J Mater Sci (2009) 44:5713–5724
DOI 10.1007/s10853-009-3770-7

A review on biodegradable polymeric materials for bone tissue engineering applications

Muhammad Iqbal Sabir · Xiaoxue Xu · Li Li

Received: 17 March 2009 / Accepted: 21 July 2009 / Published online: 12 August 2009

Abstract Biodegradable polymer scaffolds have played a significant role in wide range of tissue engineering application such as bone scaffolds since the last decade. The aim of this article is to provide the comprehensive overview of biocompatible and biodegradable polymer materials and composite materials with their advantages and drawbacks in the application of biomaterial scaffolds, furthermore the properties and degradation criteria of the biomaterials are discussed in this review.

Introduction

Tissue engineering is a developing science technology and can be applied to improve the numerous clinical situations, including spinal fusion, joint replacement, and fracture nonunion and pathological loss of bones [1]. The tissue engineering applications from synthetic and biodegradable polymer scaffolds have been comprehensively examined for the bone tissue replacement in lab and clinic. The polymer materials are more beneficial than others because of their biocompatibility, mechanical properties, microstructure and the degradation rate, and these properties can even be precisely controlled by composition and fabrication of scaffold polymer materials. The basic idea in all of these accessions is to seed or grow the cell on the biodegradable polymer scaffold to promote tissues growth and remodeling. During the bone tissue regeneration, cell cannot be directly entrapped, because the environment which is used to create them is brutal for the cells to inhabit [2, 3]. Tissue-engineering systems have attempted to mimic the function of ECMs by placing cells along with growth factors in synthetic scaffolds that act as temporary ECMs. As the new bone is formed, the temporary scaffold will degrade and be absorbed by the body [4, 5]. In last 15 years bone tissue engineering research has increased dramatically. The design and development of the bone scaffolds depend upon the porosity that provides interconnected pores, suitable mechanical strength, and sufficient micro chemistry of surface. It is friendly to the cell behaviors like proliferation, migration, adhesion, and differentiation [6]. There are many factors for the bone tissue engineering, but all connected one are more of the following key ingredients, (a) harvested cells, (b) recombinant signaling molecules, and (c) three dimensional (3D) matrices [7, 8]. During the tissue regeneration, all of these factors play very important roles in the healing process. In the field of bone tissue engineering three dimensional scaffolds facilitate the cells, the guilds, augment and then regenerate three dimensional tissues. After implanted into the defect sites, the scaffolds are expected to promote and direct the growth of new bone cells and make the new cells attach to intrinsic tissues nearby by degrading slowly and grow together afterwards.

This article focuses on biodegradable/bioresorbable polymer materials as scaffold for the bone growth and tissue engineering. There are two types of bones (a) compact or cortical bone and (b) trabecular or cancellous bone (spongy tissue) [9, 10]. During the remodeling process, osteoclast cells are responsible for the breakdown and removing the cells on the surface of the bone. Osteoblast

M. I. Sabir · X. Xu · L. Li (✉)
College of Material Science and Chemical Engineering, Harbin Engineering University, Harbin 150001, China
e-mail: lili_heu@hrbeu.edu.cn

M. I. Sabir
e-mail: iqbalsabir@hotmail.com

X. Xu
e-mail: xuxiaoxue99731@163.com

cells synthesize the collagenous precursors of bone matrix [11]. During the development of the bone scaffold, the basic aim is to imitate the structural and mechanical properties of cancellous bone as close as possible. The scaffold fabrication technique should be flexible to build alternative scaffold architectures in order to allow biomimetic designs. A great assortment of techniques is presently being in use for fabrication of porous polymeric scaffolds, including solid free-form fabrication, emulsion freeze-drying [12], porogen leaching [13], fiber bonding [14], gas foaming [15], electro spinning, microsphere sintering, phase separation [16, 17], 3D-plotting technique or a mixture of these techniques [18, 19]. Although the traditional scaffold fabrication methods can produce highly porous scaffolds, these methods have limited control over scaffold architecture and pore interconnectivity. Consequently, the processing technique applied to manufacture a polymer scaffold with the desired characteristics must be selected or developed appropriately. Numerous novel manufacturing techniques have been developed to process synthetic polymers into porous scaffolds with large void volumes for cell seeding and adequate surface area for cell attachment. Each technique has particular drawbacks, such as the use of toxic solvent and lack of uniform architecture and poor strength, while the advantages are ease of fabrication, superior structural strength, the ability to incorporate, and deliver bioactive molecules, but none can be regarded as an ideal technique of scaffold fabrication to be applied to all tissues. The selection of a scaffold fabrication technique is, therefore, a question of setting priorities to determine the vital requirements [20].

A few fundamental requirements should be met for the polymer materials used as bone scaffold [21] (a) bioresorbable/biodegradable (b) good mechanical and chemical properties and stability (c) good adhesion capability with the cells. The scaffold should positively interact with cells, enhancing cell adhesion, growth, migration, and differentiated function. The basic challenges to the material selection and scaffold design are to achieve the initial strength and stiffness; the material for the scaffold must have the sufficient interatomic and intermolecular bonding/or a physical and chemical structure which must allow hydrolytic attach and breakdown. In addition porosity and proper pore size are the important design parameters for the scaffold design and high surface area necessary for mechanical stability [22].

Materials for scaffolds

Over the last century, several biomaterials have been extensively used in surgical implantation. Polymer materials are widely used in tissue engineering, because of its good properties such as degradability, biocompatibility, and ease of process ability [23]. Osteoinduction and osteoconduction are important concepts of bone tissue engineering materials [24]. Several years ago, scientists and researchers became familiar with the osteoconductive properties of the synthetic absorbable polymer materials which are dependent on their location and structure.

There are two kinds of materials synthetic and natural polymer materials. Biodegradable synthetic polymer materials such as poly (glycolic acid), poly (lactic acid), and their copolymers, poly (*p*-dioxanone), and copolymers of trimethylene carbonate and glycolide have been used in a number of clinical applications. Natural biodegradable polymer materials are derived from the proteins such as collagen, gelatin, and albumin and the polysaccharides such as cellulose, hyaluronate, chitin, and alginate. Polymer materials are differing in their molecular weight, polydispersity, crystallinity, and thermal transition, and different degradation rate which would strongly affect polymer scaffold properties. For example, polymer hydrophobicity and crystallinity percent can affect on the cellular phenotype, and deflection in the surface charges will affect the cellular spreading. This may be the reason of changes in cellular activities [25, 26].

