01 Aug 2015

Bioactive Glass Reinforced Elastomer Composites for Skeletal Regeneration: A Review

Ehsan Zeimaran

Sara Pourshahrestani

Ivan Djordjevic

Belinda Pingguan-Murphy

et. al. For a complete list of authors, see https://scholarsmine.mst.edu/che_bioeng_facwork/1124

Recommended Citation

E. Zeimaran et al., "Bioactive Glass Reinforced Elastomer Composites for Skeletal Regeneration: A Review," *Materials Science and Engineering C*, vol. 53, pp. 175 - 188, Elsevier, Aug 2015.
The definitive version is available at https://doi.org/10.1016/j.msec.2015.04.035

Materials Science and Engineering C 53 (2015) 175–188

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Bioactive glass reinforced elastomer composites for skeletal regeneration: A review

Ehsan Zeimaran [a], Sara Pourshahrestani [a], Ivan Djordjevic [a,*], Belinda Pingguan-Murphy [a], Nahrizul Adib Kadri [a], Mark R. Towler [a,b]

[a] Department of Biomedical Engineering, Faculty of Engineering, University of Malaya, Kuala Lumpur 50603, Malaysia
[b] Department of Mechanical & Industrial Engineering, Ryerson University, Toronto M5B 2K3, ON, Canada

ARTICLE INFO

Article history:
Received 27 January 2015
Received in revised form 2 April 2015
Accepted 21 April 2015
Available online 22 April 2015

Keywords:
Elastomers
Bioactive glass
Composites
Scaffolds
Bone tissue engineering
Bioactivity

ABSTRACT

Biodegradable elastomers have clinical applicability due to their biocompatibility, tunable degradation and elasticity. The addition of bioactive glasses to these elastomers can impart mechanical properties sufficient for hard tissue replacement. Hence, a composite with a biodegradable polymer matrix and a bioglass filler can offer a method of augmenting existing tissue. This article reviews the applications of such composites for skeletal augmentation.

Contents

1. Introduction . . . 176
2. Bioglass materials: concept and performance . . . 176
   2.1. Cellular response to bioglass materials . . . 176
   2.2. Antibacterial activity of bioglass materials . . . 176
3. Scaffold-guided tissue engineering and scaffold materials . . . 177
   3.1. Polymers: general requirements for bone regeneration . . . 177
   3.2. Elastomers as biomimetic scaffold materials . . . 177
4. Elastomer/bioglass composite scaffolds . . . 177
   4.1. Composite scaffolds: fabrication techniques . . . 177
   4.2. Thermoplastic elastomer/bioglass composites . . . 178
      4.2.1. Poly (α-caprolactone) based thermoplastic elastomers . . . 178
      4.2.2. Poly (hydroxyalkanoate) (PHA) based composites . . . 180
      4.2.3. Composite of polyurethane/bioglass . . . 181
   4.3. Thermoset polyester/bioglass elastomer composites . . . 182
      4.3.1. Poly (diol citrate) . . . 182
      4.3.2. Poly (glycerol sebacate) . . . 182
5. Composite materials from natural elastomers and bioglass . . . 183
6. The effect of filler size: polymer/bioglass nano- and micro-composites . . . 184
7. Conclusion and future perspectives . . . 185
Acknowledgments . . . 185
References . . . 186

* Corresponding author.
E-mail address: ivan.djordjevic@um.edu.my (I. Djordjevic).

http://dx.doi.org/10.1016/j.msec.2015.04.035
0928-4931/

1. Introduction

Bone may be damaged by insult or disease [1]. Tissue engineering can offer an effective alternative to transplant surgery by reconstructing native tissue inside the body [2,3]. A common approach utilizes a temporary, porous 3D scaffold for the delivery and integration of cells and/or growth factors at the repair site [4].

Polymers have a wide range of applications in surgery including scaffolds and fillers. The criteria for selection of polymeric materials for such applications are their molecular weight, solubility, shape, hydrophilicity/hydrophobicity, surface properties, water absorption, and mechanism of degradation [5]. Elastomers offer biocompatibility with natural extra cellular matrix (ECM) proteins [6]. Suitable elastomeric materials that have controllable mechanical properties are usually synthesized from biocompatible monomers such as citric acid, with ester bonds to promote hydrolysis degradation [7]. However, elastomers lack sufficient mechanical properties for bone tissue engineering [8]. Bioactive ceramics such as calcium phosphates and bioactive glasses lack satisfactory fracture toughness and strength for load bearing applications but composites combining the properties of both polymers and bioglasses can address these outages [9,10].

This review will discuss methods for fabricating polymer/bioglass scaffolds and will then compare and contrast the properties of these composites with respect to their suitability for skeletal reinforcement. For other tissue engineering applications of elastomeric materials, readers are referred to alternative reviews [6,11,12].

2. Bioglass materials: concept and performance

A "bioactive" material is one with specific biological activity for a targeted application [13]. A characteristic of bioactive glasses is their kinetics of surface modification as a function of time when implanted into the body. Bioactivity results from their ability to form hydroxyl carbonate apatite (HCA) which is responsible for their bonding to bone upon implantation [14,15]. In vitro apatite formation on the surface of bioactive glasses can be evaluated using simulated body fluid (SBF) which is prepared with an ionic composition equal to human blood plasma [15]. This relatively simple experiment can indicate the bioactive potential of materials in vivo [16]. Table 1 displays the composition of bioactive glasses that show promise in bone tissue regeneration. Silicate-based bioactive glasses are most commonly used for clinical applications. The first silicate-based bioglass, 45S5, was synthesized by Hench et al. and this material can positively interact with both bone and soft tissue, by means of the development of an apatite phase [17]. It was observed that high amount of modifiers such as CaO and Na_2O and high CaO/P_2O_5 ratio stimulate the glass surface reactivity in physiological environments [18]. The limitation associated with Si-based bioactive glasses is the slow rate of degradation and conversion to apatite which further complicates the rate of implant resorption and simultaneous bone growth [19]. The conversion of silica-based bioglasses to apatite in vivo is three times faster than recorded in vitro [20]. The mechanism of conversion of silicate-based glasses to hydroxyapatite has been reviewed in detail elsewhere [18].

Table 1
Composition of selected bioglasses and the common method of synthesis.

Glass name	SiO_2	P_2O_5	B_2O_3	CaO	Na_2O	K_2O	MgO	mol% or wt.%	Method of synthesis
45S5	46.1	2.6		26.9	24.4			mol%	MQ[a]
45S5B1	30.7	2.6	15.4	26.9	24.4			mol%	MQ
45S5B2	15.4	2.6	30.7	26.9	24.4			mol%	MQ
45S5B3		2.6	46.1	26.9	24.4			mol%	MQ
13–93	53	4		20	6	12	5	wt.%	MQ
13–93B3		4	53	20	6	12	5	wt.%	MQ
58S	60	4		36				mol%	SG[b]
77S	80	4		16				mol%	SG
S53P4	53	4		20	23			mol%	MQ
Phosphate glass		50		30	20			mol%	MQ

[a] Melting-quench technique.
[b] Sol–gel technique.

Bioglasses can bond to both hard and soft tissues to promote cell migration and differentiation and can release ions which further stimulate the healing process at the site of injury [21]. There are some advantages of using bioglasses over other bioactive ceramics such as sintered hydroxyapatite (HAp). For example, the ionic product of bioglasses stimulates the expression of genes of osteoblastic cells which in turn modulate osteogenesis and promote bone formation [22–24].

2.1. Cellular response to bioglass materials

Silica-based bioactive glasses such as 45S5 and 13–93 (Table 1) support proliferation and differentiation of osteoblastic cells and mesenchymal stem cells either in vitro or in vivo [20,25]. The osteogenic differentiation of umbilical cord and adipose derived stem cells by bioactive glasses has been reported in several studies [26,27]. Adipose-derived stem cells are easily isolated and are available in large quantities [28]. The indirect and direct contact of these cells with 45S5 confirmed the ability of this bioglass to effectively stimulate the secretion of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in vitro. Furthermore, it demonstrated the ability to promote angiogenesis both in vitro and in vivo [29–31]. Primary osteoblast cell culture on 45S5 resulted in high osteocalcin synthesis and alkaline phosphatase activity (ALP) at day 6, indicating bioglass augmented osteoblast commitment and selection of a mature osteoblastic phenotype [32]. Regardless of the promising results obtained from mesenchymal stem cells (MSCs) which have proliferated and differentiated on bioactive glass, no augmented production of the bone differentiation marker ALP was observed for the glass in comparison to control culture plastics [33]. The apatite layer formed on the surface of bioglasses was found to stimulate osteoblastic differentiation and facilitate the attachment of undifferentiated stem cells [34]. Implantation of 13–93 glass in Fisher 344 rats confirmed its ability to support tissue infiltration and osteoid deposition when seeded with MSCs [35]. To improve biological response and facilitate healing, bioactive glasses can be doped with trace elements and other therapeutic oxides [36]. For example, Ca^+, Mg^{2+}, Sr^{2+}, Na^+ and K^+ can be incorporated into bioglass to tune bioactivity. Al^{3+} and Ga^{3+} can improve strength, and Ag^+, Zn^{2+}, Cu^{2+} and Ti^{3+} when dosed in controlled concentrations can impart antibacterial properties [29,37].

2.2. Antibacterial activity of bioglass materials

Bioglasses can be utilized as mediums for controlled release of bioactive agents [38]. Ions are incorporated into the glass structure and the overall rate of ion release is determined by the rate of glass degradation [39]. The dissolution rate of a glass is dependent on both glass chemistry and conditions in the surrounding medium [40]. Doping of bioactive agents into glasses can modify the dissolution rate as well as inducing a therapeutic effect through ion release. Biomaterial-associated infections can cause serious complications in orthopedic implant surgery [41]. Often, the only remedy is revision surgery and implant replacement, because biofilm growth protects the organisms from the host immune system and antibiotic therapies [41]. One strategy to prevent biofilm formation on the implant surface is by using antimicrobial components [42]. A suitable antibacterial agent should be effective against a broad range of Gram positive and Gram negative bacteria [39]. The exact mechanism of the antibacterial action of bioactive glasses is not fully understood but it has been suggested that bacterial depletion happens due to increasing pH and the subsequent osmotic effect as a result of ion release from glasses [43]. Ions such as Ag^+, Zn^{2+}, Cu^{2+} and Ga^{3+} are known for their bactericidal properties. These ions can be released when a bioglass is in contact with aqueous medium, thus retarding bacterial

adhesion and biofilm formation. Silica-based glasses containing bactericidal metal ions are considered to be promising candidates for such antibacterial materials [44].

3. Scaffold-guided tissue engineering and scaffold materials

3.1. Polymers: general requirements for bone regeneration

A polymer should have specific characteristics for use as a scaffold, including biodegradability, biocompatibility, lack of immunogenicity, ease of processing and strength [45]. The properties of polymers depend on the composition, structure, and arrangement of their constituent macro-molecules [5,46]. Scaffold materials can be synthetic or natural, degradable or non-degradable, depending on their application [47].

The geometry and anisotropic properties of bone make designing a scaffold challenging [48,49]. The material must be designed with a compatible resorption and degradation rate to the surrounding tissue. Sufficient mechanical properties are also necessary in order to retain adequate structural integrity of the scaffold until the newly grown tissue is capable of maintaining load [45]. Stress shielding would occur if the transplanted bone stiffness was not matched to that of natural bone [50].

Increasing porosity negatively influences scaffold strength and thus the void volume should be controlled to allow both accommodation of cells and the maintenance of the strength required in load-bearing tissues [45,48]. An ideal scaffold should degrade at a rate comparable to that of bone growth, creating open space for new bone formation, until regeneration is achieved. Bioabsorbable scaffolds can reduce the number of surgeries since there is no need to perform a second operation to remove the implant [51,52]. The degradation of polymeric materials is influenced by their structure and properties such as molecular weight and distribution, glass transition temperature and crystallinity as well as environmental conditions such as medium, temperature and pH [53].

Polymeric materials degrade by either surface or bulk erosion with chain scission caused by water or enzymatic attack. Surface erodible polymers means that the sample becomes thinner during degradation [54,55]. Additionally, there is a linear relationship between mechanical properties and degradation time. In bulk-degradable polymers weight loss occurs throughout the sample, which can cause the loss of strength with time. However, the initial sample size could remain for a long time [54,56]. The degradation rate of a scaffold is slower than a solid block polymer for the bulk-degradable polyesters. The release of acidic degradation products from a solid block polymer could lead to an autocatalytic effect [53,57]. In the case of porous scaffolds, degradation is dependent on porosity and pore size. Wu et al. observed that scaffolds with lower porosities and larger pore sizes degrade faster than those with higher porosities and smaller pore sizes [58]; attributed to the effect of wall thickness and surface area, which can cause faster acid-catalyzed degradation. Nonetheless, the influence of material composition is more significant on degradation rate than pore morphology [58]. High porosity (usually exceeding 90%) and pore interconnectivity are required to facilitate bone growth [3]. The porous network of scaffolds simulates the ECM architecture in allowing cells to interact effectively with their environment [5]. Pore sizes between 200 and 400 μm facilitate cell adhesion, ingrowth reorganization, and neovascularization. Moreover, pore interconnectivity can facilitate nutrient diffusion to cells and removal of metabolic waste [45]. In addition, bone tissue engineering scaffolds should be bioactive and osteoconductive in order to make a strong bond with the host tissue [59].

