triethylene glycol backbone that together convey amphiphilicity.^{230,231} Copolymerizing this polymer with traditional aromatic diacid monomers yields degradable polymers that can be used as long-term delivery vehicles that have shown to stabilize acid-sensitive payloads like recombinant proteins.^{220,223}

Although polyanhydrides have been extensively investigated for drug delivery applications, their low molecular weights yield poor mechanical properties precluding their use in tissue engineering. To increase their strength, methacrylated

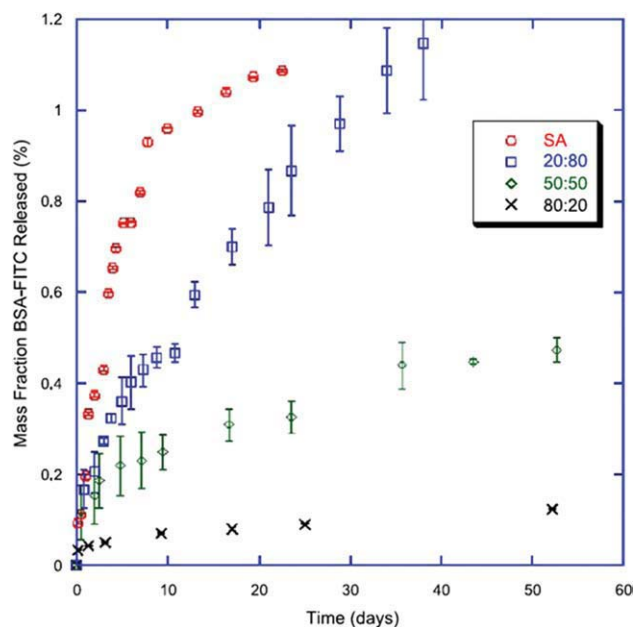


FIGURE 5 *In vitro* release of bovine serum albumin from poly(CPH:SA) microparticles in phosphate-buffered saline (pH 7.4). (Reproduced from ref. 19, with permission from Elsevier.)

polyanhydrides have been studied as injectable, crosslinkable biomaterials. Methacrylic groups are typically incorporated by reacting diacids with methacryloyl chloride to create dimethacrylate monomers.²³² Dimethacrylate monomers exist as liquids (i.e., dimethacrylic SA) or soft solids (i.e., dimethacrylic CPH, which can be injected and crosslinked into solid scaffolds for tissue engineering applications.²³³ Crosslinked polyanhydrides have been mostly studied for utilization in drug delivery and structural support for bone tissue engineering,^{234,235} but due to monomer flexibility have the potential to be used in other tissue engineering applications as well.

Polyacetals

Polyacetals are degradable polymers in which two ether bonds are connected to the same carbon molecule (geminal). The molecular closeness of the normally stable ether bonds conveys hydrolytic instability close to that seen for polyanhydrides (Table 1) and gives polyacetals surface eroding properties. Polyacetals are normally subdivided into two subgroups: polyacetals and polyketals. Although all geminal-diether polymers are technically polyacetals, the namesake is normally reserved for polymers with only one of the two other geminal bonds possessing an R group. Polyketals instead have both other geminal bonds with R groups. Both polyacetals and polyketals have gained traction in biomedical research recently because their degradation products possess no carboxylic acids yielding significantly milder pH microenvironments,²³⁶ and their degradation is acid-catalyzed.^{236–238} Milder pH microenvironments allow for the delivery of acid- and hydrolytically sensitive payloads. Dr. Niren Murthy's group has shown acid-catalyzed degradation allows for

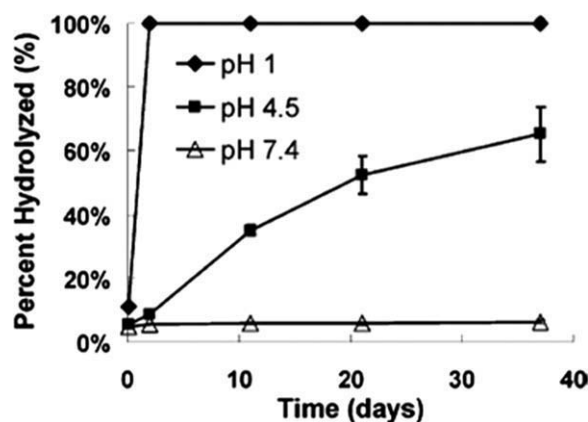


FIGURE 6 *In vitro* hydrolysis of poly(cyclohexane-1,4-diyl acetone dimethyl ketal) is greatly influenced by surrounding pH evidenced by its half-life of 24.1 days in pH 4.5 and 4 years in pH 7.4. (Reproduced from ref. 237, with permission from the American Chemical Society.)

intracellular payload delivery, because particle-based delivery vehicles are stable under normal physiological pH (7.4), but rapidly degrade when they reach lysosomal pH (4–5), as shown in Figure 6.²³⁷ So far polyketal microparticles and nanoparticles have been used to directionally deliver siRNA,²³⁸ DNA,²³⁹ and proteins^{237,240–244} in the treatment of acute inflammatory disease,^{237,242} ischemic heart disease,²⁴⁴ and cancer,²⁴¹ as well as in the delivery of vaccines.^{240,243}

For most implant applications, polyacetals have found limited use because they are often unable to be synthesized at high enough molecular weights to meet mechanical strength needs. A notable exception is Delrin[®] (polyoxymethylene), which is the homopolymer of formaldehyde that can be polymerized by acid or anionic catalysis to high molecular weights. Delrin[®]-based implants found favor as tilting disc valves in the repair of faulty heart valves in the late 1960s.²⁴⁵ Unfortunately, it was found that these implants swelled when they were used *in vivo* and other materials have since replaced Delrin[®] in artificial valves.²⁴⁶ Also, the degradation product of Delrin[®] is formaldehyde, which is toxic. To create tissue engineering scaffolds from polyacetals, cyclic polyacetal monomers with two ester acrylate end groups have been synthesized that can then be cross-linked.²⁴⁷ Cyclic polyacetal homopolymers and those copolymerized with PEG diacrylate (PEGDA) have shown preliminary promise as osteogenic biomaterials for bone tissue engineering.^{248,249}

Poly(ortho esters)

Poly(ortho esters) are hydrophobic, surface eroding polymers that have three geminal ether bonds. Like polyacetals, control of poly(ortho ester) backbone chemistry allows for the synthesis of polymers with varied acid-catalyzed degradation rates and material properties. These polymers were specifically developed for drug delivery applications by the ALZA Corporation in the early 1970's.²⁵⁰ While ALZA no longer exists, research in poly(ortho esters) is still ongoing

in the academic community. Although four classes of poly(ortho esters) have been developed (POE I–IV), inherent issues with POE I–III have led to nearly all research focusing on POE IV. POE IV incorporates short segments of lactic or glycolic acid into the polymer backbone to expedite degradation because POE I–III possess too slow erosion rates to be clinically relevant as drug delivery vehicles.²⁵⁰ POE IV polymers have been used for the delivery of analgesics,²⁵¹ DNA vaccines,^{252,253} and antiproliferative drugs.²⁵⁴ Their capacity to be used as tissue engineering scaffolds is limited due to their weak mechanical properties and their capacity to induce a mild to moderate inflammatory response.²⁵⁵

Polycarbonates

Polycarbonates are linear polymers that have two geminal ether bonds and a carbonyl bond. Although this bond is extremely hydrolytically stable (Table 1), research has shown *in vivo* degradation to be much more rapid presumably due to enzymatic degradation, which causes these polymers to be surface eroding.²⁵⁶ The most extensively studied polycarbonate is poly(trimethylene carbonate) (PTMC), which has a T_g of -17 °C.²⁵⁷ PTMC is an elastomeric aliphatic polymer with great flexibility and a slow degradation profile, but poor mechanical strength. Its degradation into biocompatible, non-acidic 1,3-propanediol, and carbonic acid make it an ideal candidate for drug delivery applications. PTMC has been fabricated into microparticles,^{258,259} discs,^{260,261} and gels^{262–264} for the delivery of angiogenic agents²⁶⁴ and antibiotics.^{260,261} To enhance the delivery potential of PTMC, it is often copolymerized with PLA,^{265,266} PCL,²⁶⁵ polyether,^{266–268} or poly(L-glutamic acid)^{269,270} to allow for the fabrication of sutures,²⁶⁵ micelles,^{266–268} and polymersomes^{267,269,270} with superior mechanical and degradation properties for delivery of chemotherapeutics^{266–268,270} and antibiotics.²⁶⁵

In addition to PTMC, new polycarbonates have been recently researched for tissue engineering applications. One approach to create stiffer polycarbonates than PTMC is the use of cyclohexane or propylene instead of trimethylene in the monomer backbone.²⁷¹ Another approach has been attaching bulky side groups through an ester bond to the β -carbon of the backbone.²⁷² A particularly interesting novel polycarbonate has been created using the glucose metabolism intermediate dihydroacetone (DHA).²⁷³ When DHA is copolymerized with methyl PEG, the resulting rapidly gelating, rapidly degrading (100% mass loss within days) copolymer has been shown to assist the body in clotting through the development of new vascular tissue²⁷⁴ and the prevention of seromas, fluid filled gaps commonly created following ablative or reconstructive surgeries.²⁷⁵ The continued exploration of new polycarbonates holds potential for the expansion of this class of degradable polymers in biomedical applications.

