

# 4.

## Biodegradable Orthopedic Implants

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### List of Abbreviations

ECM: extracellular matrix  
GAG: glycosaminoglycan  
HA: hyaluronic acid  
MMP: matrix metalloproteinase  
OPF: oligo(poly(ethylene glycol) fumarate)  
PBS: phosphate-buffered saline  
PCL: poly( $\epsilon$ -caprolactone)  
PEG: poly(ethylene glycol)  
PEG-DA: poly(ethylene glycol)-diacrylate  
PEG-DM: poly(ethylene glycol)-dimethacrylate  
PGA: poly(glycolic acid)  
PLA: poly(lactic acid)  
PLGA: poly(lactic-co-glycolic acid)  
POE: poly(orthoester)  
PPF: poly(propylene fumarate)  
PPF-DA: poly(propylene fumarate)-diacrylate  
rhBMP-2: recombinant human bone morphogenetic protein 2  
TGF- $\beta$ 1: transforming growth factor  $\beta$ 1

### 4.1 Introduction

Over the past 30 years, there have been significant advances in the development of biodegradable materials [79]. In particular, these materials have received attention for use as implants to aid regeneration of orthopedic defects [49, 91]. Every year more than 3.1 million orthopedic surgeries are performed in the United States alone [1]. However, although

current treatments using nondegradable fixation materials have proven efficacious, tissue-engineering approaches with biodegradable implants are being considered as promising future alternatives [8, 49]. One possible advantage of these systems is that biodegradable implants can be engineered to provide temporary support for bone fractures, and because they can degrade at a rate matching new tissue formation, their use can eliminate the need for a second surgery [49]. In addition to providing support for the tissue surrounding a defect, the scaffold can serve as a substrate for seeded cells, facilitating new tissue formation at the site of injury [35, 100]. The incorporation of drugs or bioactive molecules may also accelerate new tissue formation, or can be used to treat specific conditions, such as osteomyelitis [4, 10].

In designing biodegradable orthopedic implants, several important factors should be considered. First, the material should degrade over an appropriate time, so that the scaffold functions as a temporary support, but allows space for newly generated tissue to replace the defect [49, 91]. Second, neither the initially implanted biomaterials nor the degraded materials and related products, such as monomers, initiators, and residual solvents, should elicit a serious inflammatory or immunogenic response in the body [28]. Finally, the material should possess sufficient mechanical strength to sustain loads applied to defects during the healing process. Additionally, the material should show a decrease in mechanical strength as defects are replaced with new tissue to

encourage force transfer in load-bearing defects. In this way, mechanical signals are gradually transmitted to the resident cells, thus encouraging tissue remodeling via exposure to dynamic loading conditions [2, 106].

Over several decades, a number of biomaterials for orthopedic applications have been investigated and developed. In this chapter, applications, important properties, and different types of biodegradable materials will be discussed in order to provide an overview of the state of the art in orthopedic biomaterials.

## 4.2 Background

Before developing biomaterials for a particular orthopedic tissue-engineering application, it is important first to understand the basic properties of the different musculoskeletal tissues such as bone, cartilage, ligament, and tendon. This basic information allows developing materials and strategies that are specifically tailored for each type of tissue defect.

### 4.2.1 Bone

The main function of bone tissue is to support the body. Bone tissue is maintained by the balance in activity between bone-forming and bone-resorbing cells. The collagen fibers impart tensile strength, and the mineral salts, a form of calcium phosphate (hydroxyapatite), increase the toughness and hardness of the tissue [7]. Three types of cells coexist in bone: osteoblasts, osteoclasts, and osteocytes. Osteoblasts are bone-forming cells responsible for the formation of the hard extracellular matrix, whereas osteocytes are fully mature embedded bone cells that maintain the tissue structure. Osteoclasts selectively resorb bone in certain areas in response to a biochemical or biomechanical stimulus [21].

Human bones are described as compact (cortical) or spongy (cancellous), depending on their density. Compact bone consists of central canals and perforating canals surrounded by concentric rings of matrix. Spongy bone is much less dense, having irregular lattice structures where spaces are filled with bone marrow [101].

### 4.2.2 Cartilage

Cartilage is an avascular tissue composed of chondrocytes embedded in an extracellular matrix consisting of water and a solid matrix. The solid matrix consists of proteoglycans and collagens, as well as glycoproteins in lesser amounts. Three types of cartilage have been described, which differ in composition: hyaline cartilage, elastic cartilage, and fibrocartilage [36, 45].

Hyaline cartilage is a glassy and homogeneous cartilage composed primarily of type II collagen fibers and proteoglycans. This unique combination of collagen fibers and hydrophilic proteoglycans gives cartilage important viscoelastic properties that allow it to disperse forces while acting as a lubricator. Elastic cartilage is similar to hyaline cartilage; however, it also contains elastic fibers and an interconnecting sheet of elastic material. It is often found in the external ears and the walls of the acoustic meatus. Fibrocartilage possesses properties that are intermediate between those of dense connective tissue and hyaline cartilage and contains both type I and II collagen. Fibrocartilage is the main constituent of tissues such as the meniscus of the knee [36, 45].