3.2. Elastomers as biomimetic scaffold materials

Elastic properties are controlled by the crosslink density of the elastomer [60]. Elastomers have found a broad range of applications in tissue engineering because of their ability to mimic the ECM of most tissues [61]. Elastomers can be divided into two categories: natural and synthetic, but synthetic elastomers offer more possibilities in terms of tailoring their properties [11] and can be processed into a range of shapes and sizes [45]. There are two types of synthetic elastomer: 1) thermoplastic elastomers (physically crosslinked) such as polyurethane (PU), poly (hydroxyalkanoate) (PHA) and poly (caprolactone) (PCL)-based elastomers; and 2) thermoset elastomers (chemically crosslinked) such as poly (polyol sebacate) (PPS) and poly (diol citrate) (PDC). Fig. 1 provides the basic classification of elastomeric materials used for biomedical applications.

Thermoplastic Elastomers (TPEs) contain crosslinks which are reversible under the action of heat or solvents [11,54]. Such elastomers can be synthesized using monomers containing two or more hydroxyl (–OH) or carboxyl (–COOH) functional groups in a polyesterification reaction. Other TPEs can be synthesized by ring opening polymerization or double bond reactivity [54,63]. A significant feature of TPEs is that they are recyclable because of the thermo-reversible nature of such networks. The physical crosslinks in TPEs disappear at elevated temperatures and the materials show flow behavior typical of a low molecular weight polymer, whereas they behave as irreversible crosslinks at service temperature [64]. Furthermore, the degradation of TPEs can be controlled by changing constituent segments [6]. However, thermoplastic materials undergo heterogeneous degradation due to crystalline regions which can cause further nonlinear loss of mechanical properties [9]. In addition, the weak physical crosslinks can result in creep in the long term or under cyclic mechanical deformation [12]. In contrast, thermoset elastomers (TSEs) are chemically cross-linked or covalently cross-linked, which is usually irreversible and stronger than using physical crosslinks [54]. Thermoset biodegradable elastomers synthesized through polycondensation of multifunctional monomers, ring opening polymerization, or microbial polymerization can crosslink mainly through thermo-curing or photo-curing. Curing locks the elastomer's shape and reheating cannot cause TSEs to flow like TPEs. Thermoset elastomers can be synthesized in completely amorphous form. This can lead to homogenous weight loss through a combination of bulk and surface erosion degradation which is the main reason for maintaining the 3D structure of scaffolds prepared from thermoset elastomers [6,65]. In some cases, curing may lead to some limitations since it may cause difficulties with materials processing. An example of these harsh curing conditions is the high temperature (more than 100 °C) along with vacuum for days in the curing of PGS [66].

4. Elastomer/bioglass composite scaffolds

The concept of using bioceramics as a reinforcing phase in polymeric composites was introduced by Bonfield et al. [67]. Polymers suffer from insufficient strength and poor bioactivity whereas bioactive glasses suffer from low fracture toughness, brittleness and low flexibility when used alone [9,68–70]. In order to produce materials with suitable mechanical properties for hard tissue replacement, bioactive glasses can be sintered or combined with polymers [71–76]. Table 2 provides an overview of elastomer/bioactive glass composites and their physical properties.

4.1. Composite scaffolds: fabrication techniques

Different methods have been used for fabricating porous composite scaffolds with tuned pore sizes and interconnectivity (Table 3). Detailed descriptions of these methods can be found elsewhere [9,103,104], but the most popular technique for scaffold fabrication is solvent casting/particulate leaching (SCPL). However, there is a limit on the amount of bioglass that can be incorporated into the polymer matrix [80]. The effect of various solvents [82] and porogens [80] was investigated on scaffolds made from PCL/bioglass using the porogen-leaching technique in order to evaluate physical, structural and mechanical properties. Using dioxane instead of dimethylcarbonate as the solvent, and a mixture of

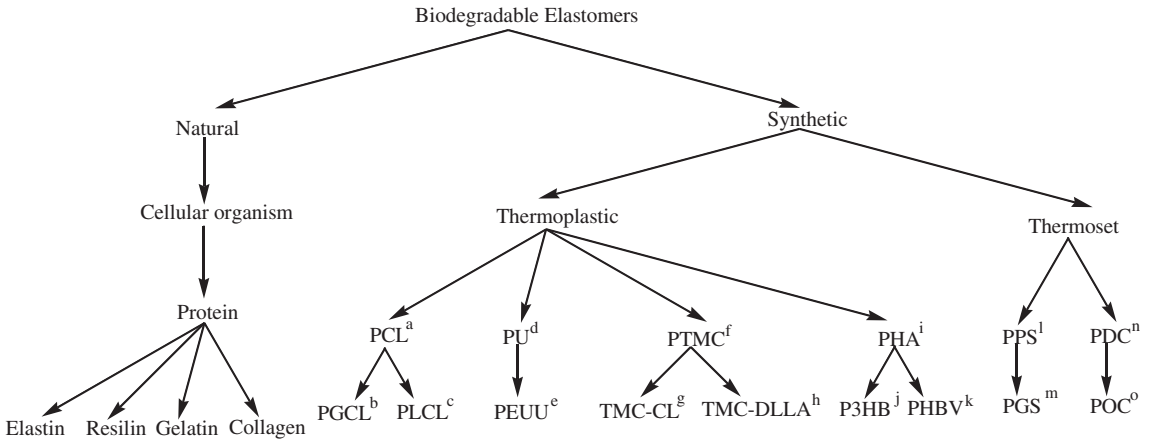

Fig. 1. Classification of elastomers accompanied by examples of each group [6,56,62]: [a]poly (ε-caprolactone/glycolide); [b]poly (ε-caprolactone/lactide); [c]polyester urethane urea; [d]poly (1,3-trimethylene carbonate); [e]poly (1,3-trimethylene carbonate/caprolactone); [f]poly (1,3-trimethylene carbonate/D,L-lactide); [g]poly (3-hydroxybutyrate); [h]poly (3-hydroxybutyrate-co-3-hydroxyvalerate); [i]poly (glycerol sebacate); [j]poly (1,8-octanediol) citrate.

$NaCl–NaHCO_3$ as the porogen, led to the attainment of larger, more homogenously distributed pores. Conversely, the pores in scaffolds prepared by SCPL were thicker and poorly interconnected leading to a significant reduction of strength after 2 weeks of immersion in SBF. However, the high interconnectivity of TIPS scaffold was the main reason for releasing the degradation product and thus the scaffold maintained its integrity for a longer time [105]. Nonetheless, SCPL is the most common method used for scaffold fabrication from thermoset bioelastomers [106]. Fabbri et al. believed that the SLPS technique has advantages over TIPS and SCPL [82] as using a miscible solvent (such as ethanol to remove the frozen solvent instead of vacuum sublimation in TIPS) can lead to complete and effective solvent removal. In a study by Boccaccini et al., composite scaffolds prepared by two different methods of TIPS and slurry-dipping coating were compared in terms of bioactivity [107]; coated scaffolds induced higher bioactivity in respect to filled scaffolds.

SFF was originally developed for the manufacturing industry to enable fabrication of objects with unique materials, combinations, and complex geometries, which could not be achieved by conventional techniques [115]. SFF is widely used for porous scaffold fabrication as it provides highly reproducible scaffolds and allows optimal control over porosity, controlled pore size distribution, and interconnectivity [115,116]. There are no available published reports for the fabrication of elastomer/bioglass composites using the SFF technique.

4.2. Thermoplastic elastomer/bioglass composites

4.2.1. Poly (α-caprolactone) based thermoplastic elastomers

Poly (α-hydroxyl esters) such as poly (lactic acid) (PLA), poly (glycolic acid) (PGA), and their copolymers (PLGA) have been used in tissue engineering and drug delivery due to their excellent biocompatibility [9]. However, the stiffness mismatches with ECM and their plastic deformation under cyclic loading limits applicability [8,61]. The alternative to polylactides/glycolides is poly (α-caprolactone) (PCL), a thermoplastic polyester elastomer approved by the FDA [9]. However, due to its hydrophobicity, PCL degrades slowly [12,117]. Copolymers of PCL with PLA, PGA and PLGA have been fabricated with the aim of overcoming the problems of single polymer systems. Most of these copolymers have been synthesized by ring opening polymerization using $Sn(Oct)_2$ as the catalyst [118]. The mechanical and thermal properties as well as degradation rate of these copolymers can be tuned by controlling the composition and molecular weight of the copolymer phase [71]. Copolymers show faster degradation than homopolymers and the properties of copolymers can vary from crystalline to amorphous depending on the co-monomer ratio. In addition, due to possessing ester moiety, their degradation proceeds by hydrolysis through di-esterification. The degradation products can be easily removed during the metabolic process [11]. The concerns about the acidic nature of degradation products, which can cause inflammation should not be neglected [119].

Bioglass particle size, composition and method of fabrication have a significant influence on the mechanical properties of PCL-based scaffolds [80]. In general, both modulus and bioactivity are dependent on bioglass content [82]. Ródenas-Rochina et al. compared scaffolds of PCL, PCL-nano-HAp and PCL-micro-bioglass composites prepared by particle leaching/freeze extraction using polyethylmethacrylate beads as porogen [81]. All scaffolds showed good mechanical properties (modulus = 0.12–6.8 MPa and yield strength = 0.02–1 MPa) and high interconnected porosity (about 86%), but elastic modulus decreased with increased filler content, likely caused by an agglomeration phenomenon. The study showed that addition of 5% inorganic filler promoted osteoblastic cell adhesion but did not stimulate cell differentiation in comparison to pure PCL. Additionally, differentiation was inhibited by HAp, while cell adhesion was improved with HAp as a result of enhanced protein adsorption [81].

The properties of composite materials are highly dependent on the shape, size and distribution of the reinforcing phase [59]. For example, Jo et al. fabricated composite of PCL with sol–gel derived bioactive glass nano-fibers ($60SiO_2–36CaO–4P_2O_5$ mol%) and compared with a composite fabricated by bioactive glass micro-particles [85]. The results showed more evenly distributed nano-fibers due to their uniform shape and size in comparison to the micro-particulates. The incorporation of nano-fibers into the matrix effectively increased stiffness and elastic modulus of PCL, while micro-particulates had no significant influence on mechanical integrity. Ahmed et al. also fabricated composites of PCL and phosphate-based bioglass fibers (P_2O_5–CaO; 20–25 μm) using compression molding technique. Notably, the modulus increased from 0.5 GPa for pure PCL to approximately 2.5 GPa for composite film containing 18% volume fraction bioactive glass fiber [87]. The degradation rate of the composites was increased by increasing glass fiber content, which leached out into solution and was replaced by water residue in the structure (Fig. 2).

The in vitro biological properties of materials were examined using MC3T3-E1 osteoblastic cells [85,86]. Cell attachment, differentiation and proliferation were significantly improved for the nanocomposites. Furthermore, in vivo testing using Sprague–Dawley albino rats showed prominent biocompatibility and bone formation (Fig. 3) around nanocomposites compared to the microcomposites and pure PCL [85]. These results indicate that there was no inflammatory response of the tissue samples to the nanocomposite at the defect sites.

Table 2
Elastomer/bioglass composite materials.

Polymer		Bioglass	Percentage of bioglass	Glass particle size	Compression (C), tensile (T), flexural (F) strength (MPa)	Modulus (MPa)	Porosity (%)	Contact angle (°)	Fabrication technique	Cell type	Reference
Scaffold	Membrane										
Natural polymers											
Gelatin		SiO_2–P_2O_5–CaO	10, 20, 30, 40, 50	10–80 nm	2.8–5.6 (C)	51–78	72–86		Direct foaming/freeze-drying	SaOS-2 cells	[77]
Gelatin		SiO_2–CaO	10	6 μm					Direct foaming/freeze-drying	Human dental pulp cells	[78]
Gelatin/chitosan		SiO_2–P_2O_5–CaO	1	<100 nm					Freeze-drying	MG-63 osteoblast cells	[79]
Synthetic elastomers											
PCL		45S5	10, 50, 75	<45 μm, <75 μm					Salt-leaching		[80]
PCL		45S5	5, 10, 20	20 μm	0.04–0.12 (C)	0.45–1.15	86		Particle leaching/freeze extraction		[81]
		HA		200 nm	0.07–0.10 (C)	0.68–1.11	87				
PCL		45S5	25, 50	<45 μm	92–214 (KPa) (C)	132–251 (KPa)	88–92		Solid–liquid phase separation	MC3T3-E1	[82]
PCL		45S5	10	≤38 μm		48.35	75		Melt extrusion based additive	MC3T3	[83]
		SrBG (46.46 SiO_2 1.07 P_2O_5–26.38 Na_2O–23.08 (3SrO:1CaO))				59.18					
PCL		SiO_2–CaO (75S25C)	10, 20, 30, 40	70 nm	19–21.5 (T)	198–851		81–56	Melt blending and thermal injection molding		[84]
	PCL	SiO_2–P_2O_5–CaO	10, 20, 30	4 μm (particle)	150 (T)	9			Solvent casting	MC3T3-E1	[85]
				450 nm (fiber)	180 (T)	8					
	PCL	SiO_2–P_2O_5–CaO	20	240 nm (fiber)					Solvent casting	MC3T3-E1	[86]
	PCL	P_2O_5–CaO	18, 38, 39	20–25 μm (fiber)	25–30 (F)	0.5–2.4 (GPa)			Compression molding		[87]
P(CL/DL-LA)		S53P4 (53SiO_2, 23Na_2O–20CaO–4P_2O_5)	5, 10	<45 μm, 90–315 μm		190–900 (KPa)	60–75		Solvent casting/particulate leaching	Rat bone marrow stromal cells	[88–91]
	P(3HB)	45S5	5, 20	<5 μm		0.8–1.1 (GPa)			Solvent casting		[92]
	P(3HB)	45S5	10, 20	29 nm					Solvent casting	MG-63 human osteosarcoma	[93]
	P(3HB)	45S5	10, 20, 30	<5 μm		1.1–0.8 (GPa)		87–55	Solvent casting	MG-63 osteoblast cells	[94]
				29 nm		1.1–1.6 (GPa)		87–61			
P(3HB)		CaO–SiO_2–P_2O_5	10, 20, 30	33 nm			84		Salt-leaching		[95]
P(3HB) (coated)		45S5		<5 μm					Slurry-dipping coating		[96]
PU		45S5	5, 10, 20	<10 μm		0.12–0.81			Polymer coagulation/salt leaching		[97]
PU/PVA		SiO_2–CaO–P_2O_5	10, 25	87 nm			38–81		Freeze-drying	Rat primary osteoblasts cells	[98]
PU (coated)		SiO_2–P_2O_5–CaO-MgO–Na_2O–K_2O		<32 μm	0.12–0.1 (T)	0.12–1.35		95–87	Slurry-dipping coating		[99]
PU/PDLLA (coated)		45S5		<5 μm					Slurry-dipping coating		[100]
	PGS	45S5	5, 10, 15	5 μm	0.42–1.53 (T)	0.38–1.62			Solvent casting	SNL mouse fibroblasts	[101]
	PGS	45S5	2, 5, 10	20–50 nm		0.22–2.5			Solvent casting	SNL mouse fibroblasts	[102]

Table 3
Benefits and drawbacks of common techniques for composite scaffold fabrication [80,82,105,107–114].