Other polycarbonates that are used as fixators and in tissue engineering scaffolds are tyrosine-derived polycarbonates. These polymers are variations of poly(amino acids) in which amino acid like backbones are connected by carbonate bonds giving them strong mechanical properties while maintaining the biocompatibility of their degradation products. The most

extensively studied of these pseudo poly(amino acids) are poly(desamintyrosyl-tyrosine alkyl ester carbonates) (PDTEs). Because of aromatic groups in the polymer backbone, PDTEs possess significant mechanical strength allowing for their use in load-bearing applications. PDTEs have a variable pendant alkyl chain allowing for modulation of their thermal and mechanical properties with T_g s of 50–81 °C, T_m s of 75–118 °C, tensile strengths of 50–70 MPa and stiffnesses of 1–2 GPa.²⁷⁶ Their processibility has allowed for the fabrication of scaffolds composed of films,^{276–281} fibers,²⁸² and gels.^{283,284} PDTEs have been investigated for their potential in tissue engineering of bone,^{277,278,280} vasculature,²⁸³ and muscle.²⁸¹ Slow degradation (M_w half life of over 200 days²⁸⁵) and minimal mass loss of PDTEs allows for them to maintain their physical properties for very long times making them good candidates for slow regenerative processes.

Polyurethanes

Polyurethanes are biocompatible, biostable, moldable, strong polymers that possess ester bonds with geminal amide bonds that have a degradation rate similar to polyesters and polycarbonates (Table 1). They are typically synthesized by polycondensation of diisocyanates with alcohols and amines.²⁸⁶ Polyurethanes are composed of hard and soft segments that can undergo microphase separation allowing for these polymers to handle physical stresses very well.²⁸⁷ Polyurethanes have been used extensively in prostheses such as cardiac assist devices,²⁸⁸ small vascular shunts,²⁸⁹ and tracheal tubes.^{290,291} A commercial polyurethane product, NovoSorbTM (PolyNovo[®]), is a two component system that cures *in situ*. The self setting system is an injectable liquid that not only polymerizes at physiological temperatures creating a biomaterial that has been shown to be mechanically similar to bone cements but also promotes favorable cell adhesion and proliferation.²⁹² Under most conditions, pure polyurethanes are degradation resistant making them poor candidates for drug delivery and many tissue engineering applications. To expand the biomedical potential of polyurethanes they have been utilized in multidegradable group polymers, combination polymers, which will be discussed later in this review.

Polyphosphazenes

Polyphosphazenes are a unique class of degradable polymers in that their backbone is completely inorganic consisting of phosphorous and nitrogen bonded linearly through alternating single and double bonds. Although these polymers have been synthesized with high molecular weights since the mid 1960s,²⁹³ only in the past two decades have they been investigated in biomedical research.²⁹⁴ What distinguishes these materials is that they are highly flexible both physically and chemically. With two phosphorous side groups open to conjugation via esterification, etherification or amidification, over 500 different polyphosphazenes have been synthesized to date.²⁹⁵ Although the phosphonitrilic backbone is not intrinsically hydrolytically sensitive, careful choice of side groups greatly impacts the degradation rate (Table 1). Certain side groups, such as amino acid esters, glucosyl, glyceryl, glycolate, lactate, and imidazole, have been found to sensitize hydrolysis of the backbone to allow for the design of

clinically relevant biomaterials. In addition to control over degradation rates, physical properties of the polymer are also greatly affected by side group substitution. By changing disubstituted polyphosphazene side groups for one particular system, thermal and mechanical properties were greatly varied with $T_g = -10$ to 35 °C, contact angle 63°–107°, tensile strength 2.4–7.6 MPa, and modulus of elasticity 31.4–455.9 MPa.²⁹⁶ Another unique feature is that polyphosphazenes degrade into neutral products that have been found to have a pH buffering effect when combined with polymers, such as polyesters, that have highly acidic degradation products.²⁹⁷ A commercially available product Polyzene-F[®] (poly[bis(trifluoroethoxy)phosphazene], CeloNova BioSciences) has shown tremendous potential as stent coatings²⁹⁸ and embolizing microspheres,²⁹⁹ and was FDA approved in 2008. Although original research found the material to cause limited inflammation,³⁰⁰ a more recent study showed a significant, sustained foreign body response that is of concern.³⁰¹ More research into this phenomenon is warranted before Polyzene-F[®] can be used clinically.

Polyphosphazenes have shown significant promise in drug delivery and tissue engineering applications. The large library of side groups and the processibility of polyphosphazenes has allowed for them to be fabricated into particles,^{302–304} micelles,^{305–309} microneedle coatings,^{310,311} and gels.^{312–315} They have been used in the delivery of anti-inflammatory drugs,³⁰⁶ chemotherapeutics,^{307,309,315} growth factors,^{313,316} DNA,^{302–304} proteins,^{312,314} and vaccines.^{305,308,310,311} One particular promising application has been in the design of biodegradable microneedle coatings to deliver vaccines.³¹⁰ Andrianov and coworkers have shown polyphosphazene-vaccine covered metallic cones can be used to pierce the skin to deposit rapidly degrading polymer films (~90% in 15 min) into the dermis layer (Fig. 7). An added benefit of utilizing polyphosphazene as the delivery vehicle is that prior research has found that certain polyphosphazenes are strongly immunoactivating and hold great potential as adjuvants, nonspecific immune boosting substances.^{305,308} This research has shown the induction of stronger immune responses than comparable intramuscular injections without the pain and strong inflammation seen with traditional needle use providing promise for this new technology.

Although many rapidly degrading polyphosphazenes have shown promise in drug delivery applications, more hydrophobic side group substitutions have allowed for the use of polyphosphazenes in tissue engineering applications. Polyphosphazene scaffolds have been composed of films,^{317,318} fibers,^{319–322} and sintered microspheres.³²³ These matrices have been used to assist in nerve regeneration,^{317,319,322} but recent research has almost exclusively focused on orthopedic applications of polyphosphazenes.^{318,320,321,323} Often polyphosphazenes have been blended with polyesters to increase mechanical strength and provide a moderate pH microenvironment for developing tissues. Interestingly, miscible blends of poly[(glycine ethyl glycinato)₁ (phenylphenoxy)₁ phosphazene] and PLGA that are originally cast as films undergo

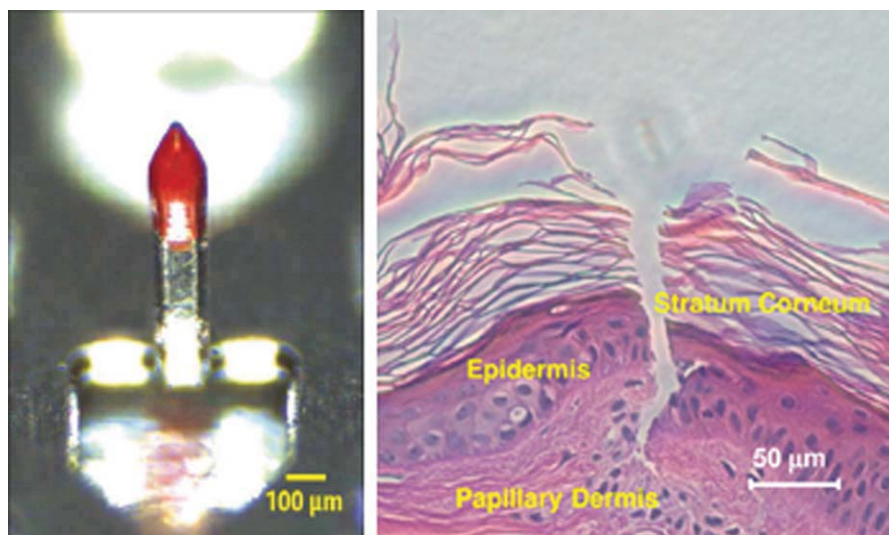


FIGURE 7 Optical microscopy image of a polyphosphazene coated metallic microneedle (left) and histological section of porcine skin after coated microneedle insertion (right). (Reproduced from ref. 310.)

varied rates of degradation of the principal components under aqueous conditions.¹³ As the PLGA degrades and erodes from the matrix the more hydrophobic polyphosphazene reforms into a scaffold with a microstructure very similar to adhered microspheres. Porous scaffolds of adhered microspheres have been used heavily in tissue engineering applications because they allow for the infiltration of host cells into the scaffold that will eventually become new tissue. Having biomaterials with the strength and flexibility of films that can form into porous scaffolds over time greatly enhances the biomedical potential of these materials.