### 4.2.3 Tendon

Tendons are dense tissues that connect muscle to bone. Tendon tissue consists of fibroblasts surrounded by type I collagen, a small amount of type III collagen, and small quantities of proteoglycans (dermatan sulfate and hyaluronic acid). Triple-helical collagen molecules are assembled into fibrils that are cross-linked through aldol or Schiff base adducts between aldehydes on one or more of the  $\alpha$ -chains of collagen molecules and aldehydes or amino groups on adjacent chains. This cross-linking imparts the high tensile strength needed for proper tendon function [5, 31].

### 4.2.4 Ligament

Ligaments are made up of closely packed fibers and are in many respects similar to tendons. However, the relative amounts of the various extracellular matrix (ECM) components are not the same as in tendons. Specifically, ligaments have less total collagen and more proteoglycans than tendons. Ligaments

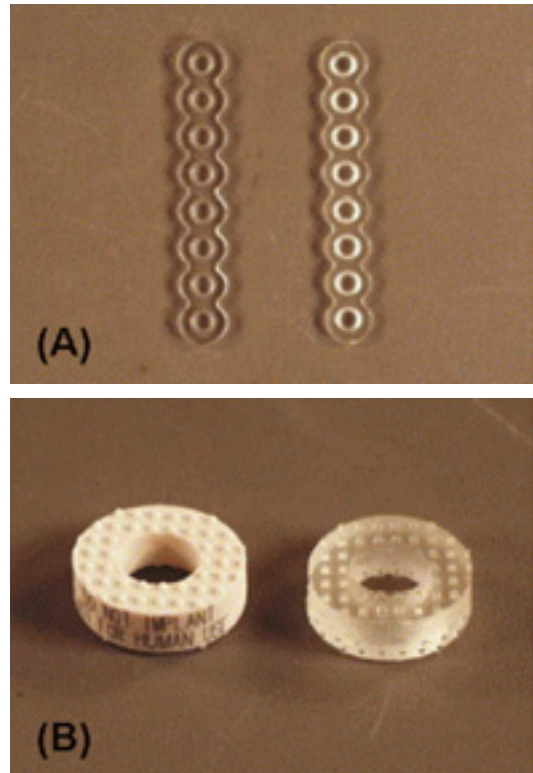
are less organized in structure but have higher DNA content than corresponding tendons [5, 31].

### 4.3 Applications of Biodegradable Orthopedic Implants

In designing scaffolds for orthopedic implants, the envisioned final application must be a primary concern from the beginning. Scaffolds may be used as internal fixation devices to support the defect site. Alternatively, scaffolds may be implanted to induce cell migration and proliferation to aid in tissue repair. Another potential strategy is the use of scaffolds to provide localized delivery of bioactive molecules, cells, or a combination to enhance defect healing.

#### 4.3.1 Systems for Mechanical Support

In many cases, biodegradable orthopedic materials have been applied during the healing process in the form of fixation implants such as screws, staples, pins, rods, and suture anchors to support areas weakened by bone fracture, sports injury, or osteoporosis [14, 37, 98]. High mechanical strength and stiffness are extremely important in designing biodegradable devices for orthopedic procedures in which high loads are applied after the devices have been implanted. Long degradation times for the biomaterials are also often desired for these applications [17, 20]. A study comparing a biodegradable interference screw made of poly(L-lactide) with a titanium interference screw in the porcine anterior cruciate ligament demonstrated that the poly(L-lactide) screw could provide a promising alternative in terms of primary fixation strength [84]. A mixture of poly(propylene fumarate) (PPF) and poly(propylene fumarate)-diacrylate (PPF-DA) has been molded into a biodegradable fixation plates (Fig. 4.1A) and a bone allograft interbody fusion spacer (Fig. 4.1B) with acceptable mechanical properties for use in these applications [98].



**Figure 4.1.** Photographs of a biodegradable fixation plate and an interbody fusion spacer fabricated by the use of transparent silicone molds. (A) 1.5-mm, eight-hole adaptation plate manufactured with 70:30 P(L/DL-LA) (left) and PPF/PPF-DA (double-bond ratio of 0.5) (right). (B) Plastic model (left) and PPF/PPF-DA (double-bond ratio of 0.5) replicate (right) of a 5-mm lordotic anterior cervical fusion (ACF) spacer. Reproduced with permission from Timmer et al. [98]. Copyright 2003, with permission from Elsevier.

