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Chemical synthesis of poly(lactic-co-glycolic acid)/hydroxyapatite composites for orthopaedic applications

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Abstract

Hydroxyapatite-biodegradable polymer composites were synthesized by a colloidal non-aqueous chemical precipitation technique at room temperature. The starting materials used for synthesizing hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$) were $Ca(NO_3)_2 \cdot 4H_2O$ and H_3PO_4, resulting in single phase HA while poly(D,L-lactic-co-glycolic acid) (PLGA) was used as the biodegradable polymer component. The composites were prepared containing 10, 20, and 30 wt.% HA in the presence of the dissolved polymer without evidence of any visible phase separation of the particulates from the PLGA polymer. In addition, the pH changes occurring in the solution during precipitation, the yield of the ceramic due to the chemical reaction, bonding characteristics between the ceramic and the polymer, the microstructure, tensile strength, and thermal stability of the composites have been investigated. Additional in vitro studies include osteoblast-like adhesion assessment on composites utilizing MG63 cells. The results of these studies are described and discussed.

Keywords: Hydroxyapatite (HA); PLGA; Biodegradable; Bone tissue engineering; MG63

1. Introduction

Defects resulting in the need for bone grafting, such as bone void fillers in tumor resections or trauma, spinal fusion, and fracture repair, pose significant health problems. In addition, the integrity of our skeletal system is dependent upon maintaining a proper balance between bone resorption and formation [1,2]. With advancing age, this equilibrium resembles more of an imbalance, as bone resorption may exceed bone formation. This in turn may cause a number of bone diseases, with osteoporosis as the most prevalent. Particularly with the increasing aging population, techniques to regenerate and restore bone tissue to its functional state have become a clinical necessity [1,3,4].

Current treatments for bone repair involve the use of donor tissue. However, both autologous and allogenic bone suffer from limitations. The current clinical ''gold standard'', autografting, requires a second surgery site, which is expensive and often associated with donor site morbidity, pain, infection, and hematoma formation. Allografting carries the potential risk of immune rejection, as well as a lessening or even complete loss of bone inductive factors [2,4–7]. By taking advantage of the body's natural regenerative capacity to form bone, tissue engineering has gained increasing support as an alternative to bone grafting.

Using natural bone as an archetype, a vast number of biomaterials have been designed. While less complex, the structures of these synthetic materials are analogous to that of natural bone. Such materials serve as a scaffold for the development of bone tissue by supplying directional and orientational information. The scaffolding material plays a pivotal role in identifying biological alternatives to

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implants because the material must satisfy several requirements in order to provide a suitable environment for bone tissue development. Failure to provide the bone cells with the appropriate structural environment proves to be detrimental to the anchorage-dependent cells [2,6,8–11].

There are numerous properties which any scaffold must possess, making the choice of scaffolding material vital to the success of the technique. Recently, attention has fallen upon composite materials of calcium-phosphate ceramics and biodegradable polymers to provide a mechanically stable, yet degradable environment for the guidance of bone tissue growth [5,7,10,12–15]. Through the combination of the bioceramic with a polymeric material, the brittleness and non-resorbability of the bioceramic is offset, while at the same time the osteoconductivity and mechanical properties of the polymer is improved. In this study, hydroxyapatite (HA) was used as the bioceramic component because of its likeness to the mineral phase of natural bone. The widespread use of poly(D,L-lactic-co-glycolic acid) (PLGA) in tissue engineering applications made the FDA-approved PLGA a logical choice for the polymer component [7–9,11,12,15]. In addition, the rate of degradation of PLGA can be adjusted by altering the ratio of lactic to glycolic acids. This is a desirable characteristic due to the fact that the rate of bone formation is dependent upon both the size and site of the defect.