Polyphosphoesters

Polyphosphoesters form another interesting class of biomaterials that is composed of phosphorous-incorporated monomers. These polymers consist of phosphates with two R groups (one in the backbone and one side group) and can be synthesized by a number of routes including ring opening polymerization, polycondensation, and polyaddition. Originally developed in the 1970s,^{324,325} polyphosphoesters have great biocompatibility and similarity to biomacromolecules such as RNA and DNA. Relatively rapid hydrolytic cleavage (Table 1) of the phosphate bonds in the backbone leads to the production of bioresorbable or excretable phosphates, alcohols, and diols. Although a commercial polyphosphoester-based microsphere delivery device (PACLIMER[®]) has shown promise in Phase I/II trials for the treatment of ovarian and lung disease, MGI Pharma discontinued further research with the product after purchasing the original development company, Guilford Pharmaceuticals. Polyphosphoesters are divided into two different classes: polyphosphonates (alkyl/aryl R groups) and polyphosphates (alkoxy/aryloxy R groups). Because of the flexibility in choosing R groups, polymers of significantly varying physical properties and degradation rates can be synthesized. To enhance physical properties, polyphosphoesters are commonly copolymer-

ized with polyethers and polyesters. Polyphosphoesters and polyphosphoester composites have shown significant promise as chemotherapy^{326–328} and DNA^{329–331} delivery devices. Polyphosphoesters have also been utilized as scaffolds in the engineering of bone tissue.^{328,329,332–335} These polymers have been formed into particles,^{328,330} micelles,^{326,327} films,^{329,331} and gels^{332–335} for these applications. Recent research utilizing polyphosphoesters has been limited, but their chemical flexibility and similarity to biomacromolecules gives them great promise for future applications.

Combination Polymers

A growing trend in degradable polymer research is the development of combination polymers. These are polymers in which monomers contain multiple degradable groups. Unlike copolymerization of different monomers, the molecular proximity of these groups yields functionally novel biomaterials. These materials often have properties that cannot be obtained by single degradable group polymer families or through simple copolymerization. With the goal of developing new polymers, this research area has yielded a large number of new families, which will not be completely reviewed in this section. Below are a couple examples of interesting degradable combination polymer families that have been recently developed.

Poly(ester ether)s are an interesting class of degradable polymers in which typically an ether bond is incorporated into the backbone of a polyester to expedite hydrolytic cleavage of the ester bond. One very common poly(ester ether) is polydioxanone (PDO). PDO is a colorless, semicrystalline polymer synthesized by ring-opening polymerization of *p*-dioxanone that has a T_g about -10 to 0 °C and a T_m of 115 °C.³³⁶ Although quicker degrading than longer aliphatic polyesters of similar backbone length, PDO can still be considered a slow degrading polymer (6–12 months for complete mass loss).²³ With a low modulus (1.5 GPa),²³ but good flexibility and strength maintenance (1–2 months), PDO has been

commercialized as the monofilament suture PDS[®] for nearly 30 years.³³⁷ In an effort to create faster degrading polyesters, research has been conducted into the synthesis of poly(ether ester)s via polycondensation. This is carried out by the use of a catalyst to create alternating blocks from dicarboxylic acids and diols. Oligomeric ethylene glycol ($n = 2-4$) and *trans*- β -hydroxybutyric acid are condensed to create low-molecular-weight poly(ether ester)s (4,000–6,000 g/mol) that are amorphous and have low T_g s (-36 to -32 °C).^{338,339} These polymers are liquid at room temperature and possess crosslinkable double bonds in their backbone making them promising biomaterials for filling nonuniform defects. By creating random copolymers between crosslinkable and noncrosslinkable (adipic acid) monomers, control over crosslinking density can be obtained. These materials are able to be synthesized with Young's moduli varying three orders of magnitude (0.02–20 MPa).³³⁹ Also, the liquid poly(ether ester)s are able to be fabricated into complex architectures not easily obtainable by solid polyesters.³³⁹

Poly(amide ester)s are cationic, degradable polymers originally investigated for their biomedical potential in the 1990s by Robert Langer.³⁴⁰ The most widely studied subgroup of these polymers are poly(β -amino esters) (PBAEs), which are synthesized by a Michael addition reaction of diester diacrylates and primary or secondary amines.^{341,342} Having control over both components' backbone chemistry, a wide range of PBAEs can be synthesized. The fidelity of the reaction and the subsequent library of polymers that can be synthesized have led to the use of combinatorial research methods to identify polymers that show particular promise as biomaterials.³⁴³⁻³⁴⁶ In one particular study, over 2,000 polymers were synthesized and screened combinatorially.³⁴⁵ PBAEs show tremendous promise in DNA delivery due to their positively charged amide bonds³⁴⁷⁻³⁵⁰ and in tissue engineering because they can be synthesized with high molecular weights and hydrolytically stable bonds allowing for long-term maintenance of their mechanical strength.³⁵¹⁻³⁵³

Although copolymers and blends of polyesters and polyanhydrides have been studied for a few decades, the synthesis of poly(anhydride ester)s for biomedical applications have only been investigated for the last decade.³⁵⁴ The original impetus for their development was the creation of prodrug polymers. If commonly used aromatic diacid monomers have two internal ester bonds instead of ether bonds, their degradation products are resorbable carboxylic diacids and salicylic acid, a nonsteroidal anti-inflammatory drug and the active compound of aspirin. Polycondensation of salicylate-containing diester diacids yields poly(anhydride ester)s very similar to classical polyanhydrides with moderate hydrophobicity, surface erosion, and good processability.^{354,355} These polymers have been found to have T_g s lower than physiological temperatures (12–34 °C),^{354,356,357} and are often copolymerized with traditional aromatic diacid monomers to improve mechanical properties.^{356,358} Salicylic acid-derived poly(anhydride ester)s and their composites have been fabricated into particles,^{357,359} fibers,³⁵⁸ and films^{355,356,360,361} for biomedical application. They have been used in the prevention

of biofilm formation,^{360,361} the prevention of bone resorption,^{356,359} and the creation of a local anti-inflammatory effect.^{356,360}

Polyurethanes have shown some applicability in biomedical research, but their hydrolytic stability limits their potential. To expedite degradation, ester bonds have been introduced into the polymer backbone. Poly(ester urethane)s are typically synthesized by reacting diisocyanates with polyester diols or triols composed of glycolide, lactide, or caprolactone to create the soft segments of the polymer.³⁶² Often the hard segments are composed of polypeptides or diols or triols of 3-hydroxybutyrate to give biomaterials that are degradable, but still relatively hydrolytically stable.^{362,363} To better commercialize the aforementioned PolySorb, more recent research has focused on including degradable ester groups into the injectable prepolymers. This has allowed for development of biomaterials that has shown promise in bone³⁶⁴ and articular cartilage regeneration.³⁶⁵ Another poly(ester urethane) is the highly porous Degrapol[®] (Ab Medica), which has shown promise in engineering tracheal soft tissue^{366,367} and bone tissue.³⁶⁸

ENZYMATICALLY DEGRADABLE POLYMERS

Enzymatically degradable polymers are materials that possess bonds that while technically hydrolytically sensitive, in reality require catalysis to undergo meaningful degradation under physiological conditions. Most of these polymers contain ether or amide bonds which have hydrolytic degradation rates much lower than the polymers discussed in the previous section (Table 1). This section details a number of these polymeric families and their application as biomaterials.

Synthetic Polyethers

Synthetically derived polyethers are highly biocompatible polymers that have been used in polymeric drug delivery and tissue engineering for over 30 years.³⁶⁹ Nearly all biomedical research with synthetic polyethers has focused on the use of PEG and poly(propylene glycol) (PPG), while a limited amount of work has been conducted using poly(tetrahydrofuran).³⁷⁰⁻³⁷³ Polyethers do not readily undergo hydrolytic degradation and while bacterial etherases have been discovered,^{374,375} human equivalents of these enzymes have yet to be identified. Instead polyether chains are normally dissociated from the biomaterial and removed via the excretory system. Because of a near absence of *in vivo* degradation and the fear of accumulation, it is recommended that only polyethers with lower molecular weights be utilized for biomedical applications. In addition to issues associated with high-molecular-weight PEG, very low-molecular-weight PEG has been found to induce bodily harm. Specifically, tetraethylene glycol and PEG 200 have been shown to induce clastogenic effects (chromosomal disruption) in Chinese Hamster epithelial liver cells.³⁷⁶ Most research with synthetic polyethers has focused on triblock Pluronic ([PEG] n -[PPG] m -[PEG] n), crosslinkable oligomers or these polymers in union with many of the previously mentioned hydrolytically degradable polymers.