Technique	Benefits	Drawbacks
Solvent casting/particulate leaching (SC/PL)	-Simplicity -Control over porosity and pore size	-Residual solvents and porogen material -Difficult to accurately design the interconnectivity of the pores -Precipitation phenomenon
Thermally induced phase separation (TIPS)	-Highly porous structure -Uniform porous scaffold -Highly interconnected structure -Highly anisotropic scaffold	-Small pore size -Long processing time -Technique sensitive
Solid–liquid phase separation (SLPS)	-Proper pore size distribution -Highly interconnected structure -High levels of porosity -Homogenous distribution of particles	-Residual solvent in thick constructs
Rapid prototyping or solid freeform (SFF)	-Customization of the products to meet the individual needs -Ability to create complex geometries and high accuracy features -Possibility to control pore size and distribution of pores within the scaffold	-Limited polymer type -Highly expensive equipment
Slurry-dipping coating of scaffold	-Simple and quick -High bioactivity	-Pore clotting - Residual solvent - Peeling-off of particles -Macrodelamination of the coating

Copolymers of PCL with PLA (PLACL) and PGA (PGACL) were synthesized with the aim of improving biodegradation and mechanical properties [71,120,121]. Rich et al. synthesized composites of poly (CL/DLLA)/bioactive glass (S53P4) by applying various bioglass particle sizes and contents. The composites with higher bioglass contents and smaller particle sizes resulted in faster HA deposition, weight loss and stiffness. Glass transition temperature (T_g) values were almost equal for all the samples, as a result of weak physical interactions between the bioglass and matrix [71]. In a similar study, Meretoja et al. prepared copolymers of poly (CL/DLLA) with two different concentrations of precursors, namely PDLLA-rich, and PCL-rich polymers filled with glass (S53P4) [88]. The results indicated that both copolymer composites had similar porosity and mass loss, while the compressive strength was higher for PCL-rich samples which also exhibited lower water absorption as a consequence of higher crosslinking density. Overall, the composites showed enhanced osteoblast adhesion and mineralization and when implanted into Sprague–Dawley rats, a random distribution of bone within the implants demonstrated that the scaffolds supported angiogenesis and osteoconductivity. The unfilled scaffold supported tissue ingrowth, but the composite showed improved ectopic bone formation [90].

In general, with the composite scaffolds composed of bioactive glasses and PCL-based materials (regardless of method of fabrication and glass size), porosity slightly decreased with glass content and pore shapes were irregular [80]. However, in most cases 1–5% reduction in porosity was observed [81]. Although higher water uptake was observed for the composites in comparison to the unfilled matrix, there was a threshold after which water uptake decreased [71,117]. The higher weight loss for composites relative to the unfilled polymer was attributed to the role of glasses in fluid ingress into the bulk of the sample as well as bioglass dissolution. As a result, voids appeared within the scaffold and subsequently the surface was exposed to increased hydrolytic attack [71,122].

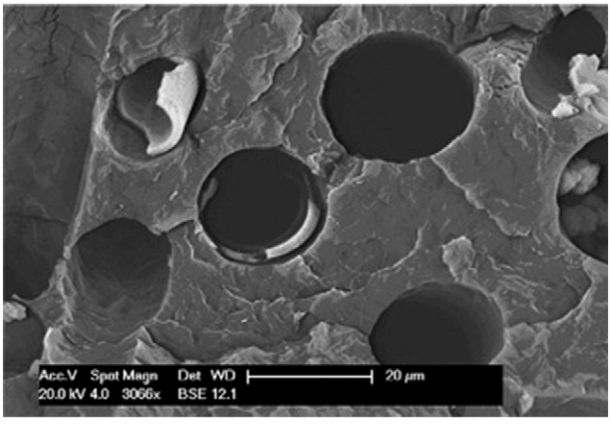

Fig. 2. SEM images of PCL/glass fiber composite after 5 weeks of immersion in deionized water [87].

4.2.2. Poly (hydroxyalkanoate) (PHA) based composites

PHAs are a class of thermoplastic aliphatic polyesters with applications in tissue engineering, due to their occurrence in nature, their nontoxic degradation products, and optimal compatibility with human cells [123]. So far, many types of PHAs (more than 100) have been reported, each with different structures and stiffnesses, from elastomeric to hard materials [124]. However the use of PHAs is mainly confined to two polymers: poly (3-hydroxybutyrate) (P(3HB)) and poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV). The main drawback associated with this group of polymers is their bioinertness. As a solution, bioglasses can be added to improve bioactivity and strength [92].

4.2.2.1. Poly (3-hydroxybutyrate). P(3HB) is a member of the PHA group and has nontoxic degradation products and mechanical properties comparable to synthetic biodegradable polyesters such as polylactide [125]. The brittleness of crystalline P(3HB) limits clinical applications, but the addition of bioactive fillers can address this. Composite films of P(3HB) and bioglass (45S5) have been prepared by Misra et al. using a solvent-casting technique [92,94]. Surprisingly, the addition of bioglass microparticles had an adverse effect on the Young's modulus of P(3HB) in comparison to the unfilled material. This reduction was more manifested for the composites with lower bioglass concentration, presumed to be as a result of low interfacial strength between the polymer chains and bioglass. The addition of bioglass to P(3HB) causes an increase of T_g and a reduction in crystallinity. In vitro, the addition of nano-bioglass to P(3HB) made the composites highly bioactive, such that HA crystals were formed on their surfaces after 5 days of immersion in SBF [92,93]. Glass particles were also coated on the surface of polymer scaffolds to enhance bioactivity [107]. Olsen-Claire et al. reported the fabrication of slurry coated P(3HB) meshes and fibers with bioglasses of mean particle size < 5 μm. The in vitro bioactivity of these samples revealed that HA crystals formed on the composite surface 3 days after immersion in SBF [96].

In vitro evaluation of P(3HB)/nano-bioglass revealed that MG-63 human osteosarcoma cell proliferation decreased with bioglass quantity, and cell proliferation significantly reduced for the composite containing 20% bioglass compared to a tissue culture plastic control [93].

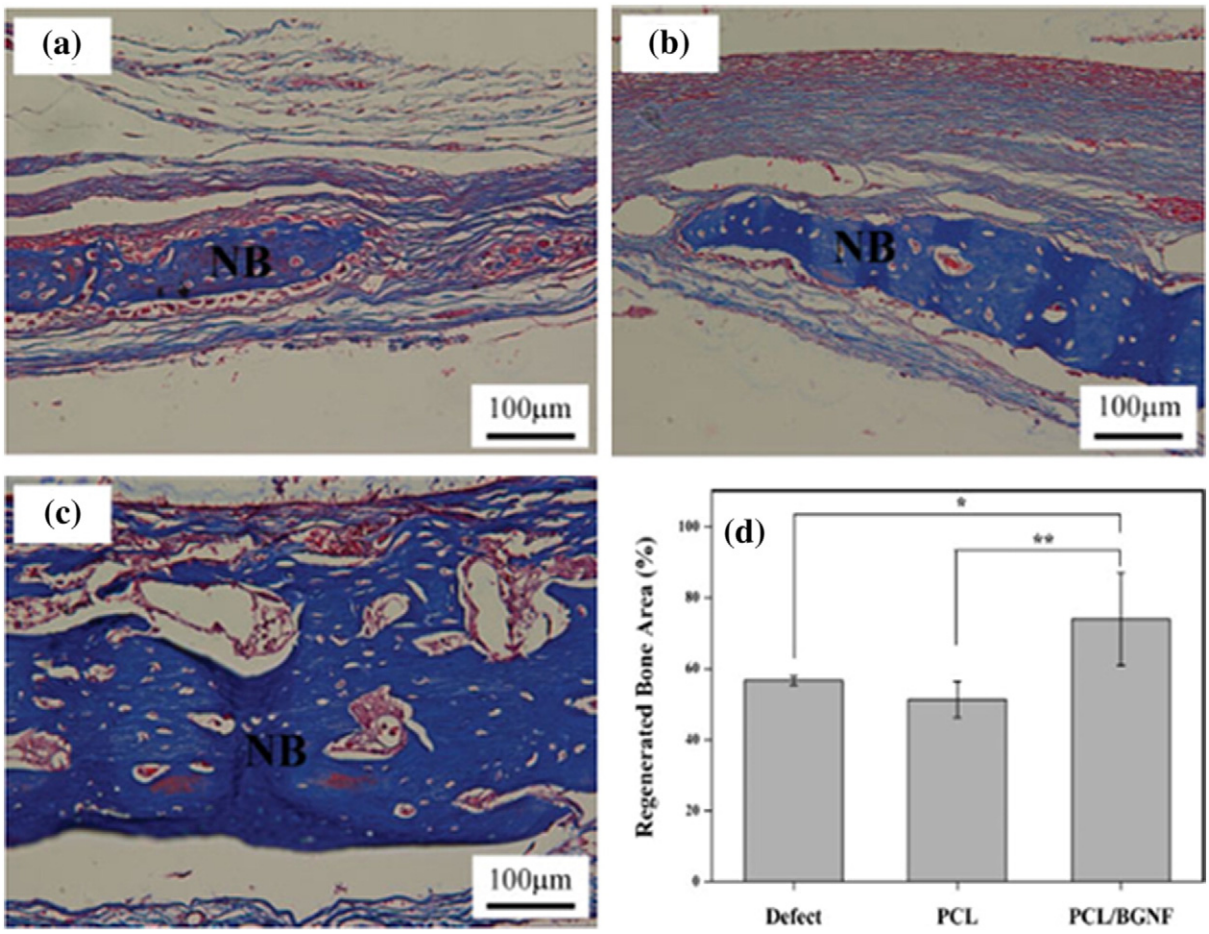

Fig. 3. Optical micrographs of the newly formed bone (NB) in the vicinity of the defect center with a higher magnification: (a) empty defect; (b) pure PCL membrane; and (c) PCL/nanofiber bioglass composite membrane [85].

4.2.2.2. Poly (3-hydroxybutyrate-co-3-hydroxyvalerate). PHBV is a copolymer of P(3HB) with a different percentage of 3-hydroxyvalerate (3HV). Incorporation of 3HV into the P(3HB) structure increases flexibility but decreases strength. Scaffolds of PHBV and bioglass (58S) were fabricated using compression molding, thermal processing, and salt particulate leaching techniques [126]. First, PHBV, bioglass and salt particulates were mixed and compression molded in a stainless steel mold. After heating in a furnace at 180 °C, the disk was immersed in water to leach the salt particulates. The compressive yield strength of the composites increased from 0.16 to 0.41 MPa with the addition of 20% bioglass. Three days of immersion in SBF revealed HA deposition on the surface [127]. The water-contact angle noticeably decreased by increasing bioglass inclusion, inferring improved hydrophilicity [127].

