



Preparation and characterization of porous calcium-phosphate microspheres

Shih-Ching Wu^{a,b}, Hsueh-Chuan Hsu^{a,b}, Shih-Kuang Hsu^{a,b}, Feng-Wei Lin^c, Wen-Fu Ho^{d,*}

^aDepartment of Dental Technology and Materials Science, Central Taiwan University of Science and Technology, Taiwan, ROC

^bInstitute of Biomedical Engineering and Materials Science, Central Taiwan University of Science and Technology, Taiwan, ROC

^cDepartment of Materials Science and Engineering, Da-Yeh University, Taiwan, ROC

^dDepartment of Chemical and Materials Engineering, National University of Kaohsiung, Kaohsiung, Taiwan, ROC

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Abstract

Porous calcium-phosphate bioceramics are very important materials in bone tissue engineering. Recently, microsphere systems have been widely utilized in the treatment of defective tissues, including bone, cartilage and muscle. In this study, porous calcium-phosphate microspheres were prepared from calcium-deficient hydroxyapatite (d-HA) powders through a water-in-oil emulsion technique using camphene as the porogen and subsequently sintered at 700, 1100, 1200, or 1400 °C for 6 h. The microspheres produced in this study were characterized according to their morphology, properties, and biodegradation. The results indicated an interconnected porous structure with pore sizes ranging between several microns to as large as 250 μm. Approximately 35–50% of the pores were larger than 100 μm. In the microspheres sintered at 700 °C (Sample H), only the hydroxyapatite (HA) phase was present; when heated to 1100 °C (Sample BH), β-TCP was observed with HA; at 1200 °C (Sample ABH), the phase compositions included β-TCP and α-TCP, as well as a small quantity of HA; and at 1400 °C (Sample AH), the phases of samples included mainly α-TCP and HA. The degradation of the scaffolds was evaluated after immersion in distilled water for up to 28 days. Obvious dissolution and precipitation behavior was seen in the samples ABH and AH. The precipitates formed on the surface of ABH and AH could be carbonate-containing calcium-deficient HA (carbonated-CDHA) after immersion in distilled water for 28 days.

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1. Introduction

Bone tissue engineering provides an alternative way to repair diseased or damaged tissue and to recover its original state and function. In the tissue engineering approach, a highly porous artificial material, or scaffold, is employed as a template to facilitate the cell attachment, proliferation, and differentiation. Therefore, these materials must satisfy the requirements of biocompatible, osteoconductivity, controlled degradation, and provide adequate mechanical properties [1]. Owing to its excellent performance as a bone substitute and its potential use as a scaffolding material in bone tissue engineering, osteoinductive calcium phosphate ceramic has attracted much research interest. Porous hydroxyapatite (HA) bioceramics, the main inorganic component of bone, with open

pore structures are of particular interest and importance, since they have excellent permeability and a large surface area, as well as excellent biocompatibility [2].

The degradation behavior of porous scaffolds plays an important role in the process of new tissue growth. The *in vivo* and *in vitro* dissolution of calcium phosphate ceramics was found to be dependent on the composition, crystallinity, and pH of the solution. However, low biodegradability of HA hinders bone ingrowth and results in chemical bonding only at the interface between the bone and the HA implant [3]. This low biodegradability is the drawback of sintered HA ceramics, which limits wide application of HA. β-tricalcium phosphate (β-TCP) is another important calcium phosphate compound used as a bone graft substitute. β-TCP has a higher resorption rate than HA and it is normally considered a biodegradable material that allows bone growth and replacement. The other typical form of TCP is α-tricalcium phosphate (α-TCP). The α-TCP powders are the main component of bioactive pastes

*Corresponding author. Tel.: +886 7 591 6217; fax: +886 7 591 6208.

E-mail address: fujii@nuk.edu.tw (W.-F. Ho).

used as bone fillers called calcium phosphate cement [4]. The solubility of α -TCP is higher than that of β -TCP, which leads to a higher rate of degradation [5].

In recent years, biphasic calcium phosphate ceramics consisting of HA/ β -TCP or HA/ α -TCP have been evaluated in both osseous and nonosseous tissues [6]. The biphasic ceramics are used in combination to stimulate osteogenic activity and resorbability during continuous remodeling [7]. A previous study demonstrated that HA ceramics containing TCP induced better osseointegration than pure HA ceramic when implanted into sheep femora [8]. Biphasic HA/TCP composite powders are commonly produced as by-products during the synthesis of pure HA or pure TCP. Also, biphasic powders can be prepared either by mechanical mixing of HA and TCP powders or by calcining the calcium-deficient HA (d-HA) above 700 °C [9,10]. The crystalline structure of d-HA is the same as stoichiometric hydroxyapatite (s-HA) at room temperature [11]; however, d-HA decomposes into TCP and s-HA when heated [12]. The use of various sintering regimes can change the microstructure/phase of d-HA, while the use of high sintering temperatures can lead to phase changes resulting in various phase compositions (e.g. biphasic or triphasic calcium phosphate).

