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Preparation and characterization of homogeneous chitosan–polylactic acid/hydroxyapatite nanocomposite for bone tissue engineering and evaluation of its mechanical properties

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Abstract

Homogeneous nanocomposites composed of hydroxyapatite and chitosan in the presence of polylactic acid were synthesized by a novel in situ precipitation method. The morphological and compositional properties of composites were investigated. Hydroxyapatite nanoparticles in a special rod-like shape with a diameter of about 50 nm and a length of about 300 nm were distributed homogeneously within the chitosan–polylactic acid matrix. The interaction between the organic matrix and the inorganic crystallite and the formation mechanism of the rod-like nanoparticles were also studied. The results suggested that the formation of the special rod-like nanoparticles could be controlled by a multiple-order template effect. High-resolution images showed that the rod-like inorganic particles were composed of randomly orientated subparticles about 10 nm in diameter. The mechanical properties of the composites were evaluated by measuring their compressive strength and elastic modulus. The data indicated that the addition of polylactic acid can make homogeneous composites scaffold resist significantly higher stress. The elastic modulus of the composites was also improved by the addition of polylactic acid, which can make them more beneficial for surgical applications.
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Keywords: In situ precipitation; Hydroxyapatite; Chitosan; Polylactic acid; Rod-like nanoparticle

1. Introduction

Bone repair or regeneration is a common yet complicated clinical problem in orthopedic surgery. Although autografts and allografts have been widely used in clinical therapy and research, they both have specific problems. Autografts need secondary surgery to procure donor bone from the patient's own body, but the amount of donor bone is limited [1,2]. Allografts bear the risk of infections and immune response [3]. Bone tissue engineering substitutes are another choice for treating bone defects, and have been heralded as an alternative strategy to regenerate bone [4].

The development of biomimetic materials has long been a major goal in the field of bone tissue engineering. Natural bone is a complex inorganic–organic nanocomposite material, in which hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$) nanocrystallites and collagen fibrils are well organized in a hierarchical architecture over several length scales [5,6]. Thus, the main way to get artificial biomaterials [7] as bone substitutes in biomimesis-inspired approaches is to produce nanocrystallites of calcium phosphate (CaP) salts, such as HA, dispersed into polymer matrices.

Natural polymers [8–10] and their derivatives [11] have been increasingly used as an alternative to synthetic poly-

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mers because of their biodegradability and biological activity. Chitosan (CS), a natural biodegradable polymer, is a low acetyl substituted form of chitin. Owing to its unique properties, including biodegradability, nontoxicity, antibacterial effect and biocompatibility, much attention has been paid to CS-based biomedical materials [12–15]. However, the lack of bone-bonding bioactivity, low mechanical strength and loosening of structural integrity under wet conditions limit its use in bone tissue engineering [16–18]. Therefore, it is desirable to develop a composite material with the favorable properties of both CS and HA. The designed composites are expected to show increased osteoconductivity and biodegradation together with sufficient mechanical strength, which will be of great importance for bone remodeling and its growth.

It has been reported that CS/HA composites show good biocompatibility and favorable bonding ability with surrounding host tissues inherent from HA [19,20]. It has also been proved that CS/HA composites can further enhance tissue regenerative efficacy and osteoconductivity [21,22]. The approaches currently used to obtain CS/HA composite materials are based on mechanical mixing [23], co-precipitation [24,25] and an alternate soaking process [26,27]. With all these methods, there is a common disadvantage that inorganic particles cannot be distributed within the organic matrices at the nanolevel; this has led to poor mechanical properties and limited applications. On the other hand, it was found that the higher the HA content in the composite, the more fragile the composite is [28]. The compressive strength of the CS/HA composites with different HA content, ranging from 50 to 80 wt.%, has been investigated and the maximum value of the compressive strength was found to be about 120 MPa, when the CS/HA composite has a weight ratio of 30/70 [29]. To the best of our knowledge, no higher value has been reported so far. A number of other organic compounds have been used in the CS/HA system and have helped to enhance the compressive strength significantly [30–32]. Verma et al. [30] synthesized a CS–polygalacturonic/HA composite with a 50/50 weight ratio; the compressive strength was measured to be about 160 MPa. Wang and Li [32] synthesized a CS–silk fibroin/HA composite with a 30/70 weight ratio, and the compressive strength was measured to be about 180 MPa, which is the highest value reported.

Polylactic acid (PLA) is a nontoxic, biodegradable material with high mechanical strength that is widely used in surgery [33,34]. In order to increase the mechanical strength of CS/HA composite scaffolds, we introduced PLA into the CS/HA system. In our previous work [35,36], we developed a new in situ precipitation method to promote high-affinity nucleation and growth of calcium phosphate in polymer hydrogel. Compared with other methods, the advantage of in situ precipitation is that uniform and nanosized HA particles can be produced and, furthermore, distributed homogeneously within the organic template. In this work, CS–PLA/HA composites were synthesized by the in situ precipitation approach. The compressive strength of the resulting composite and the chemical interaction between the mineral phase and the organic matrix were investigated. This composite, which combines high biocompatibility with high strength, provides a promising scaffold in both traditional bone-defect repair and bone tissue engineering.

2. Materials and methods

2.1. Materials

Chitosan was obtained from Nanxing Co. (Guangdong, China) with an 84% degree of deacetylation. Polylactic acid (M_w 200,000) was provided by the key laboratory of biomedical polymers of the Ministry of Education (Wuhan, China). Calcium nitrate tetrahydrate ($Ca(NO_3)_2{\cdot}4H_2O$), diammonium hydrogen phosphate ($(NH_4)_2HPO_4$), glutaraldehyde, acetic acid, hydrochloric acid, 1,4-dioxane, sodium hypochlorite solution and ammonia were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China) and were all of analytical grade. All chemicals were used as received without any further purification. Deionized ultrapure water was used throughout the experiment.

2.2. Methods

2.2.1. Preparation of composite

2.2.1.1. Synthesis of homogeneous CS–PLA/HA composites by in situ precipitation. Composites of CS–PLA/HA were synthesized by the following procedures. First, CS solution was prepared by dissolving CS in 40 ml of acetic acid solution (2 vol.%) with stirring at room temperature for 24 h to get a perfectly transparent solution. Then $Ca(NO_3)_2{\cdot}4H_2O$ and $(NH_4)_2HPO_4$ (Ca/P = 1.67) were added to the CS solution under agitation until the salts were entirely dissolved. PLA was dissolved in 20 ml of 1,4-dioxane at 40 °C. Upon complete dissolution, PLA solution was dropped slowly into the CS solution of Ca^{2+} and PO_4^{3-} with vigorous stirring at ambient temperature. After the addition, the solution was stirred continually at 85 °C for about 1 h. At this point, most of the 1,4-dioxane had evaporated and a final mixture of homogeneous emulsion was produced. Next, 0.1 ml glutaraldehyde (25 wt.%) was added to the previous mixed solution as a crosslinker. The solution was continually stirred until an opaque hydrogel was produced. The as-synthesized hydrogel was stored under ambient conditions for 24 h to achieve complete crosslinking. It was then kept in ammonia solution for 48 h at 25 °C. Under this alkaline condition, HA precipitated within the hydrogel matrix gradually [35,36]. The in situ precipitation route can be represented by the following chemical reaction:

$$10Ca^{2+} + 6HPO_4^{2-} + 8OH^- = Ca_{10}(PO_4)_6(OH)_2(\downarrow) + 6H_2O \quad (pH > 10)$$

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