4.2.3. Composite of polyurethane/bioglass

Polyurethane (PU) is the generic name for a class of synthetic polymers synthesized from polyisocyanates, polyalcohols and a chain extender [128–131]. The degradation and biocompatibility of PUs can be controlled by manipulating their macromolecular composition [132]. Generally, PUs have a linear segmented copolymer chemistry composed of a macrodiol, an isocyanate chain extender. PUs and their composites

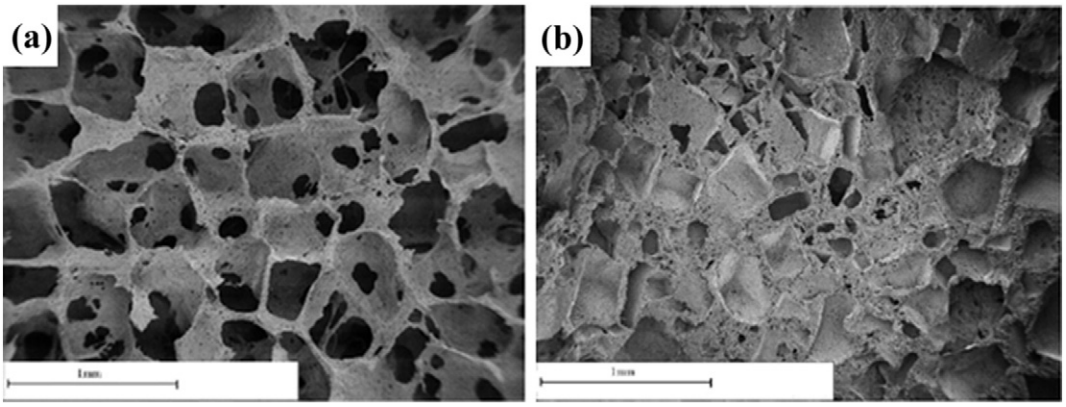

Fig. 4. SEM images of porous samples: (a) pure polyurethane and (b) composite containing 20% bioglass [97].

have been used in artificial skin [133], cardiac tissues [134], knee joint meniscus [135], and drug delivery systems [136].

Bioglasses have been added to PUs to improve their bioactivity and mechanical properties [98]. Ryszkowska et al. synthesized polyurethanes from 4,4-dicyclohexylemethane diisocyanates, poly (caprolactonediol), and ethylene glycol with different molar ratios, namely 2:1:1, 2:3:1 and 5:1:4. Scaffolds containing bioglass had a more uneven structure compared to pure PU (Fig. 4). Due to the use of PCL in PU synthesis, it is assumed that the scaffolds undergo bulk degradation through hydrolysis of ester bonds, indicating that PU soft segments (ester bonds) are more susceptible to degradation than urethane bonds. DMA results revealed that composites have both a higher storage modulus before immersion in SBF, and also a modulus increase with increasing bioglass content after 8 weeks of immersion [97].

The study by de Oliveira et al. suggested that there is a threshold for filler additions to result in improvements. In this study, nanocomposites of a degradable PU/polyvinyl alcohol (PVA) blend and bioglass nanoparticles (SiO_2–CaO–P_2O_5) were fabricated by freeze-drying [98]. The composite scaffold with 10% bioglass had higher compressive strength than the unfilled polymer, but both scaffolds recovered to about 95%. The tensile modulus increased for composite containing 10% bioglass as the glass particles react with PVA (Fig. 5). These composites also exhibited good bioactivity in vitro with improved cell growth and proliferation [98].

Other studies have investigated the influence of bioactive glass coats on the mechanical, degradative and bioactive properties of PU foams. The scaffold made of PU was coated by SiO_2–P_2O_5–CaO–MgO–Na_2O–K_2O bioactive glass using a slurry coating technique (Fig. 6). The stiffness and strength of the scaffold were higher than that of the uncoated polymer when the porosity was 8% less than the uncoated scaffold.

However, strength and stiffness were low in comparison to human bone [99]. There was a higher weight loss from composites than from pure polymers (Fig. 7) [100].

4.3. Thermoset polyester/bioglass elastomer composites

4.3.1. Poly (diol citrate)

Two members of this group of elastomers are poly (polyolsebacate) (PPS) and poly (diol citrate) (PDC). PDCs were first synthesized through a simple polycondensation reaction of non-toxic monomers such as citric acid and various aliphatic linear diols (1,6-hexanediol, 1,8-octanediol, 1,10-decanediol, or 1,12-dodecanediol) under mild conditions [137,138]. The pre-polymer is soluble in various solvents such as ethanol, dioxane and acetone that facilitate its use in the production of scaffolds of different shapes and sizes. Furthermore, PDCs can be crosslinked at body temperature [137]. Yang and coworkers observed that mechanical properties, degradation profile and surface characteristics of PDCs can be influenced by modifying curing conditions (time and temperature) and by the initial monomer molar ratio of monomers [137]. Increasing the time and temperature of curing led to enhanced crosslinking density, which subsequently improved mechanical properties and decreased degradation [139]. Among the PDCs, poly (octanediol citrate) (POC) attracts most interest because of its mechanical properties (ultimate tensile strength of 6.1 MPa, Young's modulus of 0.92–16.4 MPa, and elongation at break of 117–265%) [61,137,140]. POC has free carboxylic groups derived from citric acid which eliminates the need for surface pretreatment and consequently facilitates the conjugation of proteins such as fibronectin [139,141]. Several studies have developed composites of POC and bioceramics (e.g. HAp) for load bearing applications [142,143].

Composites from POC and gallium containing bioactive glass (SiO_2–CaO–ZnO–Ga_2O_3) have been synthesized using a solvent casting–particulate leaching technique [144]. Mechanical properties increased with bioglass content while in vitro degradation kinetics reduced. The assessment of biological properties using human osteoblast cells revealed that collagen synthesis (both type I and type III) and cell adhesion significantly increased by the incorporation of 10% bioglass (Fig. 8).

4.3.2. Poly (glycerol sebacate)

Poly (glycerol sebacate) (PGS) is a synthetic biodegradable thermoset elastomer composed of glycerol and sebacic acid [101]. Depending on the extent of crosslinking, Young's modulus can fall in the range of 0.05–1.5 MPa [102]. PGS degrades by approximately 17% in 60 days in PBS, whereas implantation in Sprague–Dawley rats reports full degradation over the same period of time [102]. Stuckey et al. observed complete PGS resorption over almost 6 weeks in vivo [145]. Therefore, fast degradation of PGS can cause an increase in the acidity of the environment, and consequently increase cellular toxicity [102,146,147]. To address the above issues, alkaline fillers such as bioglass have been mixed with PGS. Liang et al. studied the biodegradation of PGS/45S5 composite and PGS/PLA copolymer under both static and cyclic mechanical loading in buffered solution and culture medium [146]. Increasing bioglass content led to faster degradation and increased swelling; the ester-type crosslinking was depleted along with ionic linkages, and since ionic bonds were unstable in aqueous media, the rate of degradation was enhanced. Secondly, bioglass neutralized pH and thus hydrolysis rate decreased [146]. The authors also investigated the mechanical properties of pure PGS and its composites containing microbioglass (5, 10, 15%) [101]; the addition of which significantly increased elongation at break and Young's modulus in dry conditions. At the same

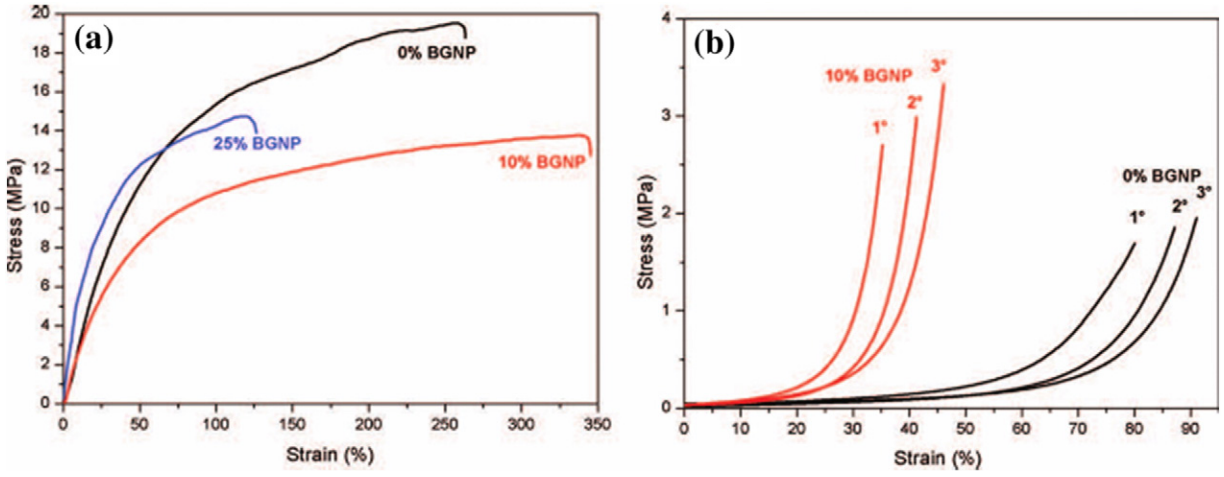

Fig. 5. (a) Tensile stress–strain curves of PU/PVA blend composites PU/PVA with 10 and 25% of BGNP; (b) compressive stress–strain curves of foams PU/PVA and PU/PVA with 10% of BGNP, essayed successive referred as 1, 2, and 3 tests, respectively [98].

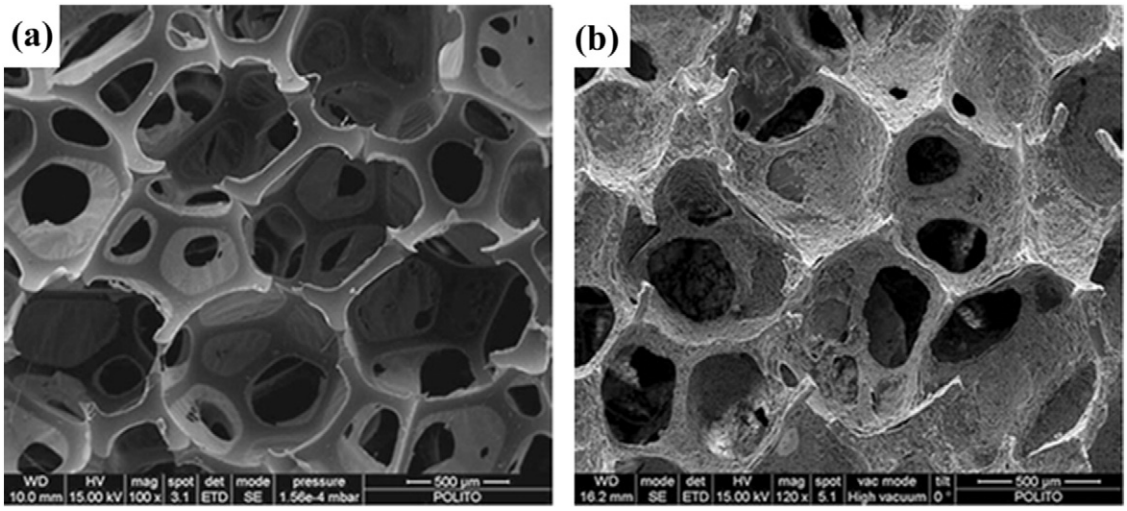

Fig. 6. SEM images show the morphology of: a) neat PU scaffold; and b) composite scaffold [99].

time, the modulus showed a dramatic decrease for composites in aqueous culture medium. Additionally, the composites with the highest bioglass content (15%) exhibited the biggest decrease in modulus from 1.62 to 0.59 after one day incubation relative to composites with 10 and 5%. This was attributed to the decline in ester bond formation since this type of bonding is more robust compared to ionic metal carboxylate bonds [147]. In a related study, Chen at al. prepared composite films of PGS and nano-bioglass [102] which exhibited higher modulus in comparison to the microcomposites even though less bioglass was used [101]. In vitro indirect cytotoxicity testing using SNL mouse fibroblasts revealed that the cytotoxicity of composites with low bioglass content was comparable with culture dish and PDLLA used as controls [101,102]. A high bioglass concentration resulted in high cytotoxicity attributed to high pH, which could be a result of the release of Ca^{2+} and Na^{+} ions. However, the addition of up to 5% nano-bioglass significantly increased biocompatibility so that the percentage of dead cells for nanocomposites was approximately similar to culture plastic dish or PDLLA controls [102]. Significant cell proliferation was observed for all the composites after 2 days of culture [101,102].

5. Composite materials from natural elastomers and bioglass

Natural polymers have low toxicity, low disposal costs, and renewability [148]. Those commonly used in bone tissue engineering include collagen, elastin, alginate, silk, chitosan and hyaluronic acid [5,149]. Natural elastomers have benefits for tissue engineering applications in terms of cell adhesion, cell responsive degradation and re-modeling [45,150]. For example, collagen and elastin play a vital role in many extracellular structural tissues due to their wide range of elastic properties, including complete recovery after deformation [151]. Nonetheless, they suffer from inadequate physical properties in terms of solubility and rapid degradability [45,152]. Therefore, it is required to hydrolyze the natural macromolecules into shorter chains, which are usually soluble in water. For example, the soluble derivatives of elastin (i.e. elastin peptides, digested elastins and tropoelastin) and collagen (i.e. gelatin) have a wide range of medical applications [153]. In terms of materials' integrity, the high degradation rate of these derivatives causes a rapid loss of mechanical properties and therefore limits their application. It is possible to blend them with synthetic polymers or inorganic materials to produce composites [152,154,155]. In many cases, various crosslinking techniques can yield natural materials with high mechanical integrity [156,157]. For example, Mozafari et al. fabricated nanocomposite scaffolds of gelatin and bioglass using a direct foaming technique followed by freeze-drying and lamination [77]. Crosslinking was carried out using glutaraldehyde. The compressive modulus and strength of the resultant scaffolds were increased by the presence of the bioglass when the porosity and pore size were comparable to cancellous bone (in the range of 72–86% and 200–500 μm respectively) [77]. Nadeem et al. also employed a direct foaming technique for the production of scaffolds from gelatin and sol–gel derived calcium silicate bioglass [78]. Crosslinking was carried out using dehydrothermal treatments over a range of temperatures and exposure periods in the sequence with genipin. The period of dehydrothermal crosslinking had a significant influence on the final properties, especially the degradation profile. The weight loss reached its lowest percentage when gelatin was treated for 48 h, suggesting an optimal degree of crosslinking and aqueous stability [158]. It is important to note that the scaffold demonstrated cellular bioactivity almost equal to neat bioglass (Fig. 9).