As previously mentioned, the design of the scaffold material affects the success of cell attachment, proliferation, and ultimately, bone tissue formation. Several different techniques have been employed, such as fiber bonding, solvent casting/particulate leaching, gas foaming, and phase separation/emulsification [11]. However, each of these methods present certain limitations to the synthesis of a biomaterial with requisite structure and mechanical properties akin to trabecular bone. With the goal of creating an ideal scaffold material for bone tissue engineering, our strategy utilizes an innovative chemical synthesis method to synthesize HA in the presence of a solubilized polymer. It is anticipated that this method of fabrication will not only permit the direct control of the crystal structure and grain size of the HA particles [14], but will also provide the ability to incorporate increased amounts of HA into the composite material. The results of such factors are twofold, affecting both the degradation and cellular reaction to the biomaterial. The process of biodegradation is considered to be directly influenced by the crystal structure of the ceramic [15–18]. In order to control the resorbability of the ceramic, it would be advantageous to regulate the grain size of HA. Through the reduction in grain sizes by generating nanostructured morphologies, it would be possible to not only accelerate the resorption but also enhance the cellular interaction of the ceramic [19–21]. Furthermore, because the biological behavior of Ca–P materials can be largely influenced by their respective physiochemical properties, it is logical to suppose that cellular reactions to the biomaterial are influenced by the shape and size of the HA granules. Not only the structure of HA, but also the amount of HA incorporated into the composite can affect the morphology and thus, the attachment of osteoblastic cells to the material surface. Therefore, the ability of the process to incorporate a greater amount of HA into the composite could conceivably increase the osteoconductivity of the scaffold.

Our method seeks to exploit the chemistry of biomimetic materials in an attempt to reproduce, in a synthetic system, aspects of the complex structure of natural bone. Synthesizing HA in the presence of the solubilized PLGA results in a biomaterial with distinct advantages over a similar biomaterial, fabricated via a physical blending approach. Such materials, as examined previously in our laboratory were found to possess mechanical properties ~1/3 those of trabecular bone [7]. This study demonstrated that the interfacial characteristics of the polymer and HA would be important in improving the mechanical properties of the scaffold material. The present paper describes the synthesis and characterization of HA/PLGA composites generated using a novel non-aqueous chemical approach. Such an approach could enhance the interaction between the ceramic and the polymer, thus imparting improved mechanical properties, as well as increased osteogenic response, to the scaffold.

2. Materials and methods

2.1. Chemical synthesis of HA/PLGA composites

Fig. 1 illustrates the procedure used for synthesizing HA/PLGA scaffold material. Using tetrahydrofuran (THF, Acros) as the solvent, the starting materials for synthesizing HA, namely calcium nitrate tetrahydrate ($Ca(NO_3)_2 \cdot 4H_2O$, 99.0%, Aldrich) and phosphoric acid (H_3PO_4: 85 wt.% solution in water, Aldrich) were combined in the desired stoichiometry. 1.0 g THF-soluble poly(D,L-lactic-co-glycolic acid) (Birmingham Polymers, Inc., 85:15 PLGA, i.v. 0.55–0.75), was added to the solution during the formation of the HA. NH_4OH (Assay 28.0–30.0%, Aldrich) was utilized to adjust the pH of the reaction.

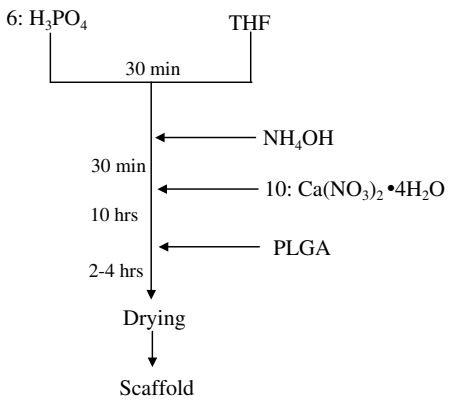

Fig. 1. Schematic diagram of the chemical synthesis procedure.

ID	Title	Pages
2182	Chemical synthesis of poly(lactic-co-glycolic acid)/hydroxyapatite composites for orthopaedic applications	10