Synthetic biodegradable polymer materials offer more advantages than natural materials; they can be synthesized to give various properties such as predictable lot to lot uniformity, free from concerns immunogenicity, and reliable source of raw material because the polymer materials with the fundamental building block units having simple and well know structure and properties. This review mainly focuses on the synthetic biodegradable materials for bone scaffold (Table 1), which gives the information about the physical properties of human hard tissues as reference of selection of polymer materials.

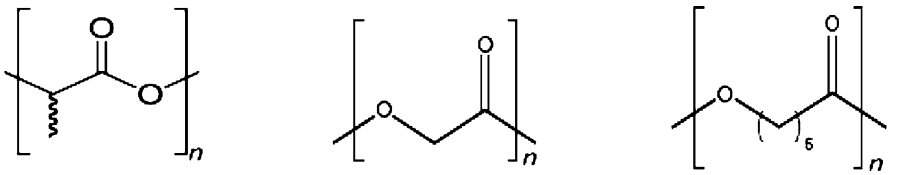
Saturated aliphatic polyesters (PLA, PGA, and PCL)

Saturated aliphatic polymer materials are one of the ancient and most frequently used grouped of materials in the field of bone Tissue engineering [29]. In this family, there are poly (lactic acid) (PLA) and poly (glycolic acid) (PGA), poly (lactic-coglycolide) (PLGA) and copolymers. PLA has three forms D-PLA PDLA, L-PLA (PLLA), and blend of D, L-PLA (PDLLA), PLA, PGA, and PLGA are the most widely used materials in the bone scaffold application. High molecular weight aliphatic polyesters are mostly synthesized by the condensation polymerization. The most popular synthetic aliphatic polyesters, poly(L-lactide), PLA, and PCL are synthesized by ring-opening polymerization (ROP) of the respective cyclic monomers, catalysts can be used such as Sb(antimony), Zn (zinc), or Pb(Lead) [30]. The basic chemical structure of all aliphatic polyester

Table 1 Mechanical property of human tissues [27, 28]

	Tensile strength (Mpa) [43]	Compressive strength (Mpa)	Young modulus (Gpa)	Fracture toughness (Mpa ml/2)
Cancellous bone	7.4	4–12	0.02–0.5	N/a
Cottrial bone	60–160	130–180	3–30	2–12
Cartilages	3.7–10.5		0.7–15.3 (Mpa)	N/A
Ligament	13–46	N/A	0.065–0.541	N/A
Tendon	24–112	N/A	0.143–2.31	N/A

Fig. 1 Structures of aliphatic polyesters



Poly (lactate acid) **Poly (glycolic acid)** **Poly (ε-caprolactone)**

materials is the same and the only difference is the pendent groups as shown Fig. 1. And change in pendent groups contributed differences in molecular weight, crystallinity which directly affects the kinetics of degradation. As a result, the degradation rate of PLA and PGA copolymer depends on the ratio of PLA and PGA present in the material.

Poly (glycolic acid)

PGA is a rigid thermoplastic material, with high crystallinity (45–55%), high melting point, and high glass transition temperature (see Table 2). Due to its high degree of crystallization, it is not soluble in most organic solvents. It is only possible in highly fluorinated solvents (hexafluoroisopropanol). PGA is an acidic and more hydrophilic than PLA. PGA can be processed by the common fabrication techniques such as extrusion, injection, and compression molding. PGA can fabricate into foam and porous scaffolds. The properties and the degradation can be affected by the type of processing technique, and PGA is highly sensitive to the degradation; it requires precise control on processing conditions. Solvent casting leaching method and compression moulding are used to fabricate the PGA based porous scaffolds.

The strength and modulus of PGA are very high and that is why the fiber of PGA is used in as sutures [23]. PGA has other monomers which are co- polymerized to reduce the stiffness in fibers. PGA is used in bone tissue engineering and medical application because its degradation properties and the decomposed product glycolic acid are natural metabolite. PGA has two degradation steps. In the first step water is diffused into the amorphous regions of matrix and hydrolytic chain scission of the ester group start. In the second step of degradation there are crystalline areas of the polymer, which dominated when the amorphous part has been eroded. Although the degradation product, glycolic acid, is resorbable at high concentration, it may cause the increase of the localized acid concentration which will cause the tissue damage. PGA was also investigated for development of bone fixation device (Biofix) [31, 32].

Poly (lactic acid)

PLA is synthesized by the cyclic dimer of lactic acid that exists as two optical isomers: D &L- lactate is the naturally occurring isomer, and DL-lactide is the synthetic blend of D-lactide and L-lactide. The homopolymer L-lactide (LPLA) is a semi crystalline polymer. This material has high tensile strength, elongation, and modulus that make it more suitable for the load bearing applications such as sutures and orthopedic fixation. Poly (lactic acid) has linear structure, and has one pendent methyl group which makes it more amorphous and hydrophobic than PGA due to the increase in the amorous behavior; the solubility in the organic solvents also amplify.

PLA can be dissolved in various organic solvent, such as chloroform, methylene chloride, methanol, ethanol, benzene, acetone, DMF, and etc. Poly (lactic acid) also can be degraded by the homogenous hydrolysis erosion. The poly (L-lactic acid) releases the lactic acid on decomposition/degradation, when carboxylic acid monomers are released during the degradation they help to reduce the PH and further induce degradation, which phenomenon is known as auto catalysis. The degradation time of P (D, L) LA is less than LPLA. LPLA requires 2 years to complete absorption. Copolymers of LPLA and glycolide are prepared to disrupt the crystallinity and accelerate the