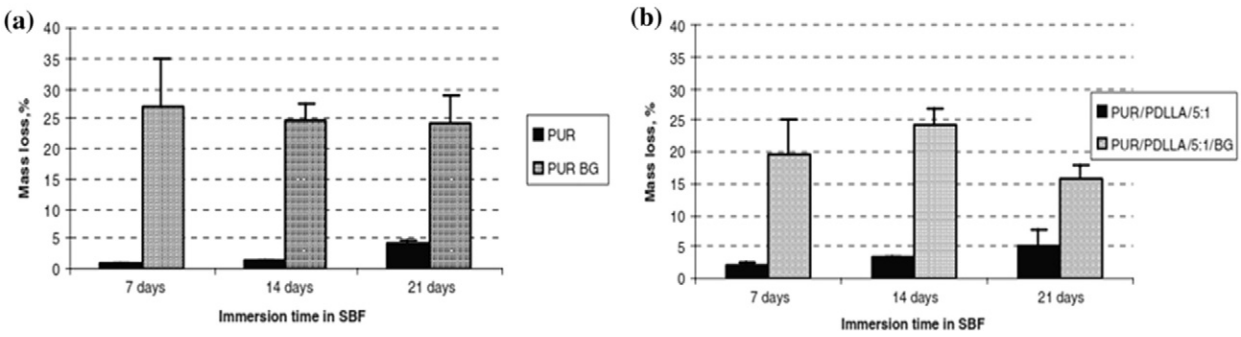

Fig. 7. Comparison of biodegradation in vitro: (a) bioglass-coated and uncoated PUR; and (b) PUR/PDLLA scaffolds during immersion in SBF for up to 21 days [100].

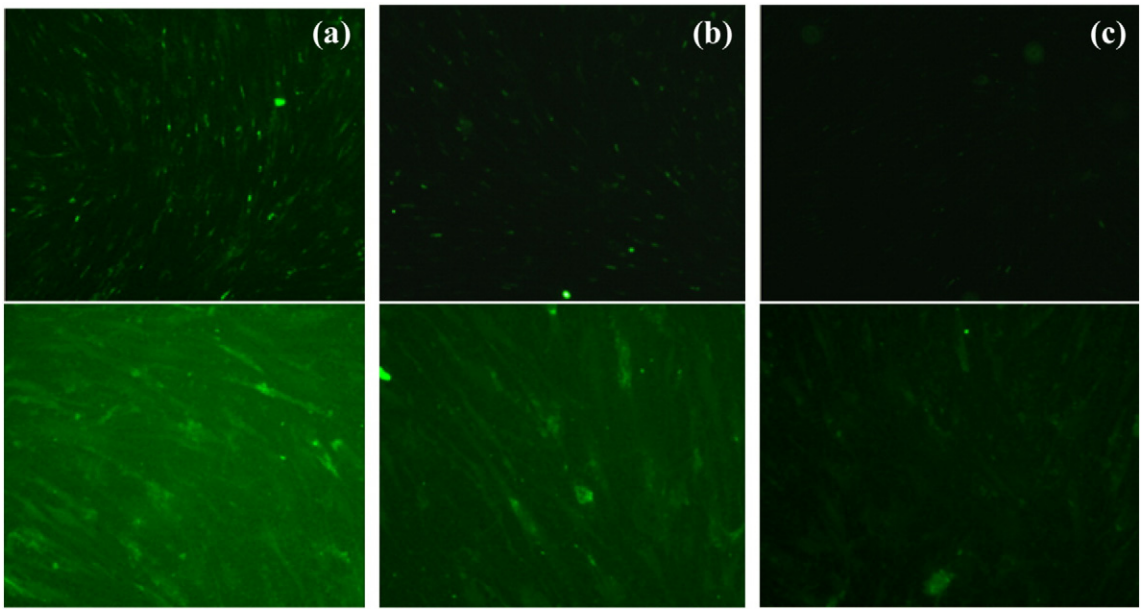

Fig. 8. Fluorescent images of indirect immunostaining of collagen type I synthesis (top) and type III collagen synthesis (down) on composite scaffolds after 7 days in culture: (a) POC-BG-10%; (b) POC-BG-20%; and (c) POC-BG-30% [144].

Peter et al. prepared composite scaffolds composed of a blend of chitosan and gelatin with sol–gel derived nano-bioglass (SiO_2–CaO–P_2O_5) by a freeze-drying technique [79]. It was reported that the swelling and degradation ratios were significantly reduced for scaffolds containing bioglass which was assumed to be due to the formation of strong bonding between hydrophilic groups of gelatin and bioglass. In addition, lower degradation of scaffolds was attributed to neutralization of acidic degradation products of chitosan, as a result of bioglass leaching into the aqueous solution. Evaluation of cellular response in vitro showed that the gelatin/bioglass scaffolds had appropriate biocompatibility when seeded with SaOS-2 cells (osteoblastic cell model) and human dental pulp stems cells (HDPSCs) [77,78]. Observation of composite scaffolds by SEM after 3 days in culture revealed ECM secreted onto the surface of scaffolds, indicating the effective cellular migration and osteoconductivity of scaffolds. Higher levels of cell attachment were observed for the untreated samples within the first 3 h, which was attributed to a higher density of free amino acid groups on untreated samples, in comparison to the cross-linked ones. More amino acid groups result in a higher cumulative surface charge, which facilitates cell attachment [78]. The composite scaffolds supported HDPSC growth and maintained their osteogenic differentiation capacity as observed from alkaline phosphatase staining (Fig. 10). Incorporation of nanoparticles further increased the concentration of binding sites at the surface of the material [79]. Osteoblastic cells (MG-63) were well attached and spread on the scaffolds.

Srinivasan et al. reported the fabrication of a new nanocomposite scaffold from alginate and bioactive glass (SiO_2–CaO–P_2O_5) [159]. The results showed improved protein adsorption and MG-63 with hPDLF cell attachment and proliferation on nanocomposites in respect to pure alginate scaffold. The authors observed that there was no significant difference in cell viability of either hPDLF or MG-63 cells between all scaffolds. Furthermore, ALP activity showed a significant increase for hPDLF cells as compared to MG-63 cells.

6. The effect of filler size: polymer/bioglass nano- and micro-composites

It is established that filler size can affect strength, bioactivity and cell proliferation [160]. Misra et al. compared the influence of micro (<5 μm) and nano (29 nm) bioglass particles when mixed into a P(3HB) polymer matrix [94]. The authors observed that addition of nano-size bioglass has a greater impact on mechanical and structural properties of composite films than micro-size fillers (Fig. 11). Young's modulus for the unfilled polymer was between that of the micro and nanocomposites

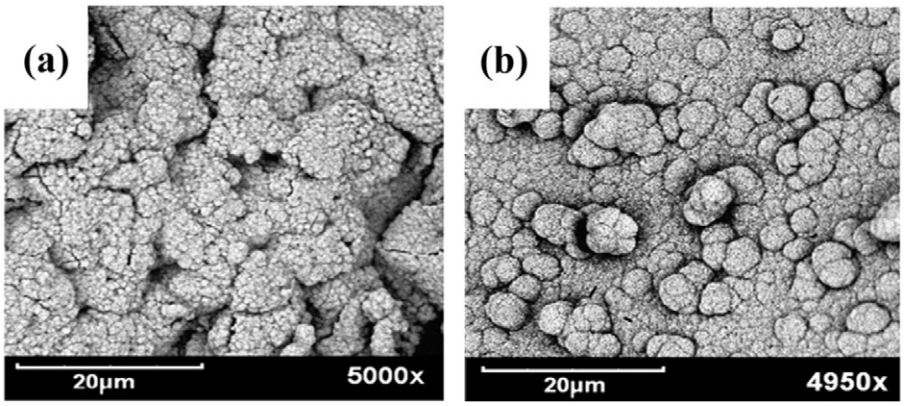

Fig. 9. SEM images of: (A) gelatin/bioglass scaffold; and (B) bioglass particles with apatite on the surface after immersion of 3 days in SBF [78].

Fig. 10. Alkaline phosphatase staining image obtained from optical microscope: left—composite and right—control [78].

while the nanocomposites with 10% bioglass demonstrated the highest modulus. The higher modulus of nanocomposites was attributed to the higher interfacial surface area which results from an increase in load transfer between polymer and filler. On the other hand, agglomeration of micro-particles is the main reason for lower strength. The obtained data for mechanical properties by Caridade et al. for composite films of chitosan/45S5 bioglass are comparable with the results from Misra et al. [161]. Results from both groups indicated an increase in Young's modulus with decrease in filler size (from nano to micro) [94]. Contrary to those results, nanocomposite scaffolds produced from PDLLA filled with nano-size 45S5 bioglass had lower strength than either pure PDLLA or microcomposite scaffolds [162]. Simultaneously, porosity was increased, by the addition of nano-bioglass, to about 93.4%, compromising mechanical properties.

In vitro assessment of P(3HB)/bioglass composites demonstrated that both weight loss and water uptake percentage increased with immersion time [94]. As expected, the increase in degradation and swelling was more obvious for nanocomposites than microcomposites. The in vitro cellular response of composites containing nano and micro bioglass was compared in some studies [94,162]. In general, the composites indicated higher protein adsorption in comparison to unfilled polymers. Nanocomposites had higher protein adsorption relative to microcomposites [94]. This can be explained by the higher roughness resulting from nano-size particles. In contrast, cell proliferation was impaired by the increased concentration of bioglass. The inverse relationship between protein adsorption and cell proliferation was elucidated by the changes in protein conformational for the thicker layers [94]. Similar results were obtained by Gerhardt et al. where the cell viability showed a decrease with an increase in the amount of bioglass added to PDLLA [162]. The destructive influence on cell viability was more significant with nano-bioglasses and was attributed to the increase in pH of the culture medium, as a result of accelerated ion release by highly reactive nano-bioglasses which could possibly compromise the beneficial influence of nano-roughness.

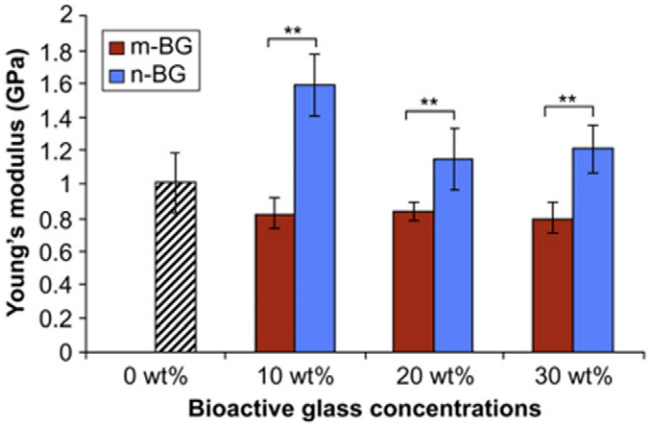

Fig. 11. Modulus comparison for various concentrations of m-BG and n-BG particles in P(3HB)/bioactive glass composites [94].

7. Conclusion and future perspectives

The literature reviewed in this article shows that the addition of bioactive glasses can improve most elastomer properties but there is a threshold limit for bioactive glass incorporation beyond which composite properties such as strength and cellular response become compromised. Apart from content, other parameters such as glass size, shape and composition can influence the final properties of composites. Smaller glass particles are more effective in improving both mechanical stability and bioactivity. Nonetheless, the strength of pure elastomers and their composites are orders of magnitude weaker than natural human bone meaning that, currently, such materials only have applicability as bone filling agents with external support.

A future focus should be on the fabrication of composite scaffolds with enhanced mechanical stability which can withstand cyclic mechanical loading. Moreover, there is a growing need for more research on the antibacterial properties of composites that would prevent infections upon surgery. A promising solution could be doping of the proper concentration of antibacterial ions to the glass such that cell adhesion and growth could be improved simultaneously. A better understanding of how specific scaffold properties affect cell behavior will also allow optimization of scaffold based tissue engineering constructs toward bone regeneration. A continuation in stem cell research with composite biomaterials is necessary due the unique properties of stem cells such as self-renewal, differentiation into other specialized cell types, and each new cell type attaining a specialized function [163]. Indeed, the stimulatory role of the biological apatite layer formed on the surface of bioactive glasses on osteoblastic differentiation of stem cells without addition of osteogenic induction factor makes bioactive glasses promising candidate for bone tissue engineering. On the other hand, the elasticity of materials is a crucial parameter in cellular responses both in vitro and in vivo [164,165]. The high elasticity of elastomers provides a large capacity for filler loading and so the addition of bioactive glasses to the elastomers offers a unique opportunity to tune the elasticity and control the differentiation of stem cells by the presence of bioglass materials within the polymer matrix. In addition, more research needs to evaluate the biological response of elastomeric composites under dynamic conditions. Using bioreactors offers an incremental improvement over traditional static culture techniques since they can satisfy the external requirement for medium flow and usually mimic in vivo cellular microenvironments. There is only limited knowledge on in vivo cell–elastomer interaction. In vivo investigations should be the focus of future studies to continue the scaffold development. Elastomeric composites may show completely different behavior in vivo. Associated citotoxicity with polymeric degradation products and release of high concentrations of some trace elements from bioactive glasses detected in the confined culture wells may have a different effect in vivo.