Pluronic is of particular interest, because PEG is hydrophilic whereas PPG is hydrophobic allowing for the formation of very small micelles (10–100 nm in diameter)³⁷⁷ by self-assembly in water. These micelles allow for high payload loading (30 wt %)³⁷⁸ of hydrophobic drugs into the core while the hydrophilic shell makes the particles easy to administer. Drug delivery devices composed of Pluronic micelles have been used to deliver chemotherapeutics,^{379–381} antibacterials,^{382,383} antidiuretics,³⁸⁴ anti-inflammatory drugs,³⁸⁵ and DNA.³⁸⁶ Pluronic has also been formulated into hydrogels. These hydrogels possess relatively weak mechanical properties (maximum shear storage modulus of 13.7 kPa at 20 wt % Pluronic)³⁸⁷ making them candidates for drug delivery^{388–391} and soft tissue engineering.^{392,393}

To enhance the mechanical strength of polyether-based hydrogels, crosslinkable oligomers are synthesized by reacting PEG with excess acryloyl chloride or methacryloyl chloride yielding the products PEGDA or PEG dimethacrylate (PEGDMA), respectively. PEGDA and PEGDMA can then be polymerized by their double bond yielding crosslinked networks, which upon degradation yield poly(acrylic acid) or poly(methacrylic acid) and PEG. PEGDA hydrogels (shear storage modulus of 68 kPa at 20 wt %)³⁹⁴ and PEGDMA hydrogels (shear storage modulus of 125 kPa at 20 wt %)³⁹⁵ are stronger than their Pluronic counterparts. PEGDA, PEGDMA, and PEGDA/PEGDMA hydrogels have been used in the delivery of chemotherapeutics,³⁹⁶ hormones,³⁹⁷ antibacterials,³⁹⁸ and anti-inflammatory drugs³⁹⁹ as well as scaffolds in the engineering of cartilage,^{400,401} bone,^{402–404} endothelial,⁴⁰⁵ and vascular tissues.⁴⁰⁶

Although synthetic polyethers have shown some promise when utilized by themselves, they have much greater biomedical potential when utilized in combination with other degradable polymers. PEG is commonly used to cap (PEGylation) or coat other degradable polymers to convey steric stabilization limiting the interactions between the device and the host. This is especially important in preventing phagocytosis, cellular uptake, of particle-based delivery vehicles.^{407–409} Unlike polyanhydrides and polyesters, PEG does not initiate the complement cascade, which is known to facilitate particle phagocytosis.⁴¹⁰ PEG incorporation has been used to enhance the biocompatibility and delivery properties of polyanhydrides,^{411–414} poly(ortho esters),⁴¹⁵ PLA,^{416–419} PLGA,^{420–423} and PCL.^{424–427} Of particular interest is the work being conducted with poly(ether anhydride)s. The addition of a low-molecular-weight PEG shell to polyanhydride microparticles and nanoparticles conveys “virus-like” behavior and allows for them to pass through mucosal membranes much more rapidly than uncoated particles.^{428,429} Being able to transport drug delivery devices across mucosal barriers is important in improving therapeutic efficacy against diseases such as cystic fibrosis⁴³⁰ and lung cancer⁴¹⁴ (lung mucosa) and HIV⁴³¹ (vaginal mucosa).

PEGDA and PEGDMA have also been heavily researched in composite systems with other acrylated and methacrylated degradable polymers, most commonly polyesters,^{432–434}

polyanhydrides,^{232,234,235,435,436} and chitosan,^{437,438} a polysaccharide that will be discussed later in this review. The polyether diacrylate monomers give the crosslinked network hydrophilicity whereas the other degradable components convey significantly greater mechanical strength (compressive moduli as great as ~100 MPa)²³² than crosslinked polyether diacrylate homopolymers. Greater strength and component flexibility have led to the use of these composites in a wide range of tissue engineering applications including in the regeneration of ligament,⁴³³ cartilage,⁴³⁴ bone,^{232,432} and epithelial tissue.⁴³⁷

Proteins and Poly(amino acids)

Proteins are essentially high-molecular-weight polymers composed of amino acid monomers joined by amide bonds. They often occur in 3D folded structures and are one of the most common materials found in the human body. Proteins and amino acid-derived polymers have been utilized as biomaterials in sutures, scaffolds, and drug delivery devices. Although amide bonds are hydrolytically stable, the body possesses a wide-array of proteases that can rapidly degrade proteins.

Collagen

Collagen is the most abundant protein in the human body and is a major component of ligament, cartilage, tendon, skin, and bone. It also forms the structural network of other tissues such as blood vessels. Collagen is composed of polypeptide strands bearing triamino acid blocks of Glycine-X-Y where X and Y can be any of a number of different amino acids and are most commonly proline and hydroxyproline.⁴³⁹ These polypeptides are formed into left-handed triple helix microfibrils that organize together in a number of different architectures to create collagen fibers with appropriate mechanical properties for their function. To date, at least 28 different types of collagen have been identified, however types I, II, III, and IV are the most heavily investigated with over 90% of all collagen being type I.⁴⁴⁰

Collagen has been extensively researched for various medical applications due to its biocompatibility, mechanical strength, and enzymatic degradability by collagenases and metalloproteinases.⁴⁴¹ In addition, it is very processable with high solubility in acidic aqueous solutions allowing for the fabrication of collagen sponges,^{442–444} tubes,^{445,446} sheets,⁴⁴⁷ powders,⁴⁴⁸ and injectables.^{449–452} Collagen has been used for centuries as a suture material of which one form, catgut, is still sometimes utilized in surgery,^{453,454} but due to collagen suture's increased infection rates and inflammation, synthetic sutures are much more commonly used today. Collagen has also been used as a depot payload delivery device in the local extended release of antibiotics,^{455,456} DNA,^{457,458} siRNA,^{459,460} and proteins.^{461–463} In each case collagen had a burst release due to bulk erosion making it less ideal than the aforementioned surface eroding hydrolytically sensitive polymers for drug delivery applications.

More recently collagen has found use as a haemostatic sealant.⁴⁶⁴ Collagen is highly thrombogenic and plays a role in the body's natural clotting process by activating fibrogen

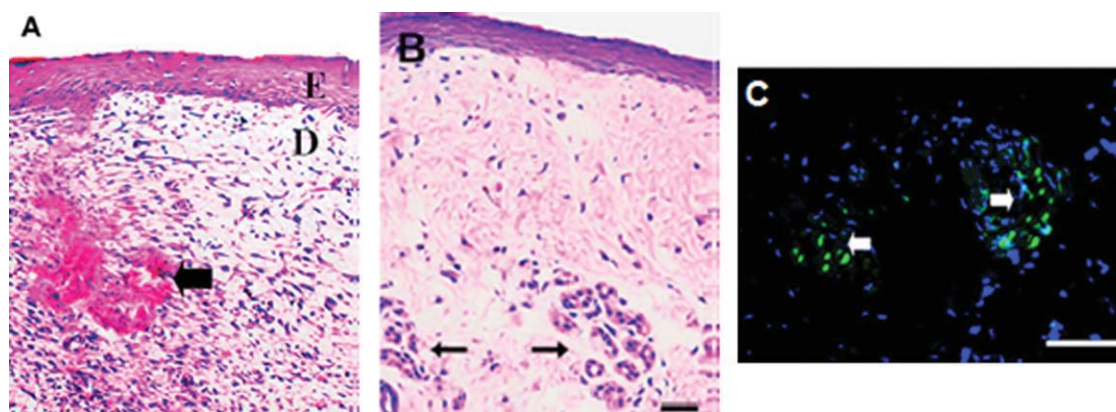


FIGURE 8 Photomicrographs of keratinocyte-fibroblast coculture engineered skin tissue with the addition of collagen microsphere supported sweat gland cell constructs. (A) Hemotoxylin and Eosin (H&E) staining after 2 weeks of *in vitro* cocultivation showed differentiated tissue layers (E: epithelium and D: dermis) with a bud-like structure (black arrow) where sweat gland constructs were loaded. (B) H&E staining of 6-week postimplantation *in vivo* skin tissue showed the continued presence of bud-like structures in the dermis layer (black arrow). (C) Fluorescence microscope observation showed DiO-positive cells (green) confirming the presence of still viable sweat glands. (Reproduced from ref. 485, with permission from Elsevier.)

conversion into fibrin, heavily crosslinked mesh networks of fibrogen. Fibrin captures activated platelets to make a clot. By creating a collagen based sealant, wounds can be coated and blood flow halted much more quickly. The FDA has approved a couple of collagen-containing solutions, including Helistat[®] (Integra Life Sciences) and FloSeal[®] (Baxter), for the treatment of bleeding during surgery.

