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Review

Biodegradable ceramic-polymer composites for biomedical applications: A review

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ABSTRACT

The present work focuses on the state-of-the-art of biodegradable ceramic-polymer composites with particular emphasis on influence of various types of ceramic fillers on properties of the composites. First, the general needs to create composite materials for medical applications are briefly introduced. Second, various types of polymeric materials used as matrices of ceramic-containing composites and their properties are reviewed. Third, silica nanocomposites and their material as well as biological characteristics are presented. Fourth, different types of glass fillers including silicate, borate and phosphate glasses and their effect on a number of properties of the composites are described. Fifth, wollastonite as a composite modifier and its effect on composite characteristics are discussed. Sixth, composites containing calcium phosphate ceramics, namely hydroxyapatite, tricalcium phosphate and biphasic calcium phosphate are presented. Finally, general possibilities for control of properties of composite materials are highlighted.

Contents

Abbreviations: $ABTS^{\bullet+}$, 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) radical cation; ACP, amorphous calcium phosphate; ALP, alkaline phosphatase; BBG, borate-based glass; BCP, biphasic calcium phosphate; BET SSA, Brunauer-Emmett-Teller specific surface area; BG, bioactive glass/bioglass; BMP-2, bone morphogenetic protein 2; BSP, bone sialoprotein; CAM, cylinder chorioallantoic membrane; CaP, calcium phosphate; CBF-alpha-1, core-binding factor alpha-1; CMC, carboxymethylcellulose; CS, chitosan; DEX, dexamethasone; $DPPH^{\bullet}$, 2,2-diphenyl-1-picrylhydrazyl radical; DSC, differential scanning calorimetry; ECM, extracellular matrix; EDX, energy dispersive X-ray spectroscopy; FN, fibronectin; FTIR, Fourier transform infrared spectroscopy; FTIR-ATR, attenuated total reflectance Fourier transform infrared spectroscopy; gHAp, grafted hydroxyapatite; HAp, hydroxyapatite; hAT-MSCs, human adipose tissue-derived mesenchymal stem cells; hBMSCs, human bone marrow mesenchymal stem cells; HCA, carbonated hydroxyapatite; HOC, human osteoblastic cells; MSCs, mesenchymal stem cells; MSNs, mesoporous silica nanoparticles; mWS, mesoporous wollastonite particles; nHAp, nano-sized hydroxyapatite; NMR, nuclear magnetic resonance; OC, osteocalcin; ON, osteonectin; OPN, osteopontin; Osx, osteoblast-specific transcription factor Osterix; PBG, phosphate glass; PBS, phosphate buffer saline; PBSu, poly(butylene succinate); PCL, poly(ε-caprolactone); PDGF, platelet-derived growth factor; PDLLA, poly(D,L-lactide); PEG, polyethylene glycol; PEI, polyethylenimine; PEO, poly(ethylene oxide); PGA, poly(glycolic acid); PHB, poly(3-hydroxybutyrate); PHBV, poly(3-hydroxybutyrate-co-3-hydroxyvalerate); PIXE, proton-induced X-ray emission; PLA, poly(lactic acid); PLDLA, poly(L-lactide-co-D,L-lactide); PLGA, poly(lactic-co-glycolic acid); PLLA, poly(L-lactide); PRP, platelet-rich plasma; rBMSCs, rat bone marrow mesenchymal stem cells; RT-PCR, reverse transcription polymerase chain reaction; RUNX2, runt related transcription factor 2; SBF, simulated body fluid; SBG, silicate bioactive glass; SCPL, solvent-casting particulate leaching; SF, silk fibroin; TCP, tricalcium phosphate; TGF, transforming growth factor; TIPS, thermally induced phase separation; VEGF, vascular endothelial growth factor; WAXS, wide-angle X-ray scattering; wHAp, hydroxyapatite whiskers; WS, wollastonite; XRD, X-ray diffraction.

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1. Introduction

On account of rapid development of novel biomedical technologies, including tissue engineering, regenerative medicine, gene therapy and controlled drug delivery, new materials are being developed to meet specific requirements of these fields. Conventional single-component ceramic or polymer materials cannot satisfy them. In addition, in order to fully meet the basic requirements such as biocompatibility, biodegradability, appropriate mechanical properties, there is a need to obtain materials fulfilling several advanced functions at once. For example, a multifunctional material for bone tissue regeneration should induce formation of new bone tissue without an addition of organic bone growth factors (e.g. BMP-2), degrade progressively at a rate matching the regeneration of new bone, induce new blood vessels formation and exhibit antibacterial and anti-inflammatory activity. Therefore, key material and biological features can be achieved by design and development of multi-component materials, including selection of matrix and modifier materials, their parameters (e.g. shape, distribution, content), as well as fabrication techniques of composites. In particular, this work deals with the introduction of ceramic modifiers into biodegradable polymer matrices to obtain composites with specific properties for biomedical applications, especially tissue engineering and regenerative medicine. The most widely used ceramic modifiers including bioactive glasses and calcium phosphates, as well as less widespread silica and wollastonite, with focus on their beneficial effects on material and biological properties of the composites will be discussed.