#### 4.3.2 Systems for Delivery of Cells or Bioactive Factors

##### 4.3.2.1 Bioactive Factors

In addition to providing physical support, scaffolds have been employed to introduce bioactive molecules at the defect site [39, 66]. In one strategy, scaffolds can be used to control the release of bioactive molecules, thus accelerating the healing process [41]. In other cases, the effectiveness of less stable drugs may be extended by encapsulating them inside a matrix [50]. Several delivery systems have been developed, including nano- or microparticles and hydrogel-based implants.

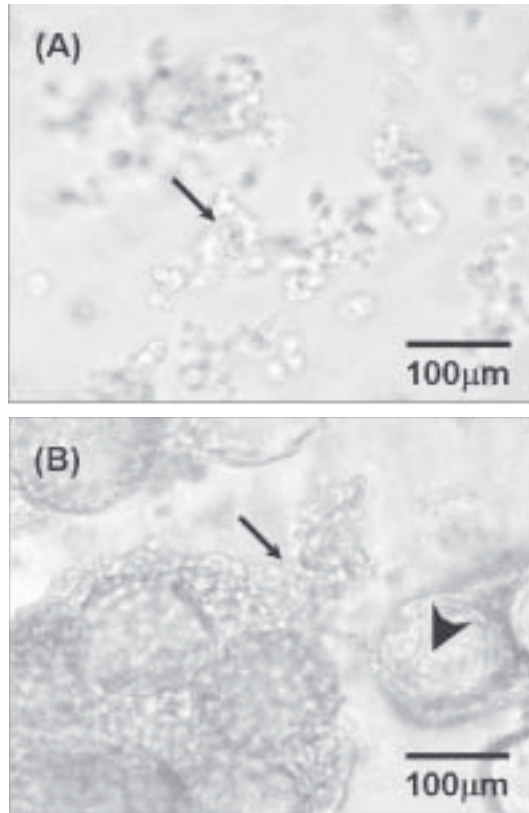
#### 4.3.2.1.1 Nano- or Microparticles

Nano- or microparticles are among the most common types of delivery vehicle for bioactive molecules. A variety of microparticles fabricated with polymers such as poly( $\epsilon$ -caprolactone) (PCL), poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), or blends of PLGA with poly(ethylene glycol) (PEG) have been investigated as delivery matrices for orthopedic applications. These microparticles can be formed by several methods, such as a single/double emulsion technique or a solvent evaporation-extraction process. Because the mechanism by which bioactive molecules are released in these systems is mainly diffusion, the release rate and total amount released can be adjusted by altering fabrication parameters such as loading concentration, polymer molecular weight, copolymer ratio, and particle structure [24, 47, 89, 104].

Alternatively, release from nano- or microparticles made of naturally derived materials can be controlled through directed degradation rather than a diffusion mechanism, as in the polymeric systems described above. When transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1) was incorporated into gelatin microspheres, the release profiles depended on the presence of a gelatinase enzyme in the medium. In this case, it is likely that the polyionic complexation between the growth factor and the gelatin retards its release until the gelatin microparticle is degraded by the enzyme. Because enzymes such as matrix metalloproteinases (MMPs) are up-regulated in injured cartilage, this system may provide a unique mechanism to encourage drug release in areas undergoing tissue remodeling [41]. An additional advantage of gelatin microspheres is that when they are encapsulated in hydrogels, they can serve as porogens, thus providing additional space for tissue formation at the defect site (Fig. 4.2) [41, 77].

#### 4.3.2.1.2 Hydrogels

Hydrogels are three-dimensional polymers physically or chemically cross-linked and swollen by water. This enables them to entrap various drugs and later release them in a controlled manner. The release kinetics of drugs from hydrogels can be modulated by external stimuli such as changes in pH [52], temperature [50], or protein levels [80]. For the treatment of orthopedic defects, hydrogels have the advan-



**Figure 4.2.** Light microscopy of oligo(poly(ethylene glycol) fumarate) (OPF) hydrogel composites containing chondrocytes at day 21. Arrows indicate encapsulated chondrocytes, and arrow heads indicate encapsulated microparticles. OPF hydrogel composites containing only chondrocytes are depicted in (A), while (B) shows OPF hydrogel composites containing chondrocytes and TGF- $\beta$ 1-loaded microparticles. Reproduced with permission from Park et al. [77]. Copyright 2005, with permission from Elsevier.

tage that they can be designed to function as biomimetic support materials, as well as drug-delivery matrices [85]. Moreover, depending on their composition, hydrogels may be injectable, allowing for their use in minimally invasive procedures. In one study, PEG-based macromers were photopolymerized to encapsulate DNA. By changing the monomer chemistry in this system, the DNA release profile was tailored to provide release over 6 to 100 days [82]. Another PEG-based oligomer, oligo(poly(ethylene glycol) fumarate), has also been developed as an injectable hydrogel carrier for growth factors useful for both bone and cartilage tissue engineering [40, 41, 54].



### 4.3.2.2 Cells

Many types of cells are responsible for producing and maintaining the extracellular matrix essential to the function of all musculoskeletal tissues. For this reason, many research efforts have focused on developing cell carriers to aid orthopedic tissue regeneration [28, 35, 99, 100].

