



Review

A comprehensive study on the fabrication and properties of biocomposites of poly(lactic acid)/ceramics for bone tissue engineering

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ABSTRACT

The fabrication of a suitable scaffold material is one of the major challenges for bone tissue engineering. Poly(lactic acid) (PLA) is one of the most favorable matrix materials in bone tissue engineering owing to its biocompatibility and biodegradability. However, PLA suffers from some shortcomings including low degradation rate, low cell adhesion caused by its hydrophobic property, and inflammatory reactions *in vivo* due to its degradation product, lactic acid. Therefore, the incorporation of bioactive reinforcements is considered as a powerful method to improve the properties of PLA. This review presents a comprehensive study on recent advances in the synthesis of PLA-based biocomposites containing ceramic reinforcements, including various methods of production and the evaluation of the scaffolds in terms of porosity, mechanical properties, *in vitro* and *in vivo* biocompatibility and bioactivity for bone tissue engineering applications. The production routes range from traditional approaches such as the use of porogens to provide porosity in the scaffolds to novel methods such as solid free-form techniques.

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1. Introduction

The main goal of tissue engineering is the fabrication of functional replacements for impaired organs or tissues. Scaffolds play an important role in providing the necessary support for cells to proliferate and maintain their differential function. Moreover, scaffold architecture defines the ultimate shape of the new bone and cartilage [1]. An ideal scaffold should have four characteristics: (a) three-dimensional and highly porous structure with an interconnected network for cell growth and flow transport of nutrients and metabolic waste (b) biocompatible and bioresorbable with controllable degradation and resorption rate

matching cell/tissue growth *in vitro/in vivo* (c) appropriate surface chemistry for cell attachment, proliferation and differentiation (d) suitable mechanical properties to match those of the tissues at the site of implantation [2–4]. One type of materials which attempt to fulfill many of these requirements are the composites of biodegradable polymers reinforced with bioactive materials. Biocomposites has gained much attention in bone scaffolds because of their composition and structural similarity with natural bone in addition to their distinctive functional properties such as excellent mechanical properties, high surface area, enhanced bioactivity and controlled resorption rates [5–7]. Composite scaffolds can be produced in a variety of forms such as manufacturing a composite material in a porous form, coating a ceramic scaffold with a polymer, and coating a tough polymeric scaffold with a bioactive layer [8]. A range of techniques can be used to develop porous

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Nomenclature

A549	human lung carcinoma cell line
ACP	amorphous calcium phosphate
ADSCs	human adipose-derived stem cells
ALP	alkaline phosphatase
ATDC5	chondrocyte cells
α -TCP	α -tricalcium phosphate
BCP	biphasic calcium phosphate
β -TCP	β -tricalcium phosphate
BG	bioactive glass
BMP-7	bone morphogenetic protein 7
BMSCs	bone marrow stromal cells
BMCs	bone marrow cells
CaP	calcium phosphate
CMP	calcium metaphosphate
CRL-1213	rat skin fibroblasts
CRL-1459	normal human colon fibroblasts
FDA	food and drug administration
HA	hydroxyapatite
hAOB	human adult osteoblast cells
hBMCs	human bone marrow stromal cell
hFOB	human fetal osteoblast cells
hMSCs	human mesenchymal stem cells
HOBs	primary human osteoblasts
HOS-TE85	human osteosarcoma cell line
L929	mouse fibroblasts
MBG	mesoporous bioglass
m-BG	micron-sized Bioglass®
MSCs	mesenchymal stem cells
MC3T3-E1	mouse osteoblastic cell line
MG-63	human osteosarcoma cell lines
n-BG	nano-sized Bioglass®
PCL	polycaprolactone
PG	phosphate-based glass
PGA	polyglycolic acid
PHB	polyhydroxybuterate
PLA	poly(lactic acid)
PDLLA	poly(D,L-lactic acid)
PLLA	poly(L-lactic acid)
PLLA-g-HA	poly(L-lactic acid)-grafted hydroxyapatite
PMMA	poly(α -methacrylic acid)
Saos-2	human osteosarcoma cell line
SBF	simulated body fluid
SFF	solid free-form
TCP	tricalcium phosphate
TIPS	thermally induced phase separation

structure, including electrospinning [9], solvent casting and particular leaching [10], super critical gas foaming [11], emulsion freeze-drying or thermally induced phase separation (TIPS) [12], and solid free-form fabrication (SFF) [13].