Table 2 Properties and fabrication of biodegradable polymer materials

Polymer	Tensile(F)/ Compressive (C) strength (MPa)	Modulus (Gpa)	Elongation (%)	Solvent	Crystallinity %	Degradation time (Weeks)	Degradation product	Applications	Processing method	Reference
Polyglycolid	–	7.0	15–20	Hexafluoroisopropanol	45–55%	6–12	Glycolic acid	Suture anchors, meniscus repair, medical devices, drug delivery	SC, SFF, CM, ES	[33, 44–46]
Poly (L-lactide)	40–20	2.7	–	Chloroform, methylene chloride	37%	12–18	L-lactic acid	Fracture fixation, interference screws, suture anchors, meniscus repair	SC, SFF, ES	[36, 44, 28, 46]
Poly (L-lactide-co–D,L-glycolide) 75/25	–	1.9	3–10	Benzene, acetone, DMF	–	4–5	D,L-lactic acid	Orthopedic Implants, coatings, Detal	SC, SFF, Pl ES	[34, 38, 44, 46]
Poly (L-lactide-co–D,L-glycolide) 10/90	–		–	Methanol, ethanol, benzene	Amorphous	12–15	D,L-lactic acid and glycolic acid	–	SC, SFF, CM, ES	[44, 47, 46]
Poly (D, L-lactide)	–		3–10	Methanol, DMF	Amorphous	11–15	D,L-lactic acid	Orthopedic implants, drug delivary	SC, SFF, CM, ES	[44, 46, 27]
Poly (D, L-lactide-co-glycolide) 85/15	–	2.0	3–10	Ethanol, benzene	Amorphous	5–6	–	Interference screws, suture anchors, ACL reconstruction	SC, SFF, CM, ES, MSS	[44, 46]
Poly (D, L-lactide-co-glycolide) 75/25	–	2.0	3–10	DMF	Amorphous	4–5	–	Plates, mesh, screws, tack, drug delivery	SC, SFF, CM, ES	[46, 47, 27]
Poly (D, L-lactide-co-glycolide) 50/50	–	2.0	3–10	Methylene chloride	Amorphous	1–2	D,L-lactic acid and glycolic acid	–	SC, SFF,CM, ES, MSS	[46, 36, 22]
P HA and blends	20–43	–		Dichloromethane, Acetic anhydride	40%	Bulk		Drug delivery, Fixation and orthopedics implant, adhesion barriers	SC, EL, SF, IM	[48]
Poly caprolactone		0.4	300–500	Tetrahydrofuran	–	>24	Caproic acid	Suture coating, dental orthopedic implants	SC, SFF, CM, ES	[49, 50]
Polyorthoester	4–16	4–16	4.1–220			Surface		Orthopedic implants		
PPF(poly propylene fumarte)	2–30	2–3	–	Tetrahydrofuran, acetone, ethanol	37%	Depends on the formulation and composition several months >24	Fumaric acid, propylene glycol and poly(acrylic acid-co-fumaric acid)	Orthopedic implants, detal,foam coatings, drug delivery	Inject able prepolymer cross-linked via free radical initiation	[51]

Table 2 continued

Polymer	Tensile(F)/ Compressive (C) strength (MPa)	Modulus (Gpa)	Elongation (%)	Solvent	Crystallinity %	Degradation time (Weeks)	Degradation product	Applications	Processing method	Reference
Polyanhydrides	25–27	–	14–85	Chloroform,methylene chloride camphorsulfonic acid	–	0–14–1.4	–	Bone replacement,, medical devices, drug delivery	–	[52–54]
Poly(phosphazene)	–	–	–	[53] tetrahydrofuran (THF)	55	Surface	Phosphates and ammonia from backbone and other products depending on side chain structure	Fixation and bone replacement, medical devices, drug delivery, foam coatings	ES, SC, PI, EFD, MSS	[55, 56, 81]

This data summary was prepared on the information taken from the literature reviewed in this article and the data should be used as a guide only

SC solution casting, *CM* Compression molding, *SFF* solid free forming, *ES* electro spinning, *Pl* particulate leaching, *IM* injection molding, *EFD* emulsion freeze drying

degradation. PLA can be processed by various methods like petrochemical based plastics, among which include injection molding, sheet extrusion, blow molding, and thermoforming [33]. PLA and their derivates can be used for the fabrication of three dimensional scaffolds by solution casting, gel casting, solvent casting and particulate leaching, high pressure gas foaming, particulate and electro spinning [34]. To enhance the mechanical and physical properties, it is necessary to design the copolymerizing of aliphatic polyesters. The copolymers of lactic acid and glycolic acid have been investigated. The two main series are those of (l) LA/GA and (dl) LA/GA. Gilding and reed (1979) have shown that the composition in 25–75% range for (l) LA/GA and 0–70% for the (dl) LA/GA is amorphous. There is no linear relationship between the physical properties of the components of homopolymer and their co polymer. For the (l) LA/GA copolymers, resistance to hydrolysis is more pronounced at either end of the copolymers compositions range. The degradation rate of the copolymer highly depends upon the amount of each co monomer [35, 36]. Half lives of various poly (lactic acid) and poly (glycolic acid) ratios are shown in the graph (Fig. 2).

Poly (lactic acid) and poly (glycolic acid) and their copolymers have multiple uses "because of their good mechanical strength, degradation, biocompatibility" such as sutures, scaffolds for tissue engineering, drug carriers, etc. [38].

Poly (caprolactone)

PCL is an important material in the aliphatic polyesters family. It is the most widely used and investigated material. PCL is a semicrystalline polymer with low melting temperature (other physical and chemical properties listed in Table 1).The crystallinity of PCL increases with the decrease of molecular weight of the material. PCL is synthesized by the ring-opening polymerization of cyclic

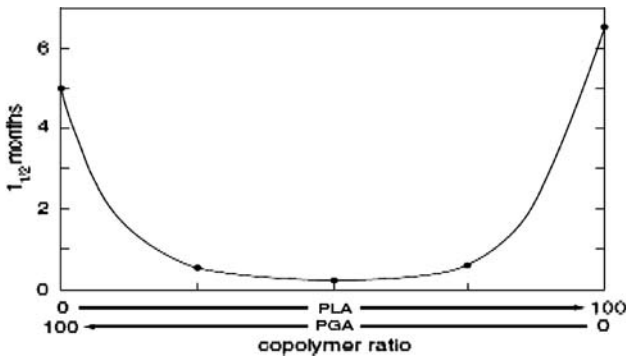


Fig. 2 Degradation of PLGA copolymers with lactic acid and glycolic acid Co polymer ratio in vivo [37]

monomer ε-caprolactone in the presence of stannous octoate, serving as a catalyst. In the polymerization low molecular alcohols are as initiator, which can also be utilized as terminator in the process. PCL is soluble in tetrahydrofuran, chloroform, methylene chloride, carbon tetrachloride, benzene, toluene, cyclohexanone dihydropyran, and 2-nitropropane; and only partially soluble in acetone, 2-butanone, ethyl acetate, acetonitrile, and dimethyl fumarate. The degradation mechanism of PCL and its copolymers are similar to PLA. This is done in two steps, random hydrolysis ester cleavage and weight loss through the diffusion of oligomeric sort from the volume. Polymer blends and copolymers can be established with different ratio according to the end requirement such as mechanical and physical, biocompatibility and degradation time. PCL degradation is three times slower than the P (D, L) LA. It can be increased by making the copolymer with DL-lactide. Thus aliphatic polyester polymers are widely used in the tissue engineering field with a wide range of benefits. The most important factors are better osteoinductive potential, low degradation time, good mechanical properties, and low emission of harmful by products.

Polypropylene fumarate (PPF)

Poly (propylene fumarate) is synthetic, unsaturated linear polyester, the synthesis of PPF commonly utilizes two steps, in the first step, what diethyl fumarate reacts with excess propylene glycol to produce is hydroxypropylfumarate in the presence of zinc chloride as acid catalyst. The structure of PPF is given in Fig. 3. PPF can be cross linked through its fumarate double bond. PPF achieves high mechanical strength when it is properly cross linked. Due to this property it is highly recommended in bone replacement scaffold. Additionally, the porous PPF scaffold gives the osteoconductive surface for bone in-growth [39, 31].