Microsphere systems have a variety of applications in biomedical fields, including vehicles for drug delivery and direct filling materials for tissue augmentation [13,14]. The granular form of bioceramics, such as calcium phosphates and bioactive glasses, have been widely used in the filling and regeneration of damaged bone tissues in the alveolar ridge, periodontal pocket, and maxillo-facial surgery [15]. From the macroscopic viewpoint, the microspheres could better perform their role as cell carriers when designed to be macroporous, in order to facilitate vascularization, nutrient supply, and to populate and deliver as many cells as possible, as in the case of porous scaffolds [15]. Of special note, unlike porous scaffolds in a block type, the microspherical form can be effectively used as an injectable system for minimally invasive surgery [16]. Recently, Yang et al. [17] prepared spherical HA granules with interconnected pore channels using camphene emulsion. The dissolution behavior of the granules was considered to be an important factor for drug delivery applications. However, Yang et al. fabricated phase-pure HA granules without containing more-soluble phases such as β -TCP or α -TCP. Therefore, more experiments and degradation assessments need to be carried out.

In the present study, porous microspheres were fabricated using a water-in-oil emulsion technique and four types of calcium-phosphate ceramics (HA, β -TCP/HA, α -TCP/ β -TCP/HA, and α -TCP/HA) were synthesized through a tailored sintering schedule. Camphene is non-toxic and thus has been used as a source for fragrance, and has recently been studied in the processing of ceramic scaffolds such as alumina and HA [18,19]. Camphene has the intriguing properties of a solidification temperature around 40 °C and an excessively high vapor pressure, thus it easily sublimates under ambient conditions [18]. Thus, pore generation occurred effortlessly due to that camphene easily sublimates under ambient conditions. In the current study, d-HA powders were combined with the binder of a PVA solution and then mixed with camphene as the porogen. The mechanical properties of these

porous calcium-phosphate microspheres were assessed using compression tests. Degradation of the microspheres and changes in surface morphology were examined after being soaked in distilled water for various periods of time.

2. Materials and methods

2.1. Materials and microsphere fabrication

d-HA (Shimakyu's Pure Chemicals Co., Osaka, Japan) was used as the base materials for the elaboration of the porous ceramic microspheres. The original powder (d-HA with an atomic ratio of Ca/P=1.5) was analyzed using differential thermal analysis (DTA; Q600 SDT, TA Inc., US) at a heating rate of 5 °C/min to determine the phase transition temperature. The DTA results provided the guiding parameters for sintering schemes required to produce a variety of phase compositions.

In the present study, four types of calcium-phosphate porous microspheres (HA, β -TCP/HA, α -TCP/ β -TCP/HA, and α -TCP/HA) were synthesized using a water-in-oil emulsion technique, to achieve mechanically stable porous microspheres through a tailored sintering schedule. The precursor solutions were prepared as follows. At first, d-HA powders (particle size < 75 μ m) were mixed with commercial camphene (C₁₀H₁₆, Nan Chung Chemical Co., Ltd., Taiwan), and the weight ratios of camphene to d-HA powders (C/H) were 2:1, 4:1, 8:1, and 10:1. The camphene was used without further purification as the porogen, and the particle size was less than 550 μ m. Porosity and pore size are easily changeable by porogen size and loading amount. Next, 0.2 g of gelatin was added into 1.8 ml of deionized water under vigorous stirring, and then mixed with the above-mentioned d-HA/camphene, and 2 ml of a polyvinyl alcohol solution (1% by weight) was added and mixed homogeneously.

Water-in-oil emulsions, with the above-mentioned precursor solution as the water phase and 60 ml of vegetable oil as the oil phase, were prepared. Then, the precursor solution was added into the vegetable oil at 83 °C. Finally, the mixed solutions were emulsified for 10 min under magnetic stirring at 550 rpm. The mixture solution became solid rapidly on dropping into a cool bath at about 4 °C, and after the solidification, the solution was further stirred at 600 rpm for additional 6 h in order to harden the microspheres and to induce pore channels. The hardened porous microspheres were ultrasonically cleaned in absolute alcohol for 10 min thrice. The obtained microspheres were dried for 24 h at 45 °C for further characterization and use. The yield of the granule production was about 81%. The dried granulates were sieved to obtain a yield of 61% of particles having a size from 0.5 mm to 1.6 mm in diameter. The as-prepared microspheres were then sintered at 700, 1100, 1200, and 1400 °C for 6 h at a heating rate of 10 °C/min, and Table 1 lists the specimen codes.

2.2. Characterization of microspheres

The apparent density was calculated for each specimen from the dry weight and volume of each sintered specimen. The porosity was then calculated by the following equation:

$$\text{Porosity} = (1 - \text{Apparent density}/\rho) \times 100\%$$

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