Scaffolds used as cell carriers generally have interconnected pore structures formed by various methods such as phase separation, solvent casting/particulate leaching, or electrospinning [15, 61, 63]. Pore morphology is especially important in the preparation of scaffolds made of hydrophobic materials, because in these cases the pore structure is a main means of providing void space for nutrient exchange and cell attachment [15, 63, 72]. PLGA scaffolds with different pore sizes have been used successfully in bone-formation experiments in vitro, resulting in osteoblast growth and differentiated cell function in 52 days [48]. In another study, knitted PLGA scaffolds seeded with bone marrow cells were employed to bridge a gap in the rabbit tendon [75]. The use of porous PGA scaffolds seeded with bovine chondrocytes also resulted in the formation of cartilaginous tissue in over 12 weeks. The compressive modulus of PGA-chondrocyte constructs reached the same order of magnitude as that of normal bovine cartilage in 9 weeks and a similar aggregate modulus was achieved in 12 weeks [68].

Unlike PLGA, PLA, and PGA, many other biodegradable polymers, both natural and synthetic, are hydrophilic, leading to the formation of hydrogels [61, 63, 88, 93]. Hydrogels have an advantage over porous hydrophobic scaffolds in that hydrogels often have mechanical and structural properties similar to the extracellular matrix of soft tissues and are easy to process in terms of the incorporation of cells and bioactive molecules [62]. In addition, the high water content of hydrogels eliminates the need for pores to facilitate nutrient diffusion deep within the construct. As with carriers for bioactive molecules, hydrogels that include cells can be injected into the tissue defect in the form of a liquid solution and subsequently cross-linked into gel constructs. This strategy simplifies the procedure of cell transplantation [16, 26, 93, 94]. Recently, an in vitro study with poly(propylene fumarate-co-ethylene glycol)

(P(PF-co-EG)) incorporated with bovine chondrocytes found both increasing cell number and glycosaminoglycan (GAG) production over the 8-day culture period [26]. A variety of other hydrophilic polymers, such as collagen, chitosan, and PEG-based materials, have also been investigated for cell-delivery applications [12, 16, 30].

## 4.4 Requirements of Biodegradable Orthopedic Implants

As mentioned above, scaffold materials must fulfill critical requirements before they can be used in orthopedic tissue engineering. The criteria include biocompatibility, biodegradability, relevant biological properties, appropriate mechanical properties, and material processability. These criteria are discussed individually below.

### 4.4.1 Biodegradability

The degradation of implanted materials in orthopedic tissue engineering is essential because it eliminates the need for implant removal in a second surgical intervention, and provides space for native tissue growth. Therefore, this degradation should be achieved at a rate that will enable native tissue to be generated in the defect site. In the meantime, partially degraded scaffolds should maintain their mechanical integrity until the newly formed tissues have sufficient strength to replace them [8, 30, 49, 92]. However, this strategy may not be ideal for patients with enhanced catabolic diseases, although ideal for healthy persons. Material degradation occurs by several mechanisms, including hydrolysis and enzymatic degradation. Most synthetic polymers are degraded by hydrolysis of their ester linkages. This degradation generally occurs by bulk or surface erosion mechanisms, depending on the water permeability of the scaffold [56]. On the other hand, many natural materials and some polymers, including degradable peptide sequences, are degraded by enzymatic mechanisms [32, 33, 85] (see Section 3.5 for specific examples of materials that degrade by each of these means).

#### 4.4.2 Biocompatibility

One of the most critical requirements biodegradable materials must meet is biocompatibility. Not only should scaffold materials avoid eliciting inflammatory and immunogenic responses, but also degraded materials and related chemicals should be biocompatible in terms of both the local and the systemic response [11, 27]. The biocompatibility of a polymer depends on both its chemical structure and the processing method that produces it. During a polymerization process, an initiator, a monomer, and sometimes a catalyst are needed, and these materials often remain in preformed implants even after purification. Residual unreacted monomers or initiators are also a particular concern for in situ forming implants. Therefore, the toxicity and concentration of these substances should be considered when assessing biocompatibility. Removal of these potentially toxic components is usually effected by prolonged rinsing in aqueous solution. Biocompatibility of the remaining material is confirmed in vitro by cytotoxicity assays that use appropriate cells in contact with test scaffolds and their degradable products. In vivo observation of the inflammatory response after implantation in animal models is also an important step before clinical application can be considered [11, 96].

#### 4.4.3 Biological Functionality

Tissue-engineering applications often require functional materials that induce cellular healing responses rather than simply provide biocompatible tissue replacements. This functionality is achieved either by the addition of soluble bioactive molecules such as growth factors and cytokines or by chemical modification of biomaterials for covalent attachment of these molecules [55, 81, 87]. For example, synthetic hydrogels that contain covalently linked peptide sequences that direct cellular attachment and migration have been shown to possess properties of natural materials, while still maintaining the advantages of synthetic materials, such as mechanical properties. Like natural materials, modified hydrogels are susceptible to degradation by enzymes [33, 55, 81, 87].