A table placed at the end of the review (Table 3) provides an overview of polymer matrices, ceramic modifiers, methods of fabrication and forms of composites discussed in this work, as well as their physical properties.

2. Biodegradable polymer matrices

Many types of biodegradable polymeric materials have already been used as matrices of ceramic-modified composites for tissue engineering applications. These materials can be classified into two major groups based on their origin, namely natural-based polymers, including proteins (soy, collagen, fibrin gels, silk) or polysaccharides (starch, alginate, chitin/chitosan, hyaluronic acid derivatives) and synthetic polymers, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(ε-caprolactone) (PCL), poly(3-hydroxybutyrate) (PHB) [1–2].

Generally, biodegradation of polymeric biomaterials involves cleavage of enzymatically (natural polymers) or hydrolytically (synthetic polymers) sensitive bonds in the polymer structure leading to the polymer erosion [3]. Naturally-derived polymers possess the ability to biological recognition, including presentation of receptor-binding ligands, that may support cell adhesion, migration, differentiation and proliferation. However, the rate of their in vivo degradation depends on availability and concentration of the enzymes at the site of implantation, therefore it is difficult to predict. The use of natural polymers alone is often restricted because of potential immunogenic reactions, possibility of disease transmission and relatively poor mechanical properties [1–3]. Synthetic polymers have more predictable properties including degradation kinetics that can be controlled by chemical composition and configurational structure, molecular weight, polydispersity, crystallinity, material morphology (e.g. porosity, surface area), chain orientation and overall hydrophilicity [1]. Synthetic polymers possess relatively good mechanical strength and their properties (e.g. porosity, shape) can be tailored for specific applications. However, the surfaces of synthetic polymers are hydrophobic and lacking in cell-recognition sequences [1–2].

In addition to the biodegradability, the composites take advantage of high formability of polymer matrices. Many methods have been developed to fabricate composite materials for biomedical applications, including solvent casting [4–6], tape casting [7], particulate leaching [8], freeze drying [9], phase separation [10], thermal processing [11—12], gas foaming [13], electrospinning [14] and rapid prototyping [15]. These methods allow obtaining the required properties, especially the form and microstructure of the composites.

3. Silica based composites

Reports on silica (silicon dioxide, SiO_2) as a filler or a nanofiller of polymer matrix composites showed many advantages of composite or nanocomposite materials based on biodegradable polymers [16–55]. Silica particles, incorporated into polymer matrices, cause higher biocompatibility and bioactivity of the materials and/or implants. These compositions stimulate biological properties interesting for bone tissue applications, such as given bioresorption rate and porosity, as well as the ability to induce formation of calcium phosphate similar to the one present in bone on biomaterials surfaces, and the introduction of biologically active agents [16–18]. Since silica reinforcements are frequently used in the form of nanoparticles, understanding of mechanisms of dissolution and metabolism of these particles in the organisms have also deserved considerable attention [17]. Nanometric particles of SiO_2 in polyesters provide many advantages compared to other nanofillers and exhibit many properties associated with an ideal material for grafting and scaffolding [19]. Due to silanol groups (Si-OH) present on the surface of silica, covalent bonds can be formed between macromolecular chains and the fillers [20]. During the process of nanocomposite synthesis, silane coupling agents play important roles in connecting the interfaces of organic (polymer chain) and inorganic phases (nanofillers, SiO_2 particles). It is because they can be functionalized at the interface to create a chemical bridge between the reinforcement and the polymer matrix, and thus improve the stability, adhesion and mechanical properties such as strength, Young's modulus or wear resistance of the nanocomposites [21–24].

Some investigations on nuclear magnetic resonance spectra (^{13}C NMR) of nanocomposite materials i.e.; PBSu/SiO_2 (poly(butylene succinate)/SiO_2) confirmed a reaction between the surface silanol groups from SiO_2 nanoparticles with hydroxyl end groups of the polymer (PBSu) leading to formation of covalent bonds [20]. These covalent bonds resulted in a substantial improvement of mechanical properties of PBSu, even in cases where amounts of SiO_2 lower than 2.5 wt.% were used [20,25]. Nano-SiO_2 in different forms i.e.; nanotubes, nanoparticles present in the polymer matrix changes also physicochemical properties of the nanocomposite surface e.g.; some of the hydroxyl groups are exposed on the surface and increase hydrophilic character of the surface of materials. This phenomenon can explain a higher hydrolysis rate of nanocomposites based on biodegradable polymers [26]. A similar accelerating effect of SiO_2 nanoparticles on a PLA hydrolysis rate was reported by many authors [27–30]. They found