Because of collagen's structural integrity conveyed by its fibrous nature, a majority of biomedical research using collagen as a biomaterial has focused on its potential as a tissue engineering scaffold, specifically in load bearing applications. Collagen sponges have been used as tissue supports and scaffolds for nearly 50 years.⁴⁶⁵ Because of collagen's ability to withstand high tensile loads (92.5 MPa ultimate tensile strength),⁴⁶⁶ it has often been used in bone tissue engineering.^{467–469} Composites of hydroxyapatite and collagen are utilized, because these materials closely mimic the composition of natural bone.^{470–472} Collagraft[®] (Angiotech Pharmaceuticals) is a synthetic bone-graft substitute composed of bovine type I collagen and hydroxyapatite/tricalcium phosphate granules, which has been approved by the FDA and used clinically.⁴⁷³ Collagen has also been widely researched as a tissue engineering scaffold for cartilage,^{474–476} tendon,^{477–479} and ligament.^{480,481}

Although often used for load bearing applications, collagen's biocompatibility and ease of use has led to its investigation as a scaffold in skin engineering as well.^{482–484} Because of

collagen's ability to improve cellular adhesion and proliferation, burn treatment and reconstructive surgery is often conducted with an acellular collagen matrix taken from human cadavers, which is marketed as Alloderm[®] (LifeCell). Although Alloderm is the most commonly used commercial product for skin engineering and wound healing, several other FDA collagen-based products exist in the market place including Promogran[®] (Johnson & Johnson), Biobrane[®] (UDL Laboratories), and OrCel[®] (Ortec International) for this appli-

cation. Although these products provide excellent support to regenerating tissue, they lack many of the constituent structures found within skin like hair, nerves and glands as well as tissue layer separation necessary to truly replicate skin's 3D structure. Several approaches to these problems have been proposed, but two concepts of particular interest are outlined. To develop sweat glands within regenerated skin, Huang and coworkers have developed growth-factor releasing collagen microspheres that can support differentiating sweat gland cells.⁴⁸⁵ These constructs are then embedded into a keratinocyte/fibroblast coculture with structural maintenance provided by a collagen matrix to create substructures within the developing skin that are maintained even after implantation *in vivo* (Fig. 8). To create keratinocyte-fibroblast separated layers, keratinocytes are normally cultured on top of a preformed fibroblast layer, which is time-consuming and inefficient. A new method has been developed for creating controlled large pore scaffolds that allow for keratinocyte and fibroblast structures to separate naturally creating better skin mimicking constructs, which are also well integrated into the collagen scaffold.⁴⁸⁶ These advances hold promise not only for collagen-based biomaterials and skin engineering but also for tissue engineering as a whole because as the field moves toward creating and regenerating more complex structures such as organs 3D patterning of multiple tissue types will be paramount to continued success.

To improve collagen's potential as a biomaterial, it has often been modified or combined with other degradable polymers. Modifications such as crosslinking,^{487–489} association of bioactive molecules,^{490,491} and enzymatic pretreatment^{492–494} have all led to novel collagen-based materials with expanded functionality. In composite materials, collagen has been combined with PLA,^{60,495,496} PLGA,^{60,497,498} PCL,^{60,497,499} and chitosan.^{500–502} These multipolymer constructs are typically either polymeric blends or intermixed devices (e.g., microparticles of

one polymer dispersed in a fibrous scaffold of another polymer).

Although heavily researched, collagen possesses many negative attributes limiting its biomedical potential and clinical utility. Collagen-based biomaterials have been known to induce a moderate immunological response *in vivo* due to collagen's terminal region composition and a series of antigenic sites in the central helix.⁵⁰³ The degree and nature of this response greatly depends on the source and postprocessing of the collagen used. Other issues include the high cost of pure collagen, significantly varying physicochemical properties, and risk of transmitted infection from the grafting source. Although current research is underway to produce recombinant human collagen,⁵⁰⁴ animals and cadavers still remain the most common sources. Until alternative biological sources are identified or purely synthetic collagen can be synthesized/collagen-based biomaterials will continue to possess significant limitations.

Elastin and Elastin-Like Polypeptides

Elastin is an insoluble, highly elastic polymer composed of heavily crosslinked tropoelastin molecules that is a major component of vascular and lung tissue and is responsible for the contraction of these tissues following stress. Soluble tropoelastin molecules are produced intracellularly by smooth muscle cells and fibroblasts and are crosslinked extracellularly to form their elastic polymeric network.⁵⁰⁵ As it is prevalent in vascular tissue, elastin has been found to not activate platelets making it a promising material for synthetic vascular grafts.^{506,507} Although some biomaterials research has been conducted with elastin, its ability to elicit an immune response and its insolubility have limited its use.⁵⁰⁸

To overcome the limitations inherent to elastin, synthetic elastins have been developed. Soluble recombinant human tropoelastin can be molded, coaservated, and crosslinked at 37 °C to create soluble elastin with controlled architecture.^{509,510} Also, tropoelastin undergoes an irreversible temperature transition (ITT) above 25 °C where its molecular organization goes from a disordered to ordered state. This transition gives synthetic elastin promise as a smart, injectable drug delivery system.^{511,512}

Another attempt to utilize elastin-based materials as biomaterials has been in the investigation of elastin-like polypeptides (ELPs). ELPs are artificial polypeptides that are composed of pentapeptide repeats (VPGXG) similar to those found in elastin where X can be any of a number of different amino acids except proline.⁵¹³ Although very flexible like elastin, ELPs are biocompatible and non-immunogenic. They also can be synthesized to undergo ITT, as well as respond to pH, ionic strength and light based on which amino acid is synthesized in the X position.⁵¹⁴ While once synthesized chemically, ELPs have been more recently produced in *E. Coli*.⁵¹⁵ Because of the variety of phase transitions that ELPs can undergo, they have been investigated as delivery vehicles for chemotherapeutics,^{516,517} antibiotics,⁵¹⁸ and proteins.^{519,520} Also, when crosslinked ELPs are seeded with

chondrocytes they have been shown to possess dynamic sheer moduli (~ 1.7 kPa)⁵²¹ similar to normal cartilage. The elastic behavior of ELPs makes them uniquely suited for the engineering of soft tissues.⁵²²⁻⁵²⁴

Albumin

Albumin is an abundant water-soluble blood protein comprising almost 50% of total plasma mass in the body. Albumin carries hydrophobic fatty acids in the blood stream as well as carefully maintains blood pH. As Albumin is essentially ubiquitous in the body, nearly all tissues have enzymes that can degrade it making it a promising polymer for biomedical applications.⁵²⁵ Albumin's solubility allows for the protein to be easily processed into a number of different shapes including fibers,^{526,527} microparticles,^{528,529} and nanoparticles.⁵³⁰⁻⁵³² Because of its serological compatibility and weak mechanical strength, albumin has been primarily investigated for payload delivery,⁵²⁹⁻⁵³¹ coating,^{533,534} and suturing applications.^{535,536} Currently, a bovine albumin-based adhesive marketed as BioGlue[®] (CryoLife) is FDA approved for vascular surgery.⁵³⁵

Fibrin

Fibrin, a large crosslinked biopolymer composed of fibrinectin, is involved in the natural clotting process. In the presence of the enzyme thrombin, cleavage of an internal fibrin linker yields linear fibrils that laterally associate into nanofibers (10–200 nm) that form a clot. This clot is able to be degraded by a complex cascade of enzymes.⁵³⁷ The use of fibrin as a biomaterial goes back centuries, and it has been shown to be biocompatible, biodegradable, injectable, and able to enhance cell proliferation.⁵³⁸ Fibrin glues has been studied as a surgical supplement under the market name Evicil[®] (Ethicon), which has been FDA approved as a tissue sealant and hemostatic agent. Fibrin glues are prepared as solutions containing thrombin and fibronectin separately that are mixed right before application. Thrombin rapidly crosslinks the fibronectin into a fibrin clot closing the wound. Fibrin has also been investigated for use as a drug delivery device⁵³⁹⁻⁵⁴² and cell carrier.⁵⁴³⁻⁵⁴⁵ Due to its potential for crosslinking, fibrin can be uniquely modified, so that its material properties can be tailored for desired applications.⁵⁴⁶

Natural Poly(amino acids)

Natural poly(amino acids) are biodegradable, ionic polymers similar to proteins in that they possess amide linkages, but poly(amino acids) are only composed of one type of amino acid. The two most commonly studied natural poly(amino acids) as biomaterials are poly(γ -glutamic acid) (γ PGA) and poly(L-lysine).