#### 4.4.4 Mechanical Properties

The location of a skeletal defect often imposes strict requirements for the mechanical properties of an implant [13]. For example, scaffolds for treating load-bearing bone defects should be sufficiently hard and stiff to sustain normal loads during healing. Similarly, materials for cartilage tissue engineering should possess viscoelastic properties similar to those of native tissue in order to withstand both the frictional and the compressive forces imparted within the joint. The mechanical properties of implants directly after implantation are especially critical, since these materials will be receiving the full load intended for the native tissue. The decrease in strength associated with material degradation should be slow and predictable, leading to graded load transfer to encourage growth of neotissue with properties similar to those of native tissue [2, 28].

Cells in scaffolds experience different mechanical signals, depending on the mechanical properties of the scaffold or the ECM, that result in altered cell function and protein production [2, 103]. For example, the load-bearing and lubrication properties of cartilage are attributed to the complex structure and composition of its extracellular matrix formed under unique biomechanical and frictional influences [103]. Therefore, proper modulation of scaffold mechanical properties is extremely important, not only to provide proper support to the surrounding tissue, but also to engineer functional replacement constructs.

#### 4.4.5 Processability: Sterility, Reproducibility, and Ease of Handling

As with other biomedical implants it must be possible to sterilize biodegradable scaffolds without affecting their chemical or physical properties and to produce and package them on a large scale for practical and economic uses. Factors such as viscosity, curing time, and implant shape should also be optimized for injectable scaffolds to facilitate their use during complex surgical procedures [28, 70, 92].

## 4.5 Materials

Depending on the defect site and strategy to be employed, certain orthopedic biomaterials may be more suitable than others. These materials can either be obtained from natural sources, with or without subsequent modification, or synthesized. The following is an overview of natural and synthetic biodegradable materials that are currently being investigated for orthopedic applications.

### 4.5.1 Natural Materials

Many natural biomaterials are either currently used or under development for tissue-engineering applications. Natural materials have the advantage over synthetic materials in being similar to materials in the body and thus may encourage tissue development by directing cell adhesion and function [62]. These materials, however, are more likely to evoke an immunogenic response or carry a risk of disease transmission [76].

#### 4.5.1.1 Collagen

Collagen is the most abundant natural polymer, constituting more than a third of the protein content in the body. Although several different types of collagen exist in the tissues, the major constituents of orthopedic tissues are the fibrillar collagens (most predominantly types I and II) [36, 76]. These collagens possess a triple-helix structure that results in fibrils with high tensile strength [59]. Recently, many scientists have investigated collagen scaffolds for tissue engineering of soft orthopedic tissues, since collagen is widely available and easily cross-linked chemically (by glutaraldehyde, formaldehyde, or carbodiimide) or physically (by ultraviolet light or heat). Thus, collagen has the potential for a wide range of scaffolding applications [60, 73, 78]. Collagen implants can be fabricated for use as both preformed and injectable scaffolds and can be easily combined with cells, growth factors, or both, thus further enhancing their usefulness for orthopedic tissue engineering. In vitro studies with anionic collagen scaffolds prepared by a hydrolysis treatment demonstrated that seeded bovine

osteoblasts showed increased alkaline phosphatase activity over 3 weeks [18, 73].

#### 4.5.1.2 Gelatin

Gelatin is a promising biomaterial prepared by the thermal denaturation of collagen isolated from animal skins and bone. It contains a mixture of collagen strands along with their oligomers and degradation products and thus has the same primary composition as collagen but is not as highly organized. Two types of gelatin are produced, depending on whether or not the preparation involves alkaline pretreatment, which converts asparagine and glutamine residues to their respective acids. Acidic pretreatment of pig skin produces type A gelatin, whereas alkaline pretreatment of cattle hides and bones produces type B gelatin. Gelatin is used mainly as a scaffold for regeneration of soft tissues or for delivery of bioactive molecules [29, 46, 57]. Gelatin has also been investigated as an injectable scaffold for cartilage tissue engineering, because of its ease of gelation in situ [46]. Other work has shown that gelatin microparticles provide a promising delivery system for various growth factors, because their release is regulated by enzymatic degradation of the microparticle carriers [40, 57].

#### 4.5.1.3 Polysaccharides: Agarose, Alginate, Chitosan, and Hyaluronic Acid

Agarose is prepared by extraction from seaweed, such as agar or agar-bearing algae. It is a linear polysaccharide composed of the basic repeat unit, made up of alternating  $\beta$ -D-galactose and 3,6-anhydro- $\alpha$ -L-galactose units. In orthopedic tissue engineering, agarose is mainly used in the form of a gel prepared by cooling an agarose solution to allow cross-linking of the network. The mechanical properties of agarose gels vary with the concentration of agarose [9, 62]. Agarose-based materials have been used in several studies for cartilage regeneration and found to promote cell proliferation, cell retention and chondrogenesis in vivo and in vitro [64, 69, 74].

