Materials Science and Engineering C 42 (2014) 562–568

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Fabrication of dispersible calcium phosphate nanocrystals via a modified Pechini method under non-stoichiometric conditions

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ARTICLE INFO

Article history:
Received 28 March 2014
Received in revised form 19 May 2014
Accepted 30 May 2014
Available online 6 June 2014

Keywords:
Calcium phosphate
Nanoparticle
Nanocrystal
Dispersible
Pechini method

ABSTRACT

Various techniques for preparing ceramic nanoparticles have been developed; however, most of them start from a preparation of precursor nanoparticles that are generally amorphous or in poorly crystallized phases. Thermal treatments used to obtain crystalline phases typically result in the sintering of the products into large polycrystals. In this study, we developed a process to fabricate dispersible hydroxyapatite (HAp; $Ca_{10}(PO_4)_6(OH)_2$) nanocrystals via a modified Pechini method, which is a sol–gel like solid-state synthesis method for the preparation of multicomponent oxides. We demonstrated that the HAp nanocrystals sintered into large polycrystals ranging in size from several tens to several hundreds of microns via a conventional Pechini method using the stoichiometric Ca/P molar ratio of 1.67. When the Ca/P molar ratio in the precursor was >1.67, a mixture of HAp nanocrystals and removable CaO matrix was obtained. The HAp nanocrystals were dispersed in aqueous media mostly in the form of nanoparticles when the amount of CaO matrix was sufficiently greater than the amount of HAp.

1. Introduction

Various chemical synthesis techniques for preparing nanoscale ceramics have been proposed and developed over the last few decades. Usually, these techniques begin from a precursor solution, in which component ions are well-mixed at the molecular scale; solid precursor nanoparticles are then prepared using co-precipitation, the sol–gel method, or spray roasting [1–4]. The solid precursor nanoparticles are typically amorphous or in poorly crystallized phases; they are therefore thermally treated to induce the decomposition and chemical reaction in order to produce the desired crystalline phase. However, the precursor nanoparticles typically sinter into large polycrystals [5–9]; thus, the nanoscale ceramic crystals dispersed in liquid media are difficult to obtain via conventional solid-state thermal treatments.

Hydroxyapatite (HAp; $Ca_{10}(PO_4)_6(OH)_2$; stoichiometric Ca/P molar ratio of 1.67) is a bioceramic material, which exhibits excellent cell adhesion [10] because of its favorable adsorption capacity for bioactive substances such as cell-adhesive proteins [11]. Therefore, HAp and its composites with polymers or metals are widely used in orthopedic and dental applications [12]. The nanoparticulate form of HAp has also gained popularity as filler material in cell scaffolds [12,13], drug/gene carrier [14,15], coating agent for medical polymers [16,17], and Pickering-type emulsion stabilizer [18,19]. However, when low-crystallinity HAp nanoparticles are calcined to increase their thermal and chemical stabilities, the HAp nanoparticles also sinter into large agglomerates consisting of polycrystals [20–22].

In 2003, Peña and Vallet-Regí [23] proposed the Pechini method—a sol–gel like solid-state synthesis method for the preparation of multicomponent oxides from homogeneously mixed ion components [24]—in order to prepare HAp, tricalcium phosphate (TCP; $Ca_3(PO_4)_2$; stoichiometric Ca/P molar ratio of 1.50), and biphasic calcium phosphate (HAp/TCP) by using different initial Ca/P molar ratios ranging from 1.50 to 1.67. The Pechini method starts from the preparation of a homogenous aqueous solution comprising metallic salts and a carboxylic acid such as citrate; the solution is heated to evaporate water after the addition of a diol that increases the solution viscosity because of the formation of three-dimensional polyesters. The polymer–ion complex resin, in which the homogeneity of the ion components is retained after the removal of water, is then thermally treated to decompose the resin matrix in order to produce the desired crystalline phase with a precise homogeneity in both the composition and particle size.

Here, we report a modified Pechini method that involves an initial Ca/P molar >1.67 for the fabrication of dispersible HAp nanocrystals. We hypothesized the following: (1) the excess amount of calcium ions in the case of the initial Ca/P molar ratio that is >1.67 leads to the formation of a mixture comprising HAp and CaO; (2) individually separated HAp nanocrystals can be formed in a CaO matrix when the amount of CaO formed is sufficiently greater than the amount of HAp;