As unsaturated linear polyester, PPF can be harden/cured via thermal cross linking or photo cross linking to a strong polymer network through the active carbon chain double. The choice of cross-linking agent can affect the degradation and mechanical properties of the cross-linked polymer. The mechanical properties of the PPF may change with different choice of composition of the PPF. In several experiments PPF has been seen to be a biocompatible. In rat tibia modal, osteoblasts, osteoid, and new woven bone were in close apposition to degrading scaffold without evidence of an heightened or other unfavorable pathologic inflammatory response. PPF is soluble in methylene chloride, chloroform, tetrahydrofuran, acetone, ethanol and ethyl acetate is partially soluble in toluene and is not soluble in petroleum or water. The degradation can occur by hydrolytic chain scission of its ester groups. Propylene glycol and fumaric acid are the byproducts on degradation. These products are biocompatible and can be easily removed from the body. PPF experiences bulk degradation and the degrading time depends on the structure as well as the other factors. Both propylene glycol and fumaric acid subunits are non toxic. These subunits play a vital role in the process by which food is converted into energy. PPF degradation depends on many factors such as molecular weight, cross-linking agent, crosslink density, pore size and volume of scaffold, PH value of surroundings, and also the other copolymer or constituent ratio in the PPF composites [40].

PPF has the characteristic of injectability into the body. Before cross linking it is in liquid form, which makes the polymer easy to handle. It can also easily produce asymmetrical formed implants by injection molding. The characteristic of injectability makes it appropriate for the orthopedic implant in minimally persistent procedures.

Polyhydroxyalkanoates (PHA, PHB, PHBV, P4HB, PHBHHx, PHO)

Polyhydoxyalkanotes (PHA) are aliphatic polyesters which are generated from microorganism under unbalanced growth conditions. PHB is discovered in 1920, which is produced by the bacteria "Bacillus megaterium". PHA is a semi crystalline and has melting temperature within 160–180 °C. Further properties and processing are discussed in Table 2. The basic structures of Poly (3-hydroxybutyrate) are given in Fig. 4.

PHA polymers are biodegradable with excellent biocompatibility, which makes them attractive as scaffold for tissue engineering. There are several copolymers of polyhydoxyalkanotes (PHA), including PHB, PHBV (poly 3-hydoxybutyratevalerate) P4HB copolymer of 3-hydroxybutyrate, 3-hydroxyhexanoate (PHBHHX), and poly 3-hydroxyhexanoate PHO. PHB homopolymer is a tough, brittle polymer. The less tough copolymer has more

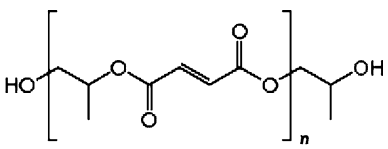


Fig. 3 Structure of Poly (propylene fumarate)

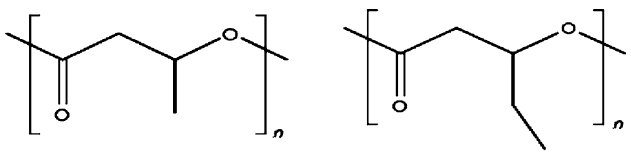


Fig. 4 Structures of Poly (3-hydroxybutyrate)

prospective as a biomaterial. Salt leaching technique is used for the fabrication of PHBHHX/PHB scaffolds [41]. In recent years, PHA, PHB, and their copolymers are widely used in the biomedical devices and biomaterial application, such as bone plates, sutures rivets staples screws, orthopedic pins and bone marrow scaffolds, meniscus regeneration devices, and various applications which are demonstrated and analyzed in [42]. Depending upon the end use requirement, PHA polymer can be copolymerized, either blended or composed with other polymer materials; enzymes or inorganic materials to further adjust their mechanical properties or biocompatibility.

The crystallinity and mechanical properties of the P(HB-HV) can change with the amendment of the percentage or ratio of the respective monomers. It experiences surface erosion by hydrolytic cleavage of the ester bonds. Copolymers degrade by the multistage process in which the greater part of the molecular weight loss occurs before the considerable mass loss. A graph of weight loss of various P(HB-HV) and copolymers (Fig. 5).

Both PHB and P(HB-HV) can be soluble in wide range of organic solvents such as chloroform, dichloromethane, propylene carbonate acetic anhydride, and 1N sodium hydroxide. They can be manufactured or processed into various forms such as films, sheet, sphere, and fibers [57]. PHB is particular for the bone tissue engineering application. It is demonstrated to produce a component fruitful bone tissue adaptation response with no verification of an undesirable chronic inflammatory response after implantation periods of upto 12 months. The major disadvantages of the PHA polymer are their restricted availability and time-taking extraction process from bacterial culture that require a proper extraction setup.

Polyanhydrides

Polyanydrides are hydrolytically unstable class of polymer which are usually either aromatic, aliphatic, or a mixture/blend of two components. Polyanhydrides are most comprehensively investigated classes of biodegradable polymer with demonstrated biocompatibility and excellent properties such as controlled release characteristics. Polyanhydrides are synthesized by dehydration of the diacid or mixture of diacids by melt polycondensation.

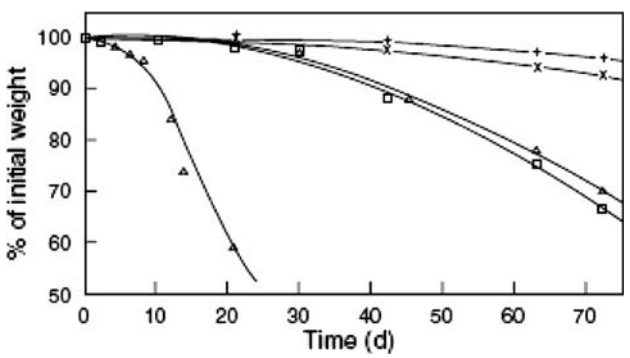


Fig. 5 Kinetics of percentage of initial weight loss for P (HB-HV) and with different copolymer ratios and molecular weight in the form of solvent–cast disks [43]

The dicarboxylic acid monomers are transformed to mixed anhydride of acetic acid by reflux in intemperance acetic anhydride. A polymer with high molecular weight is prepared by the melt polycondensation of prepolymer in vacuum and absence of nitrogen. Although polyanhydrides were best to the drug delivery application but because of their surface degradation/eroding properties, polyanhydrides have the low load bearing and mechanical properties, so it is not widely used in orthopedic implantation.