Like agarose, alginate is linear polysaccharide purified from seaweed. It consists of linear chains of  $\beta$ -D-mannuronic acid residues and  $\alpha$ -L-guluronic acid. Gelation occurs when

the presence of cations enables guluronic acid residues of adjacent chains to cross-link. The elastic compressive and shear moduli of alginate gels increase with increasing concentration of alginate, which allows specific materials to be designed for various applications. For example, varying the concentration of alginate from 1% to 3% (w/v) leads to an increase in the equilibrium compressive modulus from 0.9 to 8 kPa [9]. The ratio of mannuronic acid to guluronic acid also affects gel properties, such as biocompatibility and gel porosity [22]. This type of hydrogel has been employed to encapsulate chondrocytes and has demonstrated phenotype retention through maintenance of the cell's spherical morphology [58, 97].

Chitosan is a positively charged polysaccharide derived from chitin, a protein found in insect and crustacean shells. Chitosan is degraded *in vivo* by the action of lysozyme, and the rate of degradation is affected by the amount of residual acetyl content [76]. Chemical modification imparts a variety of physical and biological properties [9, 62]. Many derivatives of chitosan have been developed to overcome insolubility problems caused by high material crystallinity. Chitosan has also been modified to enhance cellular interactions for tissue-engineering applications [62]. Because there is no interspecies variation in terms of the chemical and physical structure of chitosan, regulation and quality assurance of this material is greatly simplified [63, 88].

Hyaluronic acid (HA), also called hyaluronan, is an anionic polysaccharide composed of repeating disaccharide units of N-acetylglucosamine and glucuronic acid. HA, a major component of cartilage ECM, has several advantages for use as a biomaterial. It is easy to isolate, can be chemically modified, and does not evoke a significant immune response [76]. Furthermore, *in vitro* studies with HA show that the material encourages chondrocyte proliferation and ECM production [29].

Although each of these natural polysaccharide materials holds promise for orthopedic applications, none is strong enough to be used as the only material at load-bearing sites. Thus, these materials are often combined with other natural or synthetic materials in a composite to improve the mechanical properties of the implant. For example, a study using chitosan-hyaluronic acid hybrid polymer fibers found a significant increase in tensile strength as com-

pared with chitosan fibers. Additionally, an *in vitro* culture using rabbit chondrocytes found significantly higher cell adhesivity, cell proliferation, and synthesis of aggrecan on hybrid polymer fibers than on chitosan fibers alone [62, 105, 107].

#### 4.5.1.4 Fibrin

Fibrin is a natural biomaterial formed in the process of wound healing, resulting from the cleavage of fibrinogen molecules by thrombin to form fibrin. Fibrin monomers are then assembled into fibrils, eventually forming fibers in a three-dimensional network (a fibrin clot). The fibrin clot enhances fibroblast infiltration and encourages proliferation necessary for the healing process [34, 76]. Unlike the above-mentioned natural materials, fibrin is not made up of ECM molecules. However, the possibility of its use in orthopedic tissue-engineering scaffolds has recently been widely examined, since fibrin not only is biocompatible and biodegradable, but also is easily formed simply by combining two components, fibrinogen and thrombin [34]. An *in vivo* study found that porcine chondrocytes produced cartilage when implanted with a fibrin polymer, whereas cells implanted alone did not produce any cartilage [53].

### 4.5.2 Synthetic Materials

Synthetic biomaterials have many advantages over natural materials. They can be synthesized in controlled environments to regulate such properties as molecular weight and molecular weight distribution. This characteristic leads to better batch-to-batch uniformity than is possible with the use of natural materials, while retaining the flexibility to tailor material properties for a given application. Several synthetic biomaterials have been used for orthopedic implants, including poly( $\alpha$ -hydroxy esters), poly( $\epsilon$ -caprolactone), poly(orthoesters), poly(anhydrides), PEG-based materials, poly(amino acids), and fumarate-based materials. These are described individually below.

#### 4.5.2.1 Poly( $\alpha$ -Hydroxy Esters)

Poly( $\alpha$ -hydroxy esters), including poly(glycolic acid) (PGA) and poly(lactic acid) (PLA), have been widely investigated as tissue-engineering



scaffolds because they are currently FDA-approved for use as suture materials and as drug-delivery systems. PGA can be highly crystalline (46%–50%), depending on its preparation method, and is hydrophilic in nature. Its high crystallinity makes it nonsoluble in many organic solvents except for those that are highly halogenated. PGA is mainly synthesized by methods employing ring-opening polymerization, and, like all polyesters, is degraded primarily by bulk hydrolysis of ester linkages at random sites. PGA crystallinity has a large impact on material degradation rate, because the more crystalline portions retard water entry and thus hydrolytic cleavage [8, 71].