Acknowledgments

This research is supported by a High Impact Research MoE Grant (UM.C/625/1/HIR/MoE/ENG/58) from the Ministry of Education, Malaysia and a University of Malaya Research Grant (UMRG, RG156-12AET).

References

[1] E. Hamed, I. Jasiuk, Elastic modeling of bone at nanostructural level, Mater. Sci. Eng. R. Rep. 73 (2012) 27–49.
[2] X. Wu, Surface Modification of Polylactic Acid Nonwoven Webs, North Carolina State University, 2012.
[3] K. Alvarez, H. Nakajima, Metallic scaffolds for bone regeneration, Materials 2 (2009) 790–832.
[4] J. Velema, D. Kaplan, Biopolymer-based biomaterials as scaffolds for tissue engineering, in: K. Lee, D. Kaplan (Eds.), Tissue Engineering I, Springer, Berlin Heidelberg 2006, pp. 187–238.
[5] B. Dhandayuthapani, Y. Yoshida, T. Maekawa, D.S. Kumar, Polymeric scaffolds in tissue engineering application: a review, Int. J. Polym. Sci. 2011 (2011).
[6] Y. Li, G.A. Thouas, Q.-Z. Chen, Biodegradable soft elastomers: synthesis/properties of materials and fabrication of scaffolds, RSC Adv. 2 (2012) 8229–8242.
[7] C.J. Bettinger, Biodegradable elastomers for tissue engineering and cell–biomaterial interactions, Macromol. Biosci. 11 (2011) 467–482.
[8] Q. Chen, C. Zhu, G. Thouas, Progress and challenges in biomaterials used for bone tissue engineering: bioactive glasses and elastomeric composites, Prog. Biomater. 1 (2012) 1–22.
[9] K. Rezwan, Q. Chen, J. Blaker, A.R. Boccaccini, Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering, Biomaterials 27 (2006) 3413–3431.
[10] Q. Fu, E. Saiz, M.N. Rahaman, A.P. Tomsia, Bioactive glass scaffolds for bone tissue engineering: state of the art and future perspectives, Mater. Sci. Eng. C 31 (2011) 1245–1256.
[11] Q. Chen, S. Liang, G.A. Thouas, Elastomeric biomaterials for tissue engineering, Prog. Polym. Sci. 38 (2013) 584–671.
[12] Z. You, Y. Wang, Bioelastomers in tissue engineering, biomaterials for tissue engineering applications, Springer, 2011. 75–118.
[13] M. Bohner, J. Lemaitre, Can bioactivity be tested in vitro with SBF solution? Biomaterials 30 (2009) 2175–2179.
[14] A.J. Salinas, M. Vallet-Regí, Bioactive ceramics: from bone grafts to tissue engineering, RSC Adv. 3 (2013) 11116–11131.
[15] T. Kokubo, Apatite formation on surfaces of ceramics, metals and polymers in body environment, Acta Mater. 46 (1998) 2519–2527.
[16] M.N. Rahaman, D.E. Day, B. Sonny Bal, Q. Fu, S.B. Jung, L.F. Bonewald, A.P. Tomsia, Bioactive glass in tissue engineering, Acta Biomater. 7 (2011) 2355–2373.
[17] L.L. Hench, R.J. Splinter, W. Allen, T. Greenlee, Bonding mechanisms at the interface of ceramic prosthetic materials, J. Biomed. Mater. Res. 5 (1971) 117–141.
[18] L.L. Hench, Bioceramics, J. Am. Ceram. Soc. 81 (1998) 1705–1728.
[19] W. Huang, D.E. Day, K. Kittiratanapiboon, M.N. Rahaman, Kinetics and mechanisms of the conversion of silicate (45S5), borate, and borosilicate glasses to hydroxyapatite in dilute phosphate solutions, J. Mater. Sci. Mater. Med. 17 (2006) 583–596.
[20] X. Liu, M.N. Rahaman, Q. Fu, Bone regeneration in strong porous bioactive glass (13–93) scaffolds with an oriented microstructure implanted in rat calvarial defects, Acta Biomater. 9 (2013) 4889–4898.
[21] S.B. Jung, Bioactive Borate Glasses, Bio-glasses, John Wiley & Sons, Ltd, 2012. 75–95.
[22] K. Anselme, Osteoblast adhesion on biomaterials, Biomaterials 21 (2000) 667–681.
[23] I.D. Xynos, A.J. Edgar, L.D. Buttery, L.L. Hench, J.M. Polak, Gene-expression profiling of human osteoblasts following treatment with the ionic products of Bioglass® 45S5 dissolution, J. Biomed. Mater. Res. 55 (2001) 151–157.
[24] L.-C. Gerhardt, A.R. Boccaccini, Bioactive glass and glass-ceramic scaffolds for bone tissue engineering, Materials 3 (2010) 3867–3910.
[25] R.F. Brown, D.E. Day, T.E. Day, S. Jung, M.N. Rahaman, Q. Fu, Growth and differentiation of osteoblastic cells on 13–93 bioactive glass fibers and scaffolds, Acta Biomater. 4 (2008) 387–396.
[26] A. Silva, A. Paula, T. Martins, A. Goes, M. Pereria, Synergistic effect between bioactive glass foam and a perfusion bioreactor on osteogenic differentiation of human adipose stem cells, J. Biomed. Mater. Res. A 102 (2014) 818–827.
[27] R. Detsch, S. Alles, J. Hum, P. Westenberger, F. Sieker, D. Heusinger, C. Kasper, A.R. Boccaccini, Osteogenic differentiation of umbilical cord and adipose derived stem cells onto highly porous 45S5 Bioglass®-based scaffolds, J. Biomed. Mater. Res. A 103 (2014) 1029–1037.
[28] J.K. Fraser, I. Wulur, Z. Alfonso, M.H. Hedrick, Fat tissue: an underappreciated source of stem cells for biotechnology, Trends Biotechnol. 24 (2006) 150–154.
[29] A. Hoppe, N.S. Güldal, A.R. Boccaccini, A review of the biological response to ionic dissolution products from bioactive glasses and glass-ceramics, Biomaterials 32 (2011) 2757–2774.
[30] A.A. Gorustovich, J.A. Roether, A.R. Boccaccini, Effect of bioactive glasses on angiogenesis: a review of in vitro and in vivo evidences, Tissue Eng. B Rev. 16 (2009) 199–207.
[31] R.M. Day, Bioactive glass stimulates the secretion of angiogenic growth factors and angiogenesis in vitro, Tissue Eng. 11 (2005) 768–777.
[32] I. Xynos, M. Hukkanen, J. Batten, L. Buttery, L. Hench, J. Polak, Bioglass® 45S5 stimulates osteoblast turnover and enhances bone formation in vitro: implications and applications for bone tissue engineering, Calcif. Tissue Int. 67 (2000) 321–329.
[33] G.C. Reilly, S. Radin, A.T. Chen, P. Ducheyne, Differential alkaline phosphatase responses of rat and human bone marrow derived mesenchymal stem cells to 45S5 bioactive glass, Biomaterials 28 (2007) 4091–4097.
[34] H. Ohgushi, Y. Dohi, T. Yoshikawa, S. Tamai, S. Tabata, K. Okunaga, T. Shibuya, Osteogenic differentiation of cultured marrow stromal stem cells on the surface of bioactive glass ceramics, J. Biomed. Mater. Res. 32 (1996) 341–348.
[35] Q. Fu, M.N. Rahaman, B.S. Bal, K. Kuroki, R.F. Brown, In vivo evaluation of 13–93 bioactive glass scaffolds with trabecular and oriented microstructures in a subcutaneous rat implantation model, J. Biomed. Mater. Res. A 95 (2010) 235–244.
[36] H. Pan, X. Zhao, X. Zhang, K. Zhang, L. Li, Z. Li, W. Lam, W. Lu, D. Wang, W. Huang, Strontium borate glass: potential biomaterial for bone regeneration, J. R. Soc. Interface 7 (2010) 1025–1031.
[37] G. Kaur, O.P. Pandey, K. Singh, D. Homa, B. Scott, G. Pickrell, A review of bioactive glasses: their structure, properties, fabrication and apatite formation, J. Biomed. Mater. Res. A 102 (2014) 254–274.
[38] S.P. Valappil, D. Ready, E.A.A. Neel, D.M. Pickup, W. Chrzanowski, L.A. O'Dell, R.J. Newport, M.E. Smith, M. Wilson, J.C. Knowles, Antimicrobial gallium-doped phosphate-based glasses, Adv. Funct. Mater. 18 (2008) 732–741.
[39] A. Ahmed, A. Ali, D.A. Mahmoud, A. El-Fiqi, Preparation and characterization of antibacterial P_2O_5–CaO–Na_2O–Ag_2O glasses, J. Biomed. Mater. Res. A 98 (2011) 132–142.
[40] O. Leppäranta, M. Vaahtio, T. Peltola, D. Zhang, L. Hupa, M. Hupa, H. Ylänen, J.I. Salonen, M.K. Viljanen, E. Eerola, Antibacterial effect of bioactive glasses on clinically important anaerobic bacteria in vitro, J. Mater. Sci. Mater. Med. 19 (2008) 547–551.
[41] H.V.D. Belt, D. Neut, W. Schenk, J.R.V. Horn, H.C.V.D. Mei, H.J. Busscher, Infection of orthopedic implants and the use of antibiotic-loaded bone cements: a review, Acta Orthop. 72 (2001) 557–571.
[42] K. Bruellhoff, J. Fiedler, M. Möller, J. Groll, R.E. Brenner, Surface coating strategies to prevent biofilm formation on implant surfaces, Int. J. Artif. Organs 33 (2010) 646–653.
[43] P. Stoor, E. Söderling, J.I. Salonen, Antibacterial effects of a bioactive glass paste on oral microorganisms, Acta Odontol. 56 (1998) 161–165.
[44] M. Catauro, M. Raucci, F. De Gaetano, A. Marotta, Antibacterial and bioactive silver-containing $Na_2O{\cdot}CaO{\cdot}2SiO_2$ glass prepared by sol–gel method, J. Mater. Sci. Mater. Med. 15 (2004) 831–837.
[45] D. Puppi, F. Chiellini, A. Piras, E. Chiellini, Polymeric materials for bone and cartilage repair, Prog. Polym. Sci. 35 (2010) 403–440.
[46] H. Tian, Z. Tang, X. Zhuang, X. Chen, X. Jing, Biodegradable synthetic polymers: preparation, functionalization and biomedical application, Prog. Polym. Sci. 37 (2012) 237–280.
[47] S. Verma, K. Garkhal, A. Mittal, N. Kumar, Biodegradable polymers for emerging clinical use in tissue engineering, Biodegradable Polym. Clin. Use Clin. Dev. (2011) 565–629.
[48] S. Bose, M. Roy, A. Bandyopadhyay, Recent advances in bone tissue engineering scaffolds, Trends Biotechnol. 30 (2012) 546–554.
[49] M.J. Olszta, X. Cheng, S.S. Jee, R. Kumar, Y.-Y. Kim, M.J. Kaufman, E.P. Douglas, L.B. Gower, Bone structure and formation: a new perspective, Mater. Sci. Eng. R. Rep. 58 (2007) 77–116.
[50] B.A. Allo, D.O. Costa, S.J. Dixon, K. Mequanint, A.S. Rizkalla, Bioactive and biodegradable nanocomposites and hybrid biomaterials for bone regeneration, J. Funct. Biomater. 3 (2012) 432–463.
[51] V. Guarino, F. Causa, P. Taddei, M. di Foggia, G. Ciapetti, D. Martini, C. Fagnano, N. Baldini, L. Ambrosio, Polylactic acid fibre-reinforced polycaprolactone scaffolds for bone tissue engineering, Biomaterials 29 (2008) 3662–3670.
[52] I. Akmaz, A. Kiral, O. Pehlivan, M. Mahiroguları, C. Solakoglu, O. Rodop, Biodegradable implants in the treatment of scaphoid nonunions, Int. Orthop. 28 (2004) 261–266.
[53] L. Wu, J. Ding, In vitro degradation of three-dimensional porous poly (D, L-lactide-co-glycolide) scaffolds for tissue engineering, Biomaterials 25 (2004) 5821–5830.
[54] Q. Liu, L. Jiang, R. Shi, L. Zhang, Synthesis, preparation, in vitro degradation, and application of novel degradable bioelastomers—a review, Prog. Polym. Sci. 37 (2012) 715–765.
[55] R. Langer, N.A. Peppas, Advances in biomaterials, drug delivery, and bionanotechnology, AIChE J. 49 (2003) 2990–3006.
[56] R. Shi, D. Chen, Q. Liu, Y. Wu, X. Xu, L. Zhang, W. Tian, Recent advances in synthetic bioelastomers, Int. J. Mol. Sci. 10 (2009) 4223–4256.
[57] S. Li, H. Garreau, M. Vert, Structure–property relationships in the case of the degradation of massive poly (α-hydroxy acids) in aqueous media, J. Mater. Sci. Mater. Med. 1 (1990) 198–206.
[58] L. Wu, J. Ding, Effects of porosity and pore size on in vitro degradation of three-dimensional porous poly (D, L-lactide-co-glycolide) scaffolds for tissue engineering, J. Biomed. Mater. Res. A 75 (2005) 767–777.
[59] M. Wang, Developing bioactive composite materials for tissue replacement, Biomaterials 24 (2003) 2133–2151.
[60] P. Cordier, F. Tournilhac, C. Soulié-Ziakovic, L. Leibler, Self-healing and thermoreversible rubber from supramolecular assembly, Nature 451 (2008) 977–980.
[61] M.C. Serrano, E.J. Chung, G. Ameer, Advances and applications of biodegradable elastomers in regenerative medicine, Adv. Funct. Mater. 20 (2010) 192–208.
[62] Z. You, Y. Wang, Bioelastomers in Tissue Engineering, Springer, 2011.
[63] E. Zeimaran, M.R.A. Kadir, H.M. Nor, T. Kamarul, I. Djordjevic, Synthesis and characterization of polyacids from palm acid oil and sunflower oil via addition reaction, Bioorg. Med. Chem. Lett. 23 (2013) 6616–6619.
[64] M. Van der Mee, J. Goossens, M. Van Duin, Thermoreversible covalent crosslinking of maleated ethylene/propylene copolymers with diols, J. Polym. Sci. A Polym. Chem. 46 (2008) 1810–1825.
[65] B. Amsden, Curable, biodegradable elastomers: emerging biomaterials for drug delivery and tissue engineering, Soft Matter 3 (2007) 1335–1348.
[66] Y. Wang, G.A. Ameer, B.J. Sheppard, R. Langer, A tough biodegradable elastomer, Nat. Biotechnol. 20 (2002) 602–606.
[67] W. Bonfield, M. Grynpas, A. Tully, J. Bowman, J. Abram, Hydroxyapatite reinforced polyethylene—a mechanically compatible implant material for bone replacement, Biomaterials 2 (1981) 185–186.
[68] M. Hacker, A. Mikos, Synthetic polymers, Foundations of Regenerative Medicine: Clinical and Therapeutic Applications 2009, p. 336.
[69] M.A. Woodruff, D.W. Hutmacher, The return of a forgotten polymer—polycaprolactone in the 21st century, Prog. Polym. Sci. 35 (2010) 1217–1256.