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http://dx.doi.org/10.1016/j.msec.2014.05.071
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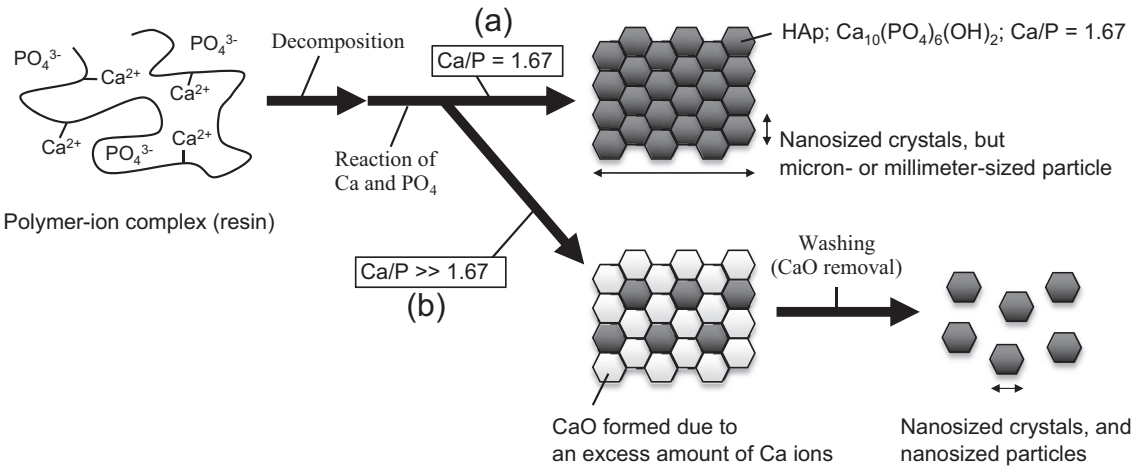

Fig. 1. Schematic models for (a) the formation of micron- or millimeter-sized HAp via the sintering of nanocrystals and (b) the fabrication of HAp nanocrystals in the form of nanoparticles via a polymer–ion complex (Pechini route) in a reaction where the Ca/P ratio is greater than the stoichiometric value for HAp (1.67).

and (3) highly dispersible HAp nanocrystals can be obtained after the CaO matrix is removed (Fig. 1).

2. Experimental section

2.1. Materials

Unless stated otherwise, all materials were of reagent grade and used as received from Wako Pure Chemical Industries, Ltd., Osaka, Japan. Milli-Q water (Millipore Corp., Bedford, MA) with a specific resistance of $18.2 \times 10^6\ \Omega \cdot cm$ was used.

2.2. Fabrication via Peña's Pechini route (condition I)

The metallic salts ($CaNO_3 \cdot 4H_2O$ and $NH_4H_2PO_4$) were dissolved in a 0.2 M citric acid (CA) aqueous solution, and ethylene glycol (EG) (at a 1:1 molar ratio with CA) was subsequently added to the solution at room temperature (~20 °C). The quantities employed to prepare different compositions are detailed in Table 1. After each solute was dissolved, the volume of the solution was reduced by slow heating on a hot plate at a solution temperature of 80 °C. The resulting yellowish resin was placed in air on an alumina crucible in a horizontal furnace at room temperature, thermally treated at 1000 °C (heating rate: 10 °C/min) for 1 h, and then naturally cooled in the furnace to room temperature. The resulting white sponge was washed centrifugally with 600 mM NH_4NO_3 aqueous solution until the pH of the aqueous medium decreased to ~7.0; the resulting white dispersion was then washed with pure water three times, and then re-dispersed in a water medium.

2.3. Fabrication via modified Pechini route (condition II)

In this condition, poly(acrylic acid) (PAA; weight-average molecular weight: 25,000) was used as a resin component instead of the EG–CA resin, and the effects of preparation parameters (shown in Table 1) were investigated in more detail. The resultant transparent resin obtained after the evaporation of PAA–$(CH_3COO)_2Ca$–$(NH_4)_2HPO_4$ aqueous solution that was prepared in the same manner as previously described was thermally treated and then washed with aqueous media in the same manner.

Table 1
Quantities of reagents used to prepare samples and the characteristics of the resultant powder samples.

		Condition I		Condition II			
Initial Ca/P molar ratio		1.67	5.00	1.67	3.34	6.68	13.36
Expected CaO/HAp weight ratio[a]		0	1.12	0	0.56	1.68	3.91
(Expected HAp wt.% in the HAp/CaO mixture)		(100)	(47.3)	(100)	(64.1)	(37.4)	(20.4)
$Ca(NO_3)_2 \cdot 4H_2O$	(g)	11.81	11.81	–	–	–	–
$(CH_3COO)_2Ca \cdot H_2O$	(g)	–	–	2.67	2.67	2.67	2.67
$NH_4H_2PO_4$	(g)	3.45	1.15	–	–	–	–
$(NH_4)_2HPO_4$	(g)	–	–	1.20	0.60	0.30	0.15
Citric acid monohydrate	(g)	21.00	21.00	–	–	–	–
Ethylene glycol	(g)	6.20	6.20	–	–	–	–
Poly(acrylic acid)[b]	(g)	–	–	6.00	6.00	6.00	6.00
NH_3 *aq.*[c]	(mL)	–	–	5	5	5	5
Water	(mL)	150	150	150	150	150	150
Resultant HAp wt.%[d]		–	35.8	98.3	62.1	24.9	12.5
Crystal size[e]	(nm)	–	–	168 ± 37	121 ± 48	76 ± 23	71 ± 31
Particle size[f]	(nm)	–	–	23,188	3495	84	70

[a] Calculated from the initial Ca/P molar ratio under the assumption that only stoichiometric HAp and CaO were formed.
[b] Molecular weight: 25,000.
[c] 28% solution.
[d] Determined from the XRD peak intensity ratio of CaO(200) and HAp(310) reflections.
[e] Number-averaged size ± standard deviation, determined from SEM images (N = 50).
[f] Number-averaged size, as measured in aqueous media with a laser-diffraction particle size analyzer (see Fig. 7).