PLA is another type of biodegradable and biocompatible poly( $\alpha$ -ester). It is also synthesized by ring opening polymerization and has two isomeric forms, D(–) and L(+). Like PGA, it is degraded by bulk hydrolysis of the ester linkage catalyzed by the presence of the degradation product, lactic acid [65]. PLA can also occur in crystalline forms, with the degree of crystallinity ranging as high as 37%. It is more hydrophobic than PGA and therefore has a slower degradation rate and a higher modulus [8, 72]. This high mechanical strength makes it a desirable material for orthopedic fixation devices [19]; however, the release of degrading crystal-like particles can be problematic.

Lactic acid and glycolic acid are often copolymerized at various ratios yielding poly(lactic-co-glycolic acid) (PLGA), with different properties from those of either of the homopolymers. The major difference is that the copolymer is amorphous within a wide range of copolymer ratios because of the disruption of the crystalline phases and therefore has a faster degradation rate and lower elastic modulus than PGA or PLA alone [8, 42, 76]. A study using two-dimensional and three-dimensional PLGA scaffolds impregnated with recombinant human bone morphogenetic protein 2 (rhBMP-2) and seeded with rabbit bone marrow stromal cells has reported in vitro osteogenic differentiation and ECM production over 2 months [44].

#### 4.5.2.2 Poly( $\epsilon$ -Caprolactone)

Poly( $\epsilon$ -caprolactone) (PCL) is a semicrystalline polymer with a melting temperature of 59 to 64°C and a glass temperature of –60°C. PCL is also synthesized by ring-opening polymeriza-

tion of the cyclic monomer  $\epsilon$ -caprolactone and is degraded by bulk hydrolysis. This material has a slower degradation rate than PLA and is easily copolymerized with other polymers [3, 70]. Recently, poly( $\epsilon$ -caprolactone) was used to fabricate three-dimensional nanofibrous scaffolds, allowing for in vitro chondrogenesis of seeded mesenchymal stem cells over 3 weeks [63].

#### 4.5.2.3 Poly(Orthoesters)

Poly(orthoesters) (POEs) are hydrophobic polymers that are degraded by surface erosion. Different degradation rates can be achieved by the addition of lactide groups, because carboxylic acids released by the degradation of the lactide segments facilitate the degradation of the orthoester [32]. An in vivo comparison between POE and PLGA scaffolds for bone tissue engineering found that POE scaffolds maintained their structural integrity after 6 and 12 weeks, whereas PLGA scaffolds partially collapsed after 6 weeks [6].

#### 4.5.2.4 Poly(Anhydrides)

Poly(anhydrides) are prepared by a melt condensation reaction of diacid molecules. They degrade by surface erosion and thus have been widely investigated as vehicles for biocompatible controlled release [90]. Poly(anhydrides), however, are not strong enough to be used as orthopedic materials, so photocross-linking or combination with other polymers such as polyimides has been used to improve the overall mechanical properties of implants [32].

#### 4.5.2.5 Poly(Ethylene Glycol)-Based Materials

Poly(ethylene glycol) (PEG) is a hydrophilic, highly biocompatible polymer with a variety of biomedical applications. Many different types of PEG-based materials have been developed as hydrogel scaffolds, including poly(ethylene glycol)-diacrylate (PEG-DA) and poly(ethylene glycol)-dimethacrylate (PEG-DM) [23, 67, 102]. Work with PEG-DM has demonstrated that it could encourage cartilage-like ECM production from encapsulated bovine chondrocytes over 4 weeks in vitro [12, 23, 67]. Although these derivatives often have limitations as scaffold materials because of their lack of degradability, PEG of

low molecular weight can readily be excreted by humans and therefore can be copolymerized with other polymers such as PLA and PPF to be used as a biodegradable scaffold material [26, 83].

#### 4.5.2.6 Poly(Amino Acids)

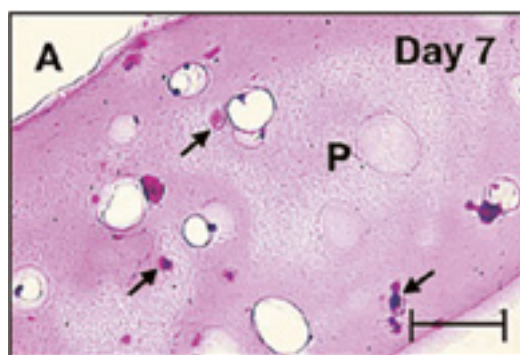
Poly(amino acids) have been considered as promising materials for biomedical applications because of their composition. However, the polymerization of pure poly(amino acids) is hard to control precisely. Furthermore, depending on the combination of amino acids, these materials can evoke an immune response in vivo [34, 76]. For these reasons, synthetic pseudo poly(amino acids), such as tyrosine-based polycarbonate, have been investigated recently. The polycarbonate not only exhibits good biocompatibility, but also supports the attachment of osteoblasts and osteoprogenitor cells. In addition, by varying the structure of the repeating unit, this material is easily modified to exhibit a range of mechanical properties, degradation rates, and bioactivity [81].