γ PGA is a water soluble, biodegradable polyamide composed of both enantiomeric D- and L-glutamic acid units commonly produced by a number of different bacteria.⁵⁴⁷⁻⁵⁴⁹ The biomaterial promise of γ PGA centers on its reactive side carboxylate, which allows for the covalent attachment of other functional groups and drugs. Benzyl ester,⁵⁵⁰ sulfonate,⁵⁵¹ sulfide,⁵⁵² and chemotherapeutic attachment^{553,554} have all allowed for its further development as a biomaterial. It has

also been used in particle-based^{555–558} delivery of antibiotics,⁵⁵⁶ vaccines,^{557,558} DNA,⁵⁵⁵ and proteins.⁵⁵⁶ As a homopolymer, it is too physically weak to be used in supportive tissue engineering scaffolds, but as a crosslinked hydrogel it has found some promise in soft tissue engineering.^{559,560} Often it is blended with other polymers such as PLA,^{561,562} PLGA,⁵⁶³ PCL,⁵⁶⁴ collagen,⁵⁶⁵ and chitosan^{566–568} to give composites that are mechanically strong but possess some hydrophilicity. Research using γ PGA as a biomaterial has been limited due to its scarcity.

Like γ PGA, poly(L-lysine) is synthesized using bacteria and is currently being investigated as a tissue engineering scaffold and drug delivery device. It has been shown to possess intrinsic antibacterial,⁵⁶⁹ antiviral,⁵⁷⁰ and antitumor activities⁵⁷¹ that make it a very promising polymer. Unfortunately, its very high positive charge causes it to be rather toxic, which has limited its applicability. It has found some use in blends with other degradable polymers such as PLA,⁵⁷² PLGA,^{573,574} PCL,⁵⁷⁵ γ PGA,^{576,577} and chitosan.⁵⁷⁸

Synthetic Poly(amino acids)

Synthetic poly(amino acids) have been investigated for a number of biomedical applications due to their similarity to naturally occurring proteins. Although several homo- and copoly(amino acids) have been synthesized and evaluated; high crystallinity, low degradation rate, unfavorable mechanical properties, and immunogenicity have kept a majority of these polymers from being utilized clinically.⁵⁷⁹ However, two poly(amino acids) have been found to function as promising biomaterials: poly(L-glutamic acid) L-PGA and poly(aspartic acid) (PAA).

L-PGA is different than γ PGA because its amide linkage is made with the α -carbon amine group instead of the γ -carbon amine group. The shorter distance between amide bonds in L-PGA makes it more flexible than its γ PGA counterpart. Also, synthetic techniques allow for L-PGA to be more easily produced. Although L-PGA is typically synthesized as a linear polymer, the development of new synthesis techniques allows for the creation of unique structures like dendrimers.⁵⁸⁰ L-PGA is very biocompatible and non-immunogenic and has been shown to be highly susceptible to degradation by lysosomal enzymes.^{581,582} Due to its negative charge at physiological pH L-PGA has found significant promise as a DNA delivery device.^{555,583} Also L-PGA's negative charge allows for the construction of LBL film assembly with negatively charged polymers such as poly(L-lysine)^{584,585} and chitosan.⁵⁸⁶ LBLs are relatively new drug delivery devices, which alternate layers of charged polymer allowing for the repeated delivery of either positively or negatively charged payloads holding significant promise for future biomedical applications. Like γ PGA, the reactive side carboxylate of L-PGA allows for conjugation. So far this has been used for the creation of soluble, long-lasting polymer-chemotherapy conjugates,^{587,588} one of which is a Paclitaxel-conjugate marketed as OPAXIO[®] (Cell Therapeutics) that has shown promise in phase III clinical trials.⁵⁸⁹ Conjugates with small molecules have yielded degradable MRI contrast

agents.^{590–592} Tian and coworkers have demonstrated the capacity of a L-PGA-gadolinium complex whose molecular weight keeps the contrast agent from diffusing out of the vasculature. When tested in rhesus monkeys, the vasculature contrast of subjects given the complex was much greater than those given a small molecular weight contrast agent (Magnevist) at 2-h post-injection (Fig. 9).⁵⁹³ This complex allows for the use of less contrast agent while getting clearer MRI of small vasculature, which can lead to earlier detection of tumors, atherosclerosis, and gross hemorrhage. L-PGA has also been combined with other degradable polymers such as PCL^{594,595} and PTMC^{269,270} for drug delivery applications and collagen⁵⁹⁶ and chitosan⁵⁹⁷ to create novel tissue engineering scaffolds.

PAA is a highly water-soluble ionic polymer with a greater carboxylate content than PGA or L-PGA because it has one less carbon atom in its backbone. Like poly(glutamic acid), PAA has been found to be degradable by lysosomal enzymes.⁵⁹⁸ It has been copolymerized with a number of degradable polymers (PLA,^{599,600} PCL,⁶⁰¹ PEG,^{600–602} etc.) to create materials that form micellar structures, which have shown promise as smart delivery vehicles. PAA can also be easily converted to a hydrogel by high energy radiation which has shown promise in biomedical applications.⁶⁰³

Polysaccharides

Polysaccharides are polymers composed of monosaccharide units joined together by glycosidic linkages, a type of ether bond. Their use as biomaterials has become much more common as new biological functions are identified for these materials. Also, the array of materials that can be investigated has increased due to new synthetic routes that have been developed for modifying polysaccharides. Their biodegradability, processability, and bioactivity make polysaccharides very promising natural biomaterials.

Human Origin

Hyaluronic acid (HA) was originally isolated by Meyer and Palmer in 1934⁶⁰⁴ and has shown significant promise as a biomaterial. HA is a linear anionic polysaccharide consisting of alternating units of *N*-acetyl-D-glucosamine and glucuronic acid making it a member of the glycosaminoglycan family. HA is the largest polymer in the family and has been found in molecular weights up to a few million.⁶⁰⁵ It has been traditionally isolated from rooster combs and bovine vitreous humor. However, recent advances in microbiological techniques have led to the production of the first animal-free sodium hyaluronate which is synthesized by *Bacillus subtilis* and has been patented by Novozymes Biopharma. HA is water soluble and forms highly viscous solutions. Synovial fluid and vitreous humor have a large quantity of HA contributing to these tissues' viscoelastic properties. HA also plays an important structural role in articular cartilage and skin.

HA possesses several properties that make it unique. It has been shown to scavenge free radicals,⁶⁰⁶ cause bacteriostasis,⁶⁰⁷ and assist in tissue repair.⁶⁰⁸ These factors have made it a promising material for tissue engineering applications,

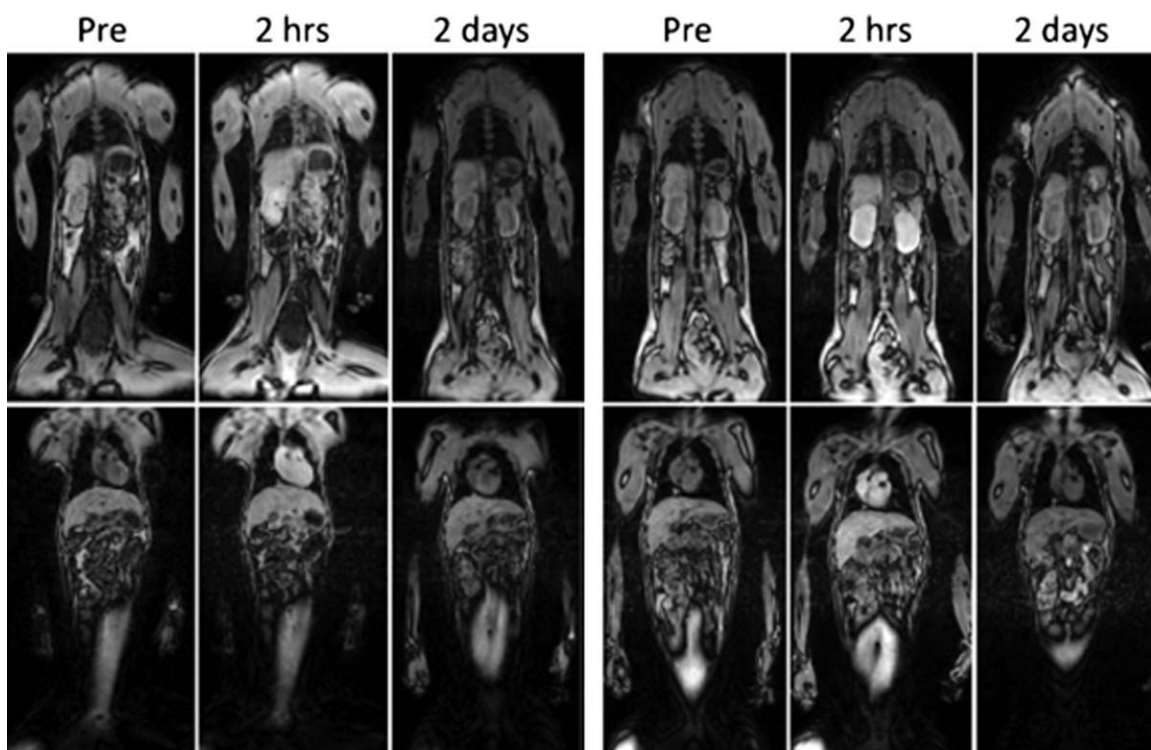


FIGURE 9 Magnetic resonance imaging of rhesus monkeys before contrast injection and at 2 h and 2 days after injection of Magnevist at 0.1 mmol Gd/kg (left) and PG-Gd 0.01 mmol Gd/kg (right). Contrast enhancements of blood vessel, heart, kidney and liver are clearly visualized at 2 h after PG-Gd injection at a tenth of the dose of Magnevist. By 2 days, the contrast agent has been mostly cleared with both contrast agents. (Reproduced from ref. 593, with permission from Wiley.)