[70] J.-M. Lü, X. Wang, C. Marin-Muller, H. Wang, P.H. Lin, Q. Yao, C. Chen, Current Advances in Research and Clinical Applications of PLGA-based Nanotechnology, 2009.
[71] J. Rich, T. Jaakkola, T. Tirri, T. Närhi, A. Yli-Urpo, J. Seppälä, In vitro evaluation of poly (ε-caprolactone-co-DL-lactide)/bioactive glass composites, Biomaterials 23 (2002) 2143–2150.
[72] A.R. Boccaccini, M. Erol, W.J. Stark, D. Mohn, Z. Hong, J.F. Mano, Polymer/bioactive glass nanocomposites for biomedical applications: a review, Compos. Sci. Technol. 70 (2010) 1764–1776.
[73] H.H. Lu, A. Tang, S.C. Oh, J.P. Spalazzi, K. Dionisio, Compositional effects on the formation of a calcium phosphate layer and the response of osteoblast-like cells on polymer-bioactive glass composites, Biomaterials 26 (2005) 6323–6334.
[74] H.W. Kim, H.H. Lee, G.S. Chun, Bioactivity and osteoblast responses of novel biomedical nanocomposites of bioactive glass nanofiber filled poly (lactic acid), J. Biomed. Mater. Res. A 85 (2008) 651–663.
[75] J. Roether, J. Gough, A.R. Boccaccini, L. Hench, V. Maquet, R. Jérôme, Novel bioresorbable and bioactive composites based on bioactive glass and polylactide foams for bone tissue engineering, J. Mater. Sci. Mater. Med. 13 (2002) 1207–1214.
[76] Q. Chen, A.R. Boccaccini, Coupling mechanical competence and bioresorbability in Bioglass®-derived tissue engineering scaffolds, Adv. Eng. Mater. 8 (2006) 285–289.
[77] M. Mozafari, M. Rabiee, M. Azami, S. Maleknia, Biomimetic formation of apatite on the surface of porous gelatin/bioactive glass nanocomposite scaffolds, Appl. Surf. Sci. 257 (2010) 1740–1749.
[78] D. Nadeem, M. Kiamehr, X. Yang, B. Su, Fabrication and in vitro evaluation of a sponge-like bioactive-glass/gelatin composite scaffold for bone tissue engineering, Mater. Sci. Eng. C 33 (2013) 2669–2678.
[79] M. Peter, N. Binulal, S. Nair, N. Selvamurugan, H. Tamura, R. Jayakumar, Novel biodegradable chitosan–gelatin/nano-bioactive glass ceramic composite scaffolds for alveolar bone tissue engineering, Chem. Eng. J. 158 (2010) 353–361.
[80] V. Cannillo, F. Chiellini, P. Fabbri, A. Sola, Production of Bioglass® 45S5–polycaprolactone composite scaffolds via salt-leaching, Compos. Struct. 92 (2010) 1823–1832.
[81] J. Ródenas-Rochina, J.L.G. Ribelles, M. Lebourg, Comparative study of PCL-HAp and PCL-bioglass composite scaffolds for bone tissue engineering, J. Mater. Sci. Mater. Med. 24 (2013) 1293–1308.
[82] P. Fabbri, V. Cannillo, A. Sola, A. Dorigato, F. Chiellini, Highly porous polycaprolactone-45S5 Bioglass® scaffolds for bone tissue engineering, Compos. Sci. Technol. 70 (2010) 1869–1878.
[83] P.S. Poh, D.W. Hutmacher, M.M. Stevens, M.A. Woodruff, Fabrication and in vitro characterization of bioactive glass composite scaffolds for bone regeneration, Biofabrication 5 (2013) 045005.
[84] L. Ji, W. Wang, D. Jin, S. Zhou, X. Song, In vitro bioactivity and mechanical properties of bioactive glass nanoparticles/polycaprolactone composites, Mater. Sci. Eng. C 46 (2015) 1–9.
[85] J.-H. Jo, E.-J. Lee, D.-S. Shin, H.-E. Kim, H.-W. Kim, Y.-H. Koh, J.-H. Jang, In vitro/in vivo biocompatibility and mechanical properties of bioactive glass nanofiber and poly (ε-caprolactone) composite materials, J. Biomed. Mater. Res. B Appl. Biomater. 91 (2009) 213–220.
[86] H.-H. Lee, H.-S. Yu, J.-H. Jang, H.-W. Kim, Bioactivity improvement of poly (ε-caprolactone) membrane with the addition of nanofibrous bioactive glass, Acta Biomater. 4 (2008) 622–629.
[87] I. Ahmed, A. Parsons, G. Palmer, J. Knowles, G. Walker, C. Rudd, Weight loss, ion release and initial mechanical properties of a binary calcium phosphate glass fibre/PCL composite, Acta Biomater. 4 (2008) 1307–1314.
[88] V. Meretoja, A. Helminen, J. Korventausta, V. Haapa-aho, J. Seppälä, T. Närhi, Crosslinked poly (ε-caprolactone/D, L-lactide)/bioactive glass composite scaffolds for bone tissue engineering, J. Biomed. Mater. Res. A 77 (2006) 261–268.
[89] E. Pamula, J. Kokoszka, K. Cholewa-Kowalska, M. Laczka, L. Kantor, L. Niedzwiedzki, G.C. Reilly, J. Filipowska, W. Madej, M. Kolodziejczyk, Degradation, bioactivity, and osteogenic potential of composites made of PLGA and two different sol–gel bioactive glasses, Ann. Biomed. Eng. 39 (2011) 2114–2129.
[90] V.V. Meretoja, T. Tirri, M. Malin, J.V. Seppälä, T.O. Närhi, Ectopic bone formation in and soft-tissue response to P (CL/DLLA)/bioactive glass composite scaffolds, Clin. Oral Implants Res. 25 (2014) 159–164.
[91] T. Jaakkola, J. Rich, T. Tirri, T. Närhi, M. Jokinen, J. Seppälä, A. Yli-Urpo, In vitro Ca-P precipitation on biodegradable thermoplastic composite of poly(ε-caprolactone-co-DL-lactide) and bioactive glass (S53P4), Biomaterials 25 (2004) 575–581.
[92] S.K. Misra, S.N. Nazhat, S.P. Valappil, M. Moshrefi-Torbati, R.J. Wood, I. Roy, A.R. Boccaccini, Fabrication and characterization of biodegradable poly (3-hydroxybutyrate) composite containing bioglass, Biomacromolecules 8 (2007) 2112–2119.
[93] S.K. Misra, T. Ansari, D. Mohn, S.P. Valappil, T.J. Brunner, W.J. Stark, I. Roy, J.C. Knowles, P.D. Sibbons, E.V. Jones, Effect of nanoparticulate bioactive glass particles on bioactivity and cytocompatibility of poly (3-hydroxybutyrate) composites, J. R. Soc. Interface 7 (2009) 453–467.
[94] S.K. Misra, D. Mohn, T.J. Brunner, W.J. Stark, S.E. Philip, I. Roy, V. Salih, J.C. Knowles, A.R. Boccaccini, Comparison of nanoscale and microscale bioactive glass on the properties of P (3HB)/Bioglass® composites, Biomaterials 29 (2008) 1750–1761.
[95] H. Hajiali, S. Karbasi, M. Hosseinalipour, H.R. Rezaie, Preparation of a novel biodegradable nanocomposite scaffold based on poly (3-hydroxybutyrate)/bioglass nanoparticles for bone tissue engineering, J. Mater. Sci. Mater. Med. 21 (2010) 2125–2132.
[96] J. Olsen-Claire, J.J. Blaker, J.A. Roether, A.R. Boccaccini, G. Schmack, K. Gliesche, Bioglass® coatings on biodegradable poly(3-hydroxybutyrate) (P3HB) meshes for tissue engineering scaffolds, Mater. Werkst. 37 (2006) 577–583.
[97] J.L. Ryszkowska, M. Auguścik, A. Sheikh, A.R. Boccaccini, Biodegradable polyurethane composite scaffolds containing Bioglass® for bone tissue engineering, Compos. Sci. Technol. 70 (2010) 1894–1908.
[98] A.A.R. de Oliveira, S.M. de Carvalho, M. de Fátima Leite, R.L. Oréfice, M. de Magalhães Pereira, Development of biodegradable polyurethane and bioactive glass nanoparticles scaffolds for bone tissue engineering applications, J. Biomed. Mater. Res. B Appl. Biomater. 100 (2012) 1387–1396.
[99] F. Baino, E. Verné, C. Vitale-Brovarone, Feasibility, tailoring and properties of polyurethane/bioactive glass composite scaffolds for tissue engineering, J. Mater. Sci. Mater. Med. 20 (2009) 2189–2195.
[100] M. Bil, J. Ryszkowska, J. Roether, O. Bretcanu, A. Boccaccini, Bioactivity of polyurethane-based scaffolds coated with Bioglass®, Biomed. Mater. 2 (2007) 93.
[101] S.-L. Liang, W.D. Cook, G.A. Thouas, Q.-Z. Chen, The mechanical characteristics and in vitro biocompatibility of poly (glycerol sebacate)-Bioglass® elastomeric composites, Biomaterials 31 (2010) 8516–8529.
[102] Q. Chen, L. Jin, W.D. Cook, D. Mohn, E.L. Lagerqvist, D.A. Elliott, J.M. Haynes, N. Boyd, W.J. Stark, C.W. Pouton, Elastomeric nanocomposites as cell delivery vehicles and cardiac support devices, Soft Matter 6 (2010) 4715–4726.
[103] A. Kramschuster, L.-S. Turng, Fabrication of tissue engineering scaffolds, Handbook of Biopolymers and Biodegradable Plastics: Properties, Processing and Applications 2012, p. 427.
[104] M. Okamoto, B. John, Synthetic biopolymer nanocomposites for tissue engineering scaffolds, Prog. Polym. Sci. 38 (2013) 1487–1503.
[105] Y. Cao, G. Mitchell, A. Messina, L. Price, E. Thompson, A. Penington, W. Morrison, A. O'Connor, G. Stevens, J. Cooper-White, The influence of architecture on degradation and tissue ingrowth into three-dimensional poly (lactic-co-glycolic acid) scaffolds in vitro and in vivo, Biomaterials 27 (2006) 2854–2864.
[106] Y. Kang, J. Yang, S. Khan, L. Anissian, G.A. Ameer, A new biodegradable polyester elastomer for cartilage tissue engineering, J. Biomed. Mater. Res. A 77 (2006) 331–339.
[107] A.R. Boccaccini, I. Notingher, V. Maquet, R. Jérôme, Bioresorbable and bioactive composite materials based on polylactide foams filled with and coated by Bioglass® particles for tissue engineering applications, J. Mater. Sci. Mater. Med. 14 (2003) 443–450.
[108] R. Narayan, Biomedical Materials, Springer, 2009.
[109] S.M. Peltola, F.P. Melchels, D.W. Grijpma, M. Kellomäki, A review of rapid prototyping techniques for tissue engineering purposes, Ann. Med. 40 (2008) 268–280.
[110] M. Liebschner, M. Wettergreen, N. Ashammakhi, P. Ferretti, Optimization of bone scaffold engineering for load bearing applications, Top. Tissue Eng. (2003) 1–39.
[111] B. Subia, J. Kundu, S. Kundu, Biomaterial scaffold fabrication techniques for potential tissue engineering applications, Tissue Eng. (2010) 141–157.
[112] J. Mano, G. Silva, H.S. Azevedo, P. Malafaya, R. Sousa, S. Silva, L. Boesel, J.M. Oliveira, T. Santos, A. Marques, Natural origin biodegradable systems in tissue engineering and regenerative medicine: present status and some moving trends, J. R. Soc. Interface 4 (2007) 999–1030.
[113] D. Puppi, F. Chiellini, A.M. Piras, E. Chiellini, Polymeric materials for bone and cartilage repair, Prog. Polym. Sci. 35 (2010) 403–440.
[114] W.-J. Li, J.A. Cooper Jr., Fibrous scaffolds for tissue engineering, biomaterials for tissue engineering applications: a review of the past and future trends, 2011. 47.
[115] C. Liu, Z. Xia, J. Czernuszka, Design and development of three-dimensional scaffolds for tissue engineering, Chem. Eng. Res. Des. 85 (2007) 1051–1064.
[116] K. Leong, C. Cheah, C. Chua, Solid freeform fabrication of three-dimensional scaffolds for engineering replacement tissues and organs, Biomaterials 24 (2003) 2363–2378.
[117] A.M. El-Kady, E.A. Saad, B.M.A. El-Hady, M.M. Farag, Synthesis of silicate glass/poly (L-lactide) composite scaffolds by freeze-extraction technique: characterization and in vitro bioactivity evaluation, Ceram. Int. 36 (2010) 995–1009.
[118] S.H. Lee, B.S. Kim, S.H. Kim, S.W. Choi, S.I. Jeong, I.K. Kwon, S.W. Kang, J. Nikolovski, D.J. Mooney, Y.K. Han, Elastic biodegradable poly (glycolide-co-caprolactone) scaffold for tissue engineering, J. Biomed. Mater. Res. A 66 (2003) 29–37.
[119] G.W. Selling, The effect of extrusion processing on Zein, Polym. Degrad. Stab. 95 (2010) 2241–2249.
[120] Z. Gan, D. Yu, Z. Zhong, Q. Liang, X. Jing, Enzymatic degradation of poly (ε-caprolactone)/poly (DL-lactide) blends in phosphate buffer solution, Polymer 40 (1999) 2859–2862.
[121] J. Holmbom, A. Södergård, E. Ekholm, M. Märtson, A. Kuusilehto, P. Saukko, R. Penttinen, Long-term evaluation of porous poly (ε-caprolactone-co-L-lactide) as a bone-filling material, J. Biomed. Mater. Res. A 75 (2005) 308–315.
[122] J.J. Blaker, V. Maquet, R. Jérôme, A.R. Boccaccini, S. Nazhat, Mechanical properties of highly porous PDLLA/Bioglass® composite foams as scaffolds for bone tissue engineering, Acta Biomater. 1 (2005) 643–652.
[123] S.K. Misra, S.P. Valappil, I. Roy, A.R. Boccaccini, Polyhydroxyalkanoate (PHA)/inorganic phase composites for tissue engineering applications, Biomacromolecules 7 (2006) 2249–2258.
[124] A. Steinbüchel, Perspectives for biotechnological production and utilization of biopolymers: metabolic engineering of polyhydroxyalkanoate biosynthesis pathways as a successful example, Macromol. Biosci. 1 (2001) 1–24.
[125] I. Engelberg, J. Kohn, Physico-mechanical properties of degradable polymers used in medical applications: a comparative study, Biomaterials 12 (1991) 292–304.
[126] H. Li, R. Du, J. Chang, Fabrication, characterization, and in vitro degradation of composite scaffolds based on PHBV and bioactive glass, J. Biomater. Appl. 20 (2005) 137–155.
[127] J.-Y. Baek, Z.-C. Xing, G. Kwak, K.-B. Yoon, S.-Y. Park, L.S. Park, I.-K. Kang, Fabrication and characterization of collagen-immobilized porous PHBV/HA nanocomposite scaffolds for bone tissue engineering, J. Nanomater. 2012 (2012) 1.
[128] G.T. Howard, Biodegradation of polyurethane: a review, Int. Biodeterior. Biodegrad. 49 (2002) 245–252.
[129] A. Rodríguez-Galán, L. Franco, J. Puiggalí, Biodegradable polyurethanes and poly(ester amide)s, Handbook of Biodegradable Polymers: Isolation, Synthesis, Characterization and Applications 2011, pp. 133–154.