The young's modulus is very low near 1.3 MPa, which does not meet the modulus of human bone (40–400 MPa) [54]. These polymer materials can be dissolved in the common organic solvents such as chloroform and methylene chloride and are extremely sensitive to aqueous environments. To get the good mechanical properties polyanhydride is copolymerized with polyimide with surface erosion characteristics.

Poly (anhydride-co-imides) has been designed specially for the orthopedic application, such as poly-[trimellitylimidoglycinr-co-bis (carboxyphenoxy) hexane)] and poly-pyromellitylimidoalanine-co-1, 6-bis (carboph-enoxy) hexane]. Poly (anhydride-e-imides) has the considerable enhanced mechanical properties. Poly (anhydride-co-imides) is established with succinic acid trimellitylimidoglycine and trimellitylimidoalanine. It has the compressive strength in range of 50–60 Mpa. Laurencin et al. have also studied the mechanical properties of poly (anhydride-co-imide) as scaffold for bone tissue engineering application. The osteocompatibility of these polymer materials was examined via the rat tibial modal. It was shown that untreated imperfections cured in 12 days. In comparison, the imperfections treated with poly (anhydride-co-imides) created endosteal bone growth on the 3rd day and formed the bridges of cortical development bone around the implanted matrices on the 30th day representing the osteocompatibility of matrices [53].

For the orthopedic application photo cross-linkable, polyanhydrides have also been developed predominantly focusing on achieving good mechanical strength. The material is based on dimethacrylated anhydrides. The curing of macro monomer is achieved by ultraviolet (UV) and visible light. Material degradation and mechanical properties are based on the monomer choice. Injectable photocrosslinked polyanhydrides can be used to renovate the irregularly shaped bone imperfection or soft tissue repairs. The degradation occurred by means of hydrolysis of anhydride bonds, subsequently the hydrolysis of imide

bonds of these copolymers. The hydrolytic degradation of polyanhydride is nontoxic and composed of the diacid molecules and water soluble linear methacrylicacid molecules [58]. Thus, the main advantages of such scaffolds are non-toxic, injectability, low degradation and high compatibility, and the various properties can be modified during the fabrication and synthesizing of scaffolds.

Poly (orthoesters)

Poly (orthoesters) is an amorphous, hydrophobic, biodegradable polymer. The unique feature of poly (orthoesters) is that, in addition to its surface wearing down mechanism, the rate of degradation is PH sensitive. These kinds of poly (orthoesters) which are PH sensitive are used in the development of several drug delivery systems. There are four different types of poly (orthoesters) have been developed the structures of poly (orthoesters), which are shown in Fig. 6. Poly (orthoesters) (POE1) is synthesized by the transesterification between a diol and diethoxy tetrahydrofuran. During the hydrolysis of POEII, the decomposed product is γ-hydroxybutyric acid [59].

Poly (orthesters) has the property of hydrophobicity; it can be easily dissolved in organic solvents together with chloroform, methylene chloride, and dioxane. It is difficult to remove the solvent in situation of solvent casting. These polymer materials are not intrinsically disposed to the degradation in the presence of water, while they can be degraded in the presence of anhydrides, glycolic acid or lactic acid. These polymer materials perform degradation heterogeneously by the surface erosion. The mechanical properties of poly (orthoesters) also vary over a wide range by the selection of starting materials with different compositions and molecular weights. For example, the tripolymerization of 3,9-bis(ethylidene 2,4,8,10-tetraoxaspiro [5] with blend of the rigid diol CDM and the flexible diol HD allows preparation of polymer material with controlled glass transition temperature with varying levels of chain elasticity [60].

Poly (phosphazene)

The phonsphazene polymer constitutes family of greatly diverse performance material. This polymer possesses backbone of alternating nitrogen and phosphorous atoms. Thus, this material has high molecular weight.

The different variety of substituents can be added to get the precise controlled properties of the final products. There are over 700 known phosphazene derivatives. The synthesis of polyphosphazene from the cyclic precursor hexachlorocyclotriphosphazene[(NPCl2)3] was attempted by Stokes in 1895. But it was without success as the polymer obtained was an insoluble cross-linked gel. The first successful synthesis of polyphosphazene was reported by Allcock and Kugel in 1965 by suspiciously controlling the parameters for the thermal ring opening polymerization of the precursor hexachlorocyclotriphosphazene. Primarily polyphosphazene such as poly [bis (trifluoro ethoxy) phosphazene] and poly[bis(aryloxy)phosphazene] developed biostability. Biodegradable polyphosphazene is synthesized by the addition of certain side groups on the phosphorous atoms which are sensitive to hydrolysis. Polyphosphazene exhibits high blood compatibility and it is studied as a material for blood connecting devices. It is feasible to control the hydrolysis of polyphosphazene over hours, days, months, or years by precise controlling the species of side group's substituents [60]. The decomposition products of this polymer were found to be the natural and non toxic. Many of the initially developed polyphosphazenes were homopolymer materials where all the phosphorous atoms in the polymer chain carried the same type of organic substituents. Polyphosphazene is an excellent polymer for drug delivery and tissue-engineering applications [55]. Biodegradable polyphosphazene has the prospective for bone tissue engineering. Due to its physical and chemical properties of osteoconductive and non-hazardous degradation byproducts, it has been widely investigated for this application by Laurencin et al. The polyphosphazene of amino acid ester group is excellent

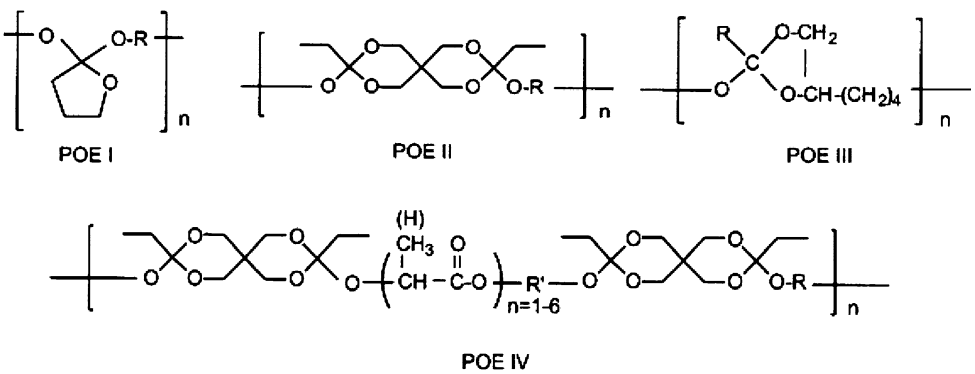


Fig. 6 This shows different structures of Poly (Ortho esters)

biodegradable material. The degradation product of this material is amino acid. The effects of different amino acid ester pendent groups were investigated by the Allcock et al. [61]. The Laurencin et al. investigated effect of relative amount of mixed substituents in poly (ethyl glycinato) (*p*-methyl phenoxy) phosphazene.