but HA homopolymer is too weak and structurally fluid to create a supportive scaffold. To overcome this limitation, HA has been crosslinked with ethyl esters or benzyl esters yielding hydrogels, which have been commercialized as HYAFF[®] (Fidia Farmaceutici). HYAFF[®] undergoes hydrolytic degradation that causes scission of the ester bond converting it back to HA. Depending on the extent of esterification, degradation rate can be varied from 1–2 weeks^{609,610} to 4–5 months.^{611,612} HYAFF[®] hydrogels are extremely versatile as shown by their capacity to be fabricated into sheets,⁶¹³ membranes,⁶¹⁴ sponges,⁶¹⁵ tubes,^{612,616,617} or fibers^{618,619} and their usefulness as scaffolds for wound healing⁶¹⁸ and the regeneration of the trachea,⁶¹³ articular cartilage,⁶¹⁹ nasal cartilage,⁶¹⁵ respiratory epithelium,⁶¹⁴ vasculature,^{612,616} and nerve tissue.⁶¹⁷ Other HA tissue engineering devices include injectables such as SYNVISIC ONE[®] (Genzyme) and ORTHOVISC[®] (Johnson & Johnson), which have been developed to be injected into the knee to relieve pain from osteoarthritis and improve joint mobility. A particularly novel injectable regenerative tissue scaffold has been developed by reacting HA with methacrylic anhydride creating injectable, crosslinkable methacrylated HA (MeHA). Dr. Jason Burdick's group has shown MeHA possesses tremendous promise as a supportive network for heart tissue that is recovering from infarction.⁶²⁰ Figure 10 shows the ease of injecting the polymer into the heart wall as well as the thicker resulting walls from sheep given these scaffolds over

untreated controls. Injectable, crosslinkable polymers such as MeHA hold tremendous promise for a number of regenerative therapies especially in soft tissue engineering because they can fit defects or structural abnormalities *in vivo*.

HA has also shown promise as a payload delivery vehicle and has been formed into nanoparticles^{621–624} and hydrogels^{625–628} for this application. These constructs have been used to deliver chemotherapeutics,^{622,624} antibiotics,⁶²⁵ analgesics,⁶²⁶ siRNA,⁶²¹ and proteins.^{623,627,628} Composites of HA with PLA,^{629,630} PLGA,^{630–632} PCL,^{633,634} PLL,^{635–637} and chitosan.^{638–641} have all been developed to create delivery vehicles with enhanced mechanical properties while retaining excellent biocompatibility.

Another human carbohydrate that has shown promise as a biomaterial is chondroitin sulfate (CS). CS is a glycosaminoglycan with very similar structure to HA (CS has a sulfate group in at least one of its side groups). It has been found to be a major component of the body's natural, hydrophilic wound healing matrix produced by fibroblasts.⁶⁴² CS has also been shown to stimulate the metabolic response of cartilage,⁶⁴³ possess anti-inflammatory properties,⁶⁴⁴ and connect cells to extracellular matrix components.⁶⁴⁵ Because of CS's role in natural wound healing and chondrogenesis, it has been studied extensively as a hydrogel for wound dressings^{135,646} and cartilage tissue engineering. In cartilage tissue engineering, the successful regeneration of cartilage requires

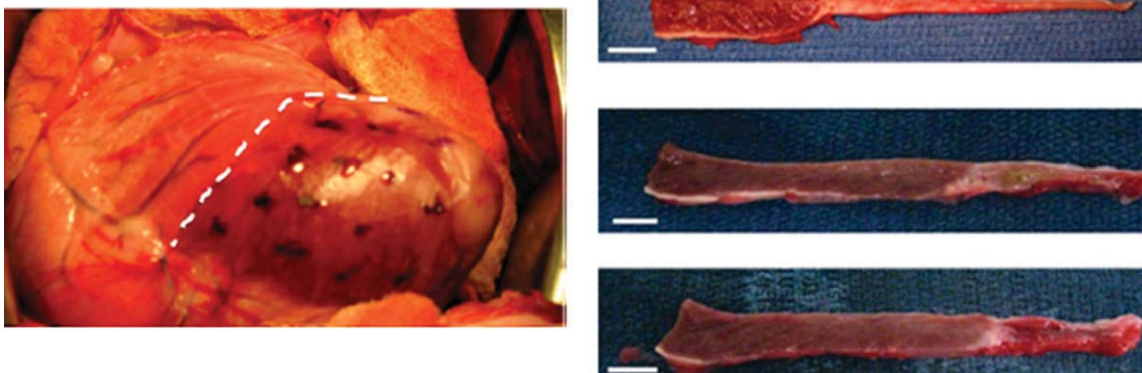


FIGURE 10 MeHA injection into a sheep heart after infarction helps prevent subsequent myocardial damage. Multiple injections (dots) of MeHA were given into the infarcted area (right of dashed line) (left). Representative images of myocardial wall thickness 8 weeks post treatment with no scaffold (top right), MeHA High scaffold (middle right), and MeHA Low scaffold (bottom right). (Reproduced from ref. 620).

a scaffold that causes the correct phenotypic development of seeded cells. Because CS plays a crucial role in the natural development of cartilage, CS,^{647,648} and CS composites with PCL,⁶⁴⁹ PEG,^{650,651} collagen,^{649,652} HA,⁶⁵³ and chitosan⁶⁵⁴ have been used to direct proper cellular chondrogenesis and successful regeneration of cartilage tissue.⁶⁵⁵

Other carbohydrates of human origin that have shown promise as potential biomaterials include heparin, keratin, and dermatan.

Non-Human Origin

In addition to polysaccharides of human origin, there exist a number of molecules from other sources that have shown promise as degradable polymeric biomaterials. Although a number of candidates have been identified, two of particular interest are chitosan found in crustacean skeletons and alginate found in brown algae.

Chitin is a linear polysaccharide consisting of β -1,4-linked *N*-acetylglucosamine units that forms the exoskeletons of many arthropods. Chitin is structurally similar to HA and has shown a similar capacity to accelerate wound healing.⁶⁵⁶ Chitin fibers,^{657,658} sponges,^{659,660} and membranes⁶⁶¹ have all been investigated as wound dressing materials. Unfortunately, chitin is insoluble in many common solvents limiting its processability and potential in biomedical applications.

To overcome insolubility issues, chitosan, a chitin derivative, is created by deacetylation of chitin giving a polysaccharide composed of randomly located units of *D*-glucosamine and *N*-acetylglucosamine. A number of enzymes have been found *in vitro* to degrade chitosan including chitosanase, lysozyme, and papain.⁶⁶² Physiologically, lysozyme is the primary degrading enzyme and chitosan degradation rate is dependent on the degree of acetylation and crystallinity.⁶⁶³ Chitosan with lower acetylation percentages have been shown to last *in vivo* up to several months.⁶⁶⁴ Side group modification has been found to be a secondary technique for modulating degradation rate. Chitosan undergoes significant hydrogen bond-

ing, which can be disrupted by the inclusion of bulky side groups like isobutyl leading to faster polymer degradation.⁶⁶⁵ Due to chitosan's processability and versatility, it has been used in a wide range of biomedical applications.