[130] O. Bayer, H. Rinke, W. Siefken, L. Ortner, H. Schild, A process for the production of polyurethanes and polyureas [Verfahren zur Herstellung von Polyurethanen bzw], Polyharnstoffen. German Patent, 728 (1937).
[131] P.A. Gunatillake, D.J. Martin, G.F. Meijs, S.J. McCarthy, R. Adhikari, Designing biostable polyurethane elastomers for biomedical implants, Aust. J. Chem. 56 (2003) 545–557.
[132] A. Asefnejad, M.T. Khorasani, A. Behnamghader, B. Farsadzadeh, S. Bonakdar, Manufacturing of biodegradable polyurethane scaffolds based on polycaprolactone using a phase separation method: physical properties and in vitro assay, Int. J. Nanomedicine 6 (2011) 2375.
[133] S. Gogolewski, A.J. Pennings, An artificial skin based on biodegradable mixtures of polylactides and polyurethanes for full-thickness skin wound covering, Makromol. Chem. Rapid Commun. 4 (1983) 675–680.
[134] C. Alperin, P. Zandstra, K. Woodhouse, Polyurethane films seeded with embryonic stem cell-derived cardiomyocytes for use in cardiac tissue engineering applications, Biomaterials 26 (2005) 7377–7386.
[135] C. Spaans, V. Belgraver, O. Rienstra, J. De Groot, R. Veth, A. Pennings, Solvent-free fabrication of micro-porous polyurethane amide and polyurethane-urea scaffolds for repair and replacement of the knee-joint meniscus, Biomaterials 21 (2000) 2453–2460.
[136] W.N. Sivak, I.F. Pollack, S. Petoud, W.C. Zamboni, J. Zhang, E.J. Beckman, Catalyst-dependent drug loading of LDI–glycerol polyurethane foams leads to differing controlled release profiles, Acta Biomater. 4 (2008) 1263–1274.
[137] J. Yang, A.R. Webb, G.A. Ameer, Novel citric acid-based biodegradable elastomers for tissue engineering, Adv. Mater. 16 (2004) 511–516.
[138] X.-Q. Zhang, H. Tang, R. Hoshi, L. De Laporte, H. Qiu, X. Xu, L.D. Shea, G.A. Ameer, Sustained transgene expression via citric acid-based polyester elastomers, Biomaterials 30 (2009) 2632–2641.
[139] J. Yang, A.R. Webb, S.J. Pickerill, G. Hageman, G.A. Ameer, Synthesis and evaluation of poly (diol citrate) biodegradable elastomers, Biomaterials 27 (2006) 1889–1898.
[140] D.G. Barrett, M.N. Yousaf, Design and applications of biodegradable polyester tissue scaffolds based on endogenous monomers found in human metabolism, Molecules 14 (2009) 4022–4050.
[141] H. Xu, K.T. Nguyen, E.S. Brilakis, J. Yang, E. Fuh, S. Banerjee, Enhanced endothelialization of a new stent polymer through surface enhancement and incorporation of growth factor-delivering microparticles, J. Cardiovasc. Transl. Res. 5 (2012) 519–527.
[142] H. Qiu, J. Yang, P. Kodali, J. Koh, G.A. Ameer, A citric acid-based hydroxyapatite composite for orthopedic implants, Biomaterials 27 (2006) 5845–5854.
[143] E.J. Chung, H. Qiu, P. Kodali, S. Yang, S.M. Sprague, J. Hwong, J. Koh, G.A. Ameer, Early tissue response to citric acid–based micro-and nanocomposites, J. Biomed. Mater. Res. A 96 (2011) 29–37.
[144] E. Zeimaran, S. Pourshahrestani, B. Pingguan-Murphy, N.A. Kadri, H.A. Rothan, R. Yusof, M.R. Towler, I. Djordjevic, Fabrication and characterization of poly (octanediol citrate)/gallium-containing bioglass microcomposite scaffolds, J. Mater. Sci. (2015) 1–13.
[145] D.J. Stuckey, H. Ishii, Q.-Z. Chen, A.R. Boccaccini, U. Hansen, C.A. Carr, J.A. Roether, H. Jawad, D.J. Tyler, N.N. Ali, Magnetic resonance imaging evaluation of remodeling by cardiac elastomeric tissue scaffold biomaterials in a rat model of myocardial infarction, Tissue Eng. A 16 (2010) 3395–3402.
[146] S.-L. Liang, X.-Y. Yang, X.-Y. Fang, W.D. Cook, G.A. Thouas, Q.-Z. Chen, In vitro enzymatic degradation of poly (glycerol sebacate)-based materials, Biomaterials 32 (2011) 8486–8496.
[147] S. Liang, W.D. Cook, Q. Chen, Physical characterization of poly (glycerol sebacate)/Bioglass® composites, Polym. Int. 61 (2012) 17–22.
[148] R. Shogren, E. Bagley, Natural Polymers as Advanced Materials: Some Research Needs and Directions, 1999.
[149] S.-H. Lee, H. Shin, Matrices and scaffolds for delivery of bioactive molecules in bone and cartilage tissue engineering, Adv. Drug Deliv. Rev. 59 (2007) 339–359.
[150] S. Varghese, J.H. Elisseeff, Hydrogels for musculoskeletal tissue engineering, Polymers for Regenerative Medicine, Springer 2006, pp. 95–144.
[151] D. Urry, T. Hugel, M. Seitz, H. Gaub, L. Sheiba, J. Dea, J. Xu, T. Parker, Elastin: a representative ideal protein elastomer, Philos. Trans. R. Soc. Lond. B Biol. Sci. 357 (2002) 169–184.
[152] A. Sionkowska, Current research on the blends of natural and synthetic polymers as new biomaterials: review, Prog. Polym. Sci. 36 (2011) 1254–1276.
[153] S.G. Wise, S.M. Mithieux, A.S. Weiss, Engineered tropoelastin and elastin-based biomaterials, in: M. Alexander (Ed.), Advances in Protein Chemistry and Structural Biology, Academic Press 2009, pp. 1–24.
[154] M.G. Cascone, G. Polacco, L. Lazzeri, N. Barbani, Dextran/poly (acrylic acid) mixtures as miscible blends, J. Appl. Polym. Sci. 66 (1997) 2089–2094.
[155] R.A. Perez, J.-E. Won, J.C. Knowles, H.-W. Kim, Naturally and synthetic smart composite biomaterials for tissue regeneration, Adv. Drug Deliv. Rev. 65 (2013) 471–496.
[156] S. Vieth, C.M. Bellingham, F.W. Keeley, S.M. Hodge, D. Rousseau, Microstructural and tensile properties of elastin-based polypeptides crosslinked with Genipin and pyrroloquinoline quinone, Biopolymers 85 (2007) 199–206.
[157] A. Bigi, G. Cojazzi, S. Panzavolta, K. Rubini, N. Roveri, Mechanical and thermal properties of gelatin films at different degrees of glutaraldehyde crosslinking, Biomaterials 22 (2001) 763–768.
[158] M.G. Haugh, M.J. Jaasma, F.J. O'Brien, The effect of dehydrothermal treatment on the mechanical and structural properties of collagen-GAG scaffolds, J. Biomed. Mater. Res. A 89 (2009) 363–369.
[159] S. Srinivasan, R. Jayasree, K. Chennazhi, S. Nair, R. Jayakumar, Biocompatible alginate/nano bioactive glass ceramic composite scaffolds for periodontal tissue regeneration, Carbohydr. Polym. 87 (2012) 274–283.
[160] M. Vollenweider, T.J. Brunner, S. Knecht, R.N. Grass, M. Zehnder, T. Imfeld, W.J. Stark, Remineralization of human dentin using ultrafine bioactive glass particles, Acta Biomater. 3 (2007) 936–943.
[161] S.G. Caridade, E.G. Merino, N.M. Alves, V.D.Z. Bermudez, A.R. Boccaccini, J.F. Mano, Chitosan membranes containing micro or nano-size bioactive glass particles: evolution of biomineralization followed by in situ dynamic mechanical analysis, J. Mech. Behav. Biomed. Mater. 20 (2013) 173–183.
[162] L.-C. Gerhardt, K.L. Widdows, M.M. Erol, C.W. Burch, J.A. Sanz-Herrera, I. Ochoa, R. Stämpfli, I.S. Roqan, S. Gabe, T. Ansari, The pro-angiogenic properties of multi-functional bioactive glass composite scaffolds, Biomaterials 32 (2011) 4096–4108.
[163] A. Bongso, C.Y. Fong, K. Gauthaman, Taking stem cells to the clinic: major challenges, J. Cell. Biochem. 105 (2008) 1352–1360.
[164] A.J. Engler, S. Sen, H.L. Sweeney, D.E. Discher, Matrix elasticity directs stem cell lineage specification, Cell 126 (2006) 677–689.
[165] G. Rohman, J.J. Pettit, F. Isaure, N.R. Cameron, J. Southgate, Influence of the physical properties of two-dimensional polyester substrates on the growth of normal human urothelial and urinary smooth muscle cells in vitro, Biomaterials 28 (2007) 2264–2274.