A matrix of amino acid ester polyphosphazene nano fibers, with or without hydroxyapatite, has been developed. That presents an open scaffold which favors the quick proliferation of osteoblasts and the accelerated augment of bone tissue. Poly phosphazene can be processed in electro spinning, solvent casting particulate leaching, and emulsion freeze drying for the bone scaffold [62, 63]. Polyphosphazene is blended or copolymerized with the widely used poly (lactic glycolic acid). These have been considered in order to consume the synergistic properties of these two polymers. These produce near-neutral PH medium by the hydrolyzing polyphosphazene assisting to neutralize the acidic hydrolysis. PLGA delays the rate of hydrolysis of the combined polymer. At the same time the PLGA puts in strength to the polyphosphazene [56].

Natural polymer materials

Collagen, fibrin, hyaluronic acid, agrose, chitosan, based alginate materials are used in the bone and cartilage tissue engineering application, because of their excellent biocompatibility. Natural polymer materials serve as intrinsic templates for cell attachment and growth. They could stimulate an immune response at the same time. The structures of the natural polymer materials are highly organized and contain extra cellular substance, named ligand that can be bound to cell receptors. Although they are known as biocompatible but there are some disadvantages of natural polymer materials such as deficiency in bulk quantity, expansive, and difficulties in the processability for scaffold in clinical applications. The degradation rate of natural polymer materials varies from patient to patient, because the degradation of natural polymer materials are depends upon enzyme which varies with patient to patient.

Collagen

Collagen has been widely used for the regeneration of tissues, mostly for the repair of soft tissues. Collagen favors the cell adhesion and provides cellular recognition for regulating cell attachment and function. Collagen may guide to the concern of unfavorable immune response. Collagen undergoes enzymatic degradation which occurs in body via enzymes, such as collagenases and metalloproteinases, to yield the corresponding amino acids [64]. Due to their enzymatic degradation, unique physicochemical, mechanical, and biological properties are studied in various applications. It can be processed in sheet, tubes sponge's foams, nano fibrous powders, fleeces, injectable viscous solution, and dispersions. The degradation rate can alter by various treatments. New spongy collagen matrix containing oxidized cellulose has been recently introduced in US and European market for treating exuding diabetic and ulcer wounds [65, 66]. Degradable collagen sponges, due to their excellent biocompatibility, and porous structure have been widely studied as scaffold material for accelerated tissue reproduction. The composite of collagen and hydroxyapatite and TCP (tri calcium phosphate) is used as biodegradable synthetic bone graft replacement. It is widely investigated as scaffold for musculoskeletal and nervous tissue engineering. The pure collagen is expansive. The drawbacks of collagen are its variable physical chemical and degradation properties and the risk of infection and difficult to handle processing [67].

Albumin

Albumin is a protein which is in excess in blood plasma, almost 50% of the total mass of the plasma. Albumin is a water soluble protein. Human body has the ability to degrade albumin. Because of its excellent blood compatibility, albumin is investigated as drug delivery.

Fibrin

Fibrin is a biopolymer similar to collagen which is involved in the natural blood clotting process. Fibrin is derived from fibrinogen and thrombin which is 362KDA protein composed of three pairs of peptide chains. It is always used as carrier for cells and in conjunction with other scaffold materials. Fibrin is completely degradable and injectable, but it has the disadvantage of poor mechanical strength for articular cartilage tissue engineering applications.

Polysaccharides

Polysaccharides are macromolecules produced from a large number of monosaccharide units joined together by glycosidic linkages. Polysaccharides have the unique property of cell signals to immune. Polysaccharides are synthesized oligosaccharide moieties. The biodegradability and ability to fabricate appropriate structures make them one of the most important and widely studied biomaterials [68].

Hyaluronic acid (HA)

HA is a member of the gylcosaminoglycan family, which is linear polysaccharide consisting of alternating units of

N-acetyl-*D*-glucosamine and glucuronic acid, being found in virtually every tissue invertebrates [69, 70]. Because of HA's immunoneutrality and the tissue repair by promoting mesenchymal and epithelial cell migration, differentiation and enhancing collagen deposition and angiogenesis HA can be used in irregular shaped defects and implanted with minimal invasion. On the other hand, it has constrained type of mechanical properties and applications.

Chondrotin sulfate(CS)

Chonodrotin sulfate is a major component of aggrecan, the most abundant glycosaminoglycan found in the proteoglycans of articular cartilage [71]. Numerous studies have investigated the effectiveness of using composite scaffolds composed of CS and other biopolymer materials, such as collagen or synthetic biodegradable polymer materials, used as scaffolds for cartilage tissue engineering.

Chitosan

Chitosan is derived from chitin. It is a cationic linear polysaccharide consisting of b (1-4) linked *D*-glucosamine with randomly located *N*-acetylglucosamine groups depending upon the degree of deacetylation of the polymer. Chitosan has a high degree of biocompatibility in vivo. Current investigation is conducted to evaluate the potential of using injectable material based on chitosan and its derivatives as a scaffold material for various tissue engineering including cartilage, skin, and bone**.** Degradation of chitosan is adjusted by residual amount of acetyl content and degradation rate can occur swiftly in vivo. The porosity of the chitosan scaffold can be controlled which may influence on the mechanical properties [72, 73].

Alginic acid

Alginic acid is a kind of polysaccharide of non-human origin. Alginate is a non-branched, binary copolymer of (1-4) glycosidically linked b-*D*-mannuronic acid and a-*L*-guluronic acid monomers. The high functionality of alginic acid makes it a biocompatible material. It is widely used as cell transplantation vehicles to grow new tissues as well as wound dressing. The drawbacks of these polymer materials are slow degradation, insufficient mechanical integrity which make it impossible for long term implants.

All these natural polymer materials have their own advantages such as available in abundance, biodegradable and bioreabsorbable, non-toxic and biocompatible, synergic with bioactive components. Generally naturally occurring biomaterials may create the native cellular milieu, large batch-to-batch variations upon separation from biological tissues are the main restriction for their wide applications. Poor mechanical strength is also a drawback for transplantation scaffolds made from natural polymer materials, such as collagen and chitin. These polymers cannot be easily melted with heat but require a special solvent. Because of these drawbacks, it is necessary to explore the synthetic biodegradable polymer or blend of natural and synthetic polymers, which gives better enhanced properties for bone tissue engineering applications.