The common artificial polymers used include poly(lactic acid) (PLA), polycaprolactone (PCL), polyglycolic acid (PGA), and polyhydroxybuterate (PHB) and several of their co-polymers [14]. PLA belongs to the family of aliphatic polyesters often fabricated from α -hydroxyacids which includes polyglycolic acid or polymandelic acid, and are regarded biodegradable and compostable. PLA is a linear aliphatic thermoplastic, high-modulus, high-strength polymer which can be produced from renewable resources such as sugar, corn, potatoes and cane for use in either industrial packaging field or the bioresorbable/biocompatible medical device market [15–17]. PLA is one of the few synthetic and biodegradable polymers with an extensive FDA

approval history [18,19]. It has interesting physical properties along with biocompatibility, suitable biodegradability and innocuous degradation products [20]. These properties are affected by stereochemical structure which can be tailored by polymerizing a controlled mixture of the L- or D-isomers to obtain high molecular weight amorphous or crystalline polymers [15,21,22]. Poly(L-Lactic acid) (PLLA) is well-known for its excellent mechanical properties among bioabsorbable polymers [23]. PLA, however, suffers from some shortcomings including low cell adhesion caused by its hydrophobic property, and inflammatory reactions *in vivo* due to its degradation product, lactic acid [24]. Moreover, PLA has a low degradation rate of between 10 months and 4 years owing to the hydrophobic methyl group in the backbone. Therefore, the addition of bioactive fillers into PLA matrix can buffer the localized pH decrease due to PLA degradation products, modulate degradation rate, and enhance cell adhesion, mechanical properties and osteoconductivity [25,26].

A bioactive material is defined as a material that undergoes specific surface reactions, when implanted into the body, resulting in the formation of an hydroxyapatite-like layer that is responsible for the formation of a firm bond with hard and soft tissues [27]. Ceramic nanomaterials including hydroxyapatite (HA) and related calcium phosphates (CaP) and bioactive glasses (BG) in particular Bioglass® are the common bioactive fillers used in biocomposites. These nanomaterials are considered bioactive since they bond to bone and improve bone tissue formation [28]. HA ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) has a similar composition with natural bone along with high mechanical strength, osteoinductivity, osteoconductivity and biodegradability. In addition, its medical products such as screws, plates and rods form a strong bond to natural bone *in vivo*. The incorporation of HA can regulate the pH of the biomaterials which prevents the inflammatory reactions and induces the growth of bone [29,30]. Tricalcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$, TCP), another CaP material, is widely used in the medical field instead of HA due to its high dissolution properties [31]. TCP can be classified as α -TCP and β -TCP. α -TCP is more reactive in aqueous systems in comparison with β -TCP, and can be hydrolyzed to HA [18,32]. Although the solubility of TCP materials is much higher than HA, from a crystallographic point of view, HA is more analogous to natural bone tissue apatite than TCP and so it represents a better structural material for bone growth [33]. Biphasic calcium phosphate (BCP), formed by the combination of HA and β -TCP, can be also used as bone substitution material and filler for composite fabrication [31]. Amorphous calcium phosphate (ACP) is another potential CaP candidate for composite reinforcements. ACP has great remineralization ability and high solubility in comparison with other CaP materials, and it plays an important role in the process of tissue mineralization [34].

BG, a system of SiO_2 -CaO-Na₂O-P₂O₅, such as Bioglass® 45S5 has a great ability to bond strongly with hard and soft tissues and to foster the growth of bone cells [35–37]. BG has an amorphous structure and its structure and chemistry can be modified over a wide range by changing glass composition, or thermal or environmental processing history [27, 38]. When implanted into the body, BG undergoes specific reactions, which results in the formation of ACP or crystalline HA phase on the surface of the glass leading to strong bonding with the surrounding tissue, and release ions that activate expression of osteogenic genes [38,39]. The gene regulating effect of the dissolution products of Bioglass® has been confirmed by researchers [32]. The size of the crystals formed on the BG surface is in nanometer scale identical to the crystal phase of bone mineral with an anisotropy mimicking the architecture of mineralized bone [40]. Phosphate-based glass materials (PG), a ternary-based P₂O₅-CaO-Na₂O glass system, also have potential for use as biomaterials since their chemical composition is close to that of natural bone. The use of PG offers a more controlled rate of dissolution in comparison with silica containing glasses. However, simple PGs do not have enough chemical durability for biomedical applications [41,42].

The present study is organized in the following manner: each section provides a comprehensive study on composites of PLA containing either

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