#### 4.5.2.7 Fumarate-Based Polymers

Poly(propylene fumarate) (PPF) is a biodegradable poly(ester) whose degradation generates 1,2-propanediol and fumaric acid, the latter of which is a naturally-occurring material produced in the Krebs cycle [2, 25, 27]. A number of methods can be used to synthesize PPF, and each produces polymers with unique physical properties [25, 32]. The backbone of this polymer contains double bonds, which lead to the formation of a three-dimensional network either by photocross-linking with bis(2,4,6-trimethylbenzoyl) phenylphosphine oxide (BAPO) or by thermal cross-linking with benzoyl peroxide [25, 98]. PPF has been investigated for use in injectable orthopedic implants because it possesses, in its cross-linked form, mechanical properties similar to those of cancellous bone [98]. Its mechanical properties can be further improved by the alteration of cross-linking agents or by the incorporation of a nanophase or microphase [43]. In an in vivo study using rabbits, photocross-linked PPF scaffolds with different pore sizes and porosities exhibited good biocompatibility [27]. Additionally, P(PF-co-EG) has been evaluated for use as a thermoreversible hydrogel scaffold

for the delivery of chondrocytes for articular cartilage replacement in tissue engineering [26].

Oligo(poly(ethylene glycol) fumarate) (OPF) is yet another novel biodegradable fumarate-based polymer. It is synthesized by the combination of PEG and fumaryl chloride in the presence of triethylamine [51]. Both in vitro and in vivo studies using this material demonstrated good biocompatibility, with a minimal inflammatory response observed after implantation for 12 weeks in cranial defects in rats and 14 weeks in osteochondral defects in rabbits [38, 86, 95]. High water absorption and mild in situ cross-linking conditions enable OPF to encapsulate living cells or bioactive growth factors for orthopedic tissue regeneration [41, 94]. Recently, OPF has been explored as a cell carrier for marrow stromal cells. After 4 weeks of culture in vitro, cells remained alive. Evidence of osteoblastic differentiation, including calcified ECM production throughout the hydrogel, was observed (Fig. 4.3) [93].



**Figure 4.3.** Histology of oligo(poly(ethylene glycol) fumarate) hydrogels containing rat marrow stromal cells after 7 (A), 21(B), and 28(C) days of in vitro culture with media supplemented with dexamethasone. Polymer is labeled P, mineralized matrix is labeled M, and arrows indicate the location of some of the cells found throughout the hydrogel. Reproduced with permission from Temenoff et al. [93]. Copyright 2004, American Chemical Society.

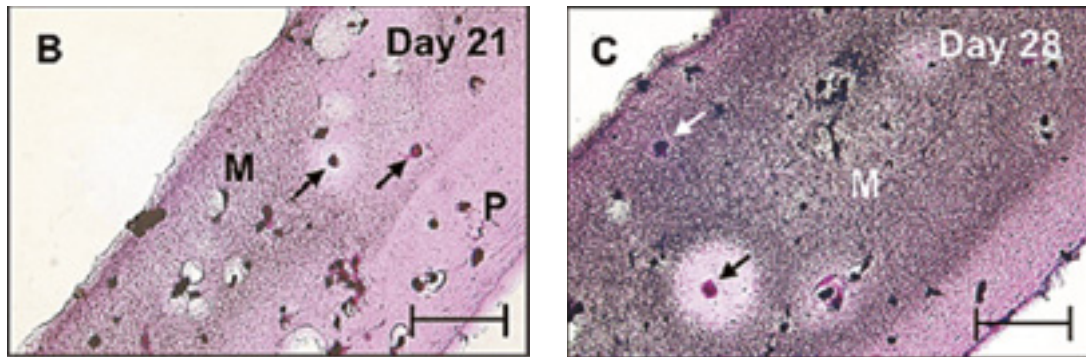


Figure 4.3. *Continued*

## 4.6 Summary

In this chapter, various applications, important properties, and different types of biodegradable materials that are candidates for use in orthopedic applications have been reviewed. For this purpose, both natural materials and synthetic polymers have been used to fabricate various types of orthopedic implants that include simple fixation devices, scaffolds for delivery of bioactive molecules, and carriers for delivery of living cell populations. In many cases, unique materials or strategies can be combined to produce a more optimal outcome that is compatible with the intended purpose. Even though they are still in the early stage of development, biodegradable scaffolds have already proven to aid in the repair of orthopedic defects. Thus, further research in this field holds great promise to effect complete regeneration of a variety of orthopedic tissues.

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