Composite material

Composite material is consisting of two or more material. These materials behave together to get the better properties of scaffold. Polymer/ceramics composite scaffolds are imitation of natural bone. As we know, the natural bone is made of HAP and organic collagen material. HAP has better osteoconductivity. HAP, as the mineral part in the formation of composites and collagen, gelatin, chitosan, chitin, elastin, poly(methymethacrylate), poly(propylene fumarate), polyphosphazenes, and poly(hydroxybutyrate), poly(lactide-co-glycolide),(PCL, PLLA PGA), poly anhydride, polyorthoester, it can be the matrix phase for the bone replacement. Bioactive phases in the polymer composite can also change the degradation behavior of the polymer materials, by allowing rapid exchange of protons in water for alkali in the glass in ceramics. This behavior is providing the PH buffering effect at the polymer surface transforming the acidic polymer degradation [74]. In addition to bioactive, glasses increase the hydrophilicity and water absorption of the hydrophobic polymer matrix which cause the change in degradation kinetics. There are different fabrication routes for the composite scaffolds with their advantages and disadvantages, such as thermal induced phase separation, solvent casting/particle leaching, solid free form, micro sintering scaffold coating. Highly porous polymer/ceramic composite scaffold appears to be a promising substrate for the bone tissue engineering because of its outstanding mechanical properties and osteoconductivity. Biodegradable polymer scaffold may provide a number of benefits for bone tissue engineering; enhanced environment for cell seeding, survival, growth, and differentiate function because of the osteoconductive function imparted by HAP, which increases mechanical properties that are essential for load bearing [75, 76].

Blends

Polymeric material blends have been produced by combination of synthetic and natural, natural–natural and synthetic–synthetic polymers in order to combine the good mechanical characteristics, easy processability, and low production and transformation costs of the former with the specific tissue, and cell compatibility of the latter [77].

Furthermore, blending synthetic and natural polymers provide a control of the degradation rate of the system as the degradation kinetics of a polymeric blend increases with increasing the natural polymer amount, the blend composition can be adjusted to make the scaffold degradation rate match with the growth rate of the regenerating tissue. There are many polymeric blends between natural and synthetic polymers, such as polylactide/chitosan, PLA/HA, PLG/geltin/elastin [58], poly(L-lactic acid)/starch, PCL/starch, etc. Blending PCL with a suitable hydrophilic natural polymer is retrieved to be a promising and easy method to improve PCL biocompatibility [78]. Starch and gellan are two suitable materials for the production of PCL based blends for SLS (selective laser sintering) fabricated tissue engineering scaffolds. PCL is a regulatory approved biodegradable and biocompatible synthetic polymer with good mechanical properties, degradation occurs through hydrolysis of its ester bonds [79]. However degradation rate of PCL is slow due to its hydrophobic and semicrystalline nature. Blend between PCL and starch has the better mechanical properties and enzymatic degradation as compared to the individual polymers. Synthetic/synthetic blends of polymers developed to get the ease in processability, mechanical and biocompatible properties and to reduce the cost [80] as compared to the parent material. Thus blends can be designed to enhance processability and better properties to the tissue engineering applications. Whereas there are some drawbacks such as having difficult miscibility in blend formation and processability for scaffold applications. Only few blends are used for the tissue engineering application. Therefore further research is needed in this field.

Summary

This review highlights the polymer materials used as in the scaffold for the bone tissue engineering and emphasizes the behavior and degradation criteria of biodegradable polymer materials, the biodegradable and synthetic polymer materials and bioactive composite and their blends. A critical evaluation in this article is peculiarly attractive as bone tissue engineering scaffolds because of the biocompatibility, and having the tailor made composition and properties corresponding to those of the host tissues and adjustable biodegradation kinetics. A careful analysis of these studies reveals the biodegradable scaffolds resorption/degradation and mechanical properties of biodegradable polymer materials are designed by the polymer scientists to meet the specific requirement of different applications. The selection of initiator and monomer during polymerization influences the mechanical properties and molecular weight and morphology effect on the degradation kinetics. Innovation in the material sciences and synthetic organic chemistry and the novel biotechnology makes the improvement of wide variety of unique polymeric materials for application of tissue engineering possible. The triumph of biodegradable scaffolds for the regeneration as well as repair of musculoskeletal tissues lies in our ability to tailor design and processing or modify present biodegradable polymer materials to get the desirable mechanical, physical, degradation, and biocompatibility properties.

References

1. Lin C-Y, Schek RM, Mistry AS, Shi X, Mikos AG, Krebsbach PH, Hollister SJ (2005) Tissue Eng 11(9–10):1589
2. Isenberg BC, Williams C, Tranquillo RT (2006) Circ Res 98:25
3. Kim BS, Putnam AJ, Kulik TJ, Mooney DJ (1998) Biotechnol Bioeng 57(1):46
4. Kalfas LH (2001) Neurosurg Focus 10(4)
5. Dimar JR, Glassman SD (2007) Curr Opin Orthopaed 18(3):226
6. Gravel M, Gross T, Vago R, Tabrizian M (2006) Biomaterials 27:1899
7. Cheung H-Y, Lau K-T, Lu T-P, Hui D (2007) Compos Part B 38:291
8. Chapekar MS (2000) J Biomed Mater Res 53:617
9. Sambrook P (ed) (2001) The musculoskeletal system, Chap 5. Elsevier Health Sciences Publishers, pp 67–84. ISBN: 0443070156, 9780443070150
10. Callaghan JJ (1997) J Bone Joint Surg (Am) 79:1416
11. Brekke JH, Toth JM (1999) J Biomed Mater Res 43(4):380
12. Whang K, Thomas CH, Healy KE (1995) Polymer 36:837
13. Oh S, Kang SG, Kim ES, Cho SH, Lee JH (2003) Biomaterials 24:4011
14. Mikos AG, Bao Y, Cima LG, Ingber DE, Vacanti JP, Langer R (1993) J Biomed Mater Res 27:183
15. Mathieu LM, Mueller TL, Bourban P-E, Pioletti DP, Muller R, Manson J-AE (2006) Biomaterials 27:905
16. Shin KC, Kim BS, Kim JH, Park TG, Nam JD, Lee DS (2005) Polymer 46:3801
17. Kim HD, Bae EH, Kwon IC, Pal RR, Nam JD, Lee DS (2004) Biomaterials 25:2319
18. Yoon JJ, Kim JH, Park TG (2003) Biomaterials 24:2323
19. Reignier J, Huneault MA (2006) Polymer 47:4703
20. Seunarine K, Gadegaard N, Tormen M, Meredith DO, Riehle MO, Wilkinson CDW (2006) Nanomedicine 1(3):281
21. Ma PX (2003) In: Kroschwitz J (ed) Encyclopedia of polymer science and technology, 3rd edn. Wiley, NJ
22. Borden M, Attawia M, Khan Y, Laurencin CT (2002) Biomaterials 23(2):551
23. Chen G, Ushida T, Tateishi T (2002) Macromol Biosci 2:67
24. Einhorn TA (2004) J Bone Joint Surg (Am) 86:1350
25. Hollinger JO, Schmitz JP (1997) Ann NY Acad Sci 831:427
26. Burg KJL, Porter S, Kellam JF (2000) Biomaterials 21:2347
27. Mauli Agrawal C, Athanasiou KA (1997) Biomed Mater Res Appl Biomater 38:105
28. Bergsma JE, de Bruijn WC, Rozema FR, Bos RRM, Boering G (1995) Biomoterids 16:25
29. Seal BL, Otero TC, Panitch A (2001) Mater Sci Eng 34(4–5):147
30. Duda A, Penczek S (2002) In: Steinbüchel A, Doi Y (eds) Biopolymers, vol 3b: Polyesters II – Properties and Chemical Synthesis, Chap 12. Wiley-VCH, Weinheim, pp 371–430