As chitosan is water absorptive, oxygen permeable, and haemostatic, it has been extensively studied as a wound dressing material over the past 20 years.^{666–668} In addition, chitosan is much more bioactive than many of its degradable polymer counterparts leading to acceleration of wound healing. Induction of interleukin-8 production from fibroblasts,⁶⁶⁹ stimulation of macrophages,^{670,671} and chemoattraction of neutrophils⁶⁷² by chitosan are all important steps necessary to initiate the body's wound healing cascade. Chitosan's intrinsic antibacterial property,⁶⁷³ minimal foreign body reaction,⁶⁶⁴ and polymer degradation into *N*-acetylglucosamine (a major component of dermal tissue) also assist in rapid wound healing. As chitosan by itself is mechanically weak, it is often crosslinked^{669,674} or combined with other degradable polymers such as PLA,⁶⁷⁵ PLGA,^{676,677} PEG,^{437,678} collagen,^{679,680} and alginate^{681,682} which are formed into films,⁴³⁷ membranes,^{667,682} sponges,^{673,678,679} particles,⁶⁷⁶ fibers,^{675,677,680} and gels^{668,669,681} to create stronger bandages. Often times, antibiotics are trapped within chitosan and chitosan-based composite wound healing materials to prevent bacterial infection.^{683,684} HemCon[®] dressings (HemCon Medical Technologies) are a FDA-approved chitosan-based wound dressing that is often used in combat,⁶⁸⁵ emergency medicine,⁶⁸⁶ and dentistry.⁶⁸⁷

Chitosan has also been investigated as a delivery device. Chitosan is so hydrophilic that it almost always is either crosslinked^{688,689} or blended with other degradable polymers to yield materials with physiologically relevant release rates. Some blended systems include chitosan with PLA,^{690–692} PLGA,^{690,692–695} PEG,^{692,696–699} collagen,^{700–702} γ PGA,^{703,704} and alginate.^{705–707} Formation of the polymer composites into particles,^{690–696,701,703,704,706,707} micelles,^{698,699} fibers,⁶⁹⁷ hydrogels,⁷⁰⁵ and porous scaffolds^{700–702} has allowed for the

delivery of chemotherapeutics,^{693,694,698} antibiotics,⁷⁰⁴ anti-inflammatory drugs,⁶⁹⁷ antipsychotics,⁶⁹⁰ immunosuppressants,⁶⁹¹ vaccines,^{695,706} DNA,^{696,699,702,703} siRNA,⁶⁹² and proteins.^{700,701,705,707} Due to chitosan's positive charge and significantly high charge density, its ability to condense DNA has made it most promising as a DNA/gene delivery material. Also, chitosan has been found to be very mucoadhesive, so it has great potential for pulmonary drug delivery.⁷⁰⁸⁻⁷¹⁰

The ease with which chitosan can be processed into porous matrices gives it promise as a tissue engineering scaffold. So far chitosan and chitosan-composites have been formed into membranes,^{500,711-713} sponges,^{443,714-716} fibers,⁷¹⁷⁻⁷²¹ fused microspheres,⁷²²⁻⁷²⁴ and hydrogels⁷²⁵⁻⁷²⁹ for regenerative applications. Cellular and acellular scaffolds have been used for the engineering of bone,^{443,719,722-724} tendon,⁷¹⁷ ligament,^{717,721} cartilage,^{428,726,728} nerve,^{714,718,725,729} skin,^{500,713,716,720} and vascular tissue.^{711,712,715} By side group modification, deacetylation and polymer blending, chitosan can be incorporated into scaffolds with a wide range of physical properties but still retain the novel bioactive function of chitosan itself.

Alginate is a linear copolymer composed of β -D-mannuronic acid and α -L-guluronic acid joined by a 1-4 glycosidic bond. The composition and patterning of the monomers is dependent on the source of the polysaccharide. The most common source of alginate is the cell wall of brown algae, and it is normally extracted via a basic solution followed by acidic precipitation to achieve alginic acid. These polymers have been found to have molecular weights up to 500 kDa. Alginate has shown great promise in biomedical applications due to the reactivity of its carboxylate side groups and its capacity to form spontaneous gelation when exposed to divalent cations such as calcium.

The simple and mild reaction conditions necessary for alginate hydrogel formation has led to its extensive use as a drug and cell delivery device, wound healing dressing and tissue engineering scaffold. Although some pure alginate hydrogel-based drug delivery devices have been used to deliver payloads,⁷³⁰⁻⁷³³ most research has focused on composite systems of blends or intermixed constructs (e.g., particles within a hydrogel). Alginate-based drug delivery composites include the incorporation of PLGA,⁷³⁴⁻⁷³⁷ PCL,^{738,739} polyethers,⁷⁴⁰⁻⁷⁴² and chitosan^{705,743-745} to effectively deliver chemotherapeutics,^{735,739} antibiotics,⁷⁴¹ anti-inflammatory drugs,^{734,738,740} calcium channel blockers,⁷⁴⁴ and proteins.^{705,736,737,742,745} Supportive alginate-based hydrogels have also been researched for the delivery of chondrocytes,⁷⁴⁶ osteoblasts,⁷⁴⁷ myoblasts,⁷⁴⁸ fibroblasts,⁷⁴⁹ keratinocytes,⁷⁴⁹ and adipose-derived stem cells.⁷⁵⁰ Alginate wound healing dressings have been FDA approved and marketed as AlgiDERM[®] (Bard Medical Division), AlgiSite M (Smith & Nephew), Hyperion Advanced Alginate Dressing (Hyperion Medical), KALTOSTAT[®] (ConvaTec), and Tegaderm[®] (3M).

Although alginate alone is too mechanically weak to be used as a structural tissue engineering scaffold, it has shown sig-

nificant promise when blended or copolymerized with other degradable polymers. Composites of PLGA,⁷⁵¹⁻⁷⁵³ collagen,⁷⁵⁴⁻⁷⁵⁷ PLL,⁷⁵⁸⁻⁷⁶² and chitosan^{746,753,763-765} with alginate have been formed into scaffolds composed of films,⁷⁶⁰ sponges,⁷⁵⁹ fibers,⁷⁶³ adhered microspheres,^{751,755,757,758,761,762} gels,^{746,753,754,756,764} and freeze casted porous networks.^{752,765} These constructs have been used in the regenerative engineering of bone,^{752,757,759} cartilage,^{746,751,753,756,765} corneal,⁷⁶⁴ liver,^{758,760} nerve,⁷⁶¹ vascular,⁷⁵⁵ pancreas,⁷⁶² and connective tissue.⁷⁵⁴

Modification of alginate through reactions with its carboxylate side groups have yielded novel, bioactive materials. Specifically, adding acetal aldehyde crosslinker yields a pH-sensitive contracting gel,⁷⁶⁶ and adding laminin peptides causes better adhesion, cell spreading, and neurite outgrowth.⁷⁶⁷ Further investigation into adding functional groups is underway and will hopefully yield promising hybrid materials that can overcome some of the current limitations found with using alginate.

Although possessing many great properties, alginate has two significant drawbacks as a biomaterial: limited *in vivo* degradation and poor cellular adhesion. Mammals do not produce alginate lyase, the enzyme that cleaves alginate polymers,⁷⁶⁸ so the *in vivo* degradation of alginate is very slow. To overcome this issue, alginate is often either irradiated or oxidized through the use of gamma radiation or periodate, respectively. Low level radiation causes cleavage at the mannuronic-gluronic glycoside bond allowing for more rapid polymer degradation and material solvation.⁷⁶⁹ Oxidation by periodate, an ion composed of iodine and oxygen, causes the formation of a hemiacetal ring with an open urinate residue with a hydrolytic bond that can cleave much more quickly than the glycoside bond normally does.⁷⁷⁰ In most tissue engineering applications, the scaffold is designed to provide structure support as well as mimic natural extracellular matrix, so poor cell attachment is highly undesirable.⁷⁷¹ Most cells that do not interact with their surroundings tend to not differentiate and eventually die off. Side group modification of alginate with the peptides RGD^{772,773} and GRGDSP^{774,775} have lead to the development of scaffolds that interact more favorably with transplanted cells and host cells.

In addition to the polymers above, a variety of other polysaccharides, such as dextran, agarose, mannan, and inulin have been investigated for potential as biomaterials.

CONCLUSIONS

There currently exists a wide range of degradable polymers that hold potential as biomaterials. With advancements in polymer synthesis techniques, the paradigm of utilizing a few well-characterized polymers (e.g., PLGA and collagen) for all biomedical applications has shifted to using polymers, both heavily researched and newly developed, that can fit certain niches (e.g., DNA and RNA association with phosphoesters and inherent bioactivity of chitosan). In addition, the emergence of combination polymers holds promise for the creation of novel materials that possess desired

properties for highly specific applications. The further development of processing techniques, especially with the assistance of computer-aided technology, is allowing for the formation of particles and scaffolds with extremely complex architectures that can mimic their biological counterparts. Although these developments in polymer research have been critical, it should be noted that the advancements in biological research have led to a better understanding of how biomaterials interact with the host on cellular, tissue, organ and systemic levels. The field of degradable polymeric biomaterials will only continue to progress if the recent creation of strong collaboration teams composed of chemists, biologists, material scientists, engineers and clinicians is encouraged.

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