31. Nair LS, Laurencin CT (2006) Adv Biochem Eng Biotechnol 102:47
32. Shalaby SW, Johnson RA (1994) In: Shalaby SW (ed) Biomedical polymers: designed to degrade systems. Hanser, New York
33. Rhim J-W, Mohanty AK, Singh SP, Perry KW (2005) J Appl Polym Sci 101:3736
34. Mauli Agrawal C, Ray RB (2001) J Biomed Mater Res 55:141
35. Middleton JC, Tipton AJ (2000) Biomaterials 21:2335
36. Athanasiou KA, Niederauer GG, Mauli Agrawal C (1996) Biomoterids 17:93
37. Miller RA, Brady JM, Cutright DE (1977) J Biomed Mater Res 11:711
38. Vert M, Li S, Garreau H, Mauduit J, Boustta M, Schwach G, Engel R, Coudane J (1997) Macromol Mater Eng 247:239
39. Peter SJ, Nolley J, Widmer M, Merwin JE, Yaszemski MJ, Yasko AW, Engel PS, Mikos AG (1997) Tissue Eng 41(1):207
40. Hedberg EL, Shih CK, Lemoine JL et al (2005) Biomaterials 26:3215
41. Domb AJ, Kost J, Wiseman DM (eds) (1998) Handbook of biodegradable polymers, Chap 5. CRC Press Publishers, pp 87–96. ISBN: 9057021536, 9789057021534
42. Kai Z, Ying D, Guo-Qiang C (2003) Biochem Eng J 16:115
43. Chen G-Q, Wu Q (2005) Biomaterials 26:6565
44. Holland SJ, Jolly AM, Yasin M, Tighe BJ (1987) Biomaterials 8:289
45. Young Y, Min B-M, Lee SJ, Lee TS, Park WH (2004) J Appl Polym Sci 95:193
46. Young Y, Lee SW et al (2005) Polym Degrad Stab 90:441
47. Sarazin P, Roy X, Favis BD (2004) Biomaterials 25:5965
48. Kuo Y-C, Leou S-N (2006) Biotechnol Prog 22:1664
49. Zhao K, Deng Y, Chen JC, Chen G-Q (2003) Biomaterials 24(6):1041
50. Yao D, Smith A, Nagarajan P et al (2005) J Biomed Mater 77b:287
51. Kweona HY, Yoo MK, Park K, Kim TH, Chul H, Lee HC (2003) Biomaterials 24:801
52. Temenoff JS, Mikos AG (2000) Biomaterials 21:2405
53. Göpferich A, Tessmar J (2002) Adv Drug Deliv Rev 54:911
54. Ibim SEM, Uhrich KE, Attawia M et al (1998) J Biomed Mater 43:374
55. Kumara N, Langer RS, Domb AJ (2002) Adv Drug Deliv Rev 54:889
56. Lakshmi S, Kattia DS, Laurencin CT (2003) Adv Drug Deliv Rev 55:467
57. Allcock HR (2006) Curr Opin Solid State Mater Sci 10:231
58. Li M, Mondrinos MJ, Chen X, Gandhi MR, Ko FK, Lelkes PI (2006) J Biomed Mater Res A 79(4):963
59. Pouton CW, Akhtar S (1996) Adv Drug Deliv Rev 18:133
60. Muggli DS, Burkoth AK, Anseth KS (1999) Biomed Mater 46:271
61. Heller J, Barr J, Ng SY (2002) Adv Drug Deliv Rev 54:1015
62. Parsons JR (1998) In: Black J, Hastings G (eds) Handbook of biomaterials properties. Chapman & Hall, New York
63. Ibim SM, Ambrosio AA, Larrier D, Allcock HR, Laurencin CT (1996) J Control Release 40:31
64. Laurencin CT, Norman ME, Elgendy HM, El-Amin SF, Allcock HR, Pucher SR, Ambrosio AA (1993) J Biomed Mater 27:963
65. Conconi MT, Lora S, Menti AM, Carampin P, Parnigotto PP (2006) Tissue Eng 12:4
66. Kang H-W, Tabata Y, Ikada Y (1999) Biomaterials 20:1339
67. Vin F, Teot L, Measume S (2002) J Wound Care 11(9):335
68. Duan X, McLaughlin C, Griffith M, Sheardown H (2007) Biomaterials 28:78
69. Ruszczak Z (2003) Adv Drug Deliv Rev 55:1595
70. Green D, Walsh D, Mann S, Oreffo ROC (2002) Bone 30:PG810
71. Barbosa MA, Granja PL, Barrias CC, Amaral IF (2005) ITBM-RBM 26:212
72. Francis Suh J-K, Matthew HWT (2000) Biomaterials 21:2589
73. Shi C, Zhu Y, Ran X et al (2006) J Surg Res 133:185
74. Maqueta V, Boccaccini AR et al (2004) Biomaterials 25:4185
75. Wei G, Ma PX (2004) Biomaterials 25:4749
76. Ramakrishna S, Mayer J, Wintermantel E, Leong KW (2001) Compos Sci Technol 61:1189
77. Cai Q, Yang J, Bei J, Wang S (2002) Biomaterials 23:4483
78. Ciardelli G, Chiono V, Vozzi G, Pracella M et al (2005) Biomacromolecules 6:1961
79. Broz ME, VanderHart DL, Washburn NR (2003) Biomaterials 24:4181
80. Kim JY, Cho D-W (2009) Microelectron Eng 86:1447
81. Nukavarapu SP, Kumbar SG, Brown JL et al (2008) Biomacromolecules 9(7):1818