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Mechanochemical–hydrothermal preparation of nano-crystallite hydroxyapatite using statistical design

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ABSTRACT

Hydroxyapatite (HA) is extensively used in medicine as an ideal substitute for bone. Mean particle size, particle size distribution critically influence the hardness of HA and its mechanical properties. Statistical design was used to determine the optimum conditions of HA preparation by mechanochemical–hydrothermal procedure in MICROS mill for varying times, speed of milling as well as the quantity of surfactant. The produced powder was subjected to X-ray diffraction to analyse its crystallinity, phases, and crystal size calculations using Scherrer's equation. Reaction and milling time seems to be the most significant factor in determining particle size, the longer the reaction and milling time the smaller the crystal size with crystallite sizes ranged from 5.55 to 23.9 nm.

1. Introduction

Hydroxyapatite (HA) is a calcium phosphate compound $\{Ca_{10}(PO_4)_6(OH)_2\}$ that is frequently used as a bone graft material substitute due to its biocompatibility with bone [1] and its higher strength compared to other calcium phosphate compounds [2]. It has several applications in the medicine and dentistry fields, including substitution by the fully dense sintered material or it acts as a coating to other bioinert metallic implants [3]. In the latter case it promotes the adhesion between prostheses and bone [4]. HA general uses include biocompatible phase, reinforcement in composites, coatings on metal implants as well as granular filler for direct incorporation into human tissues [5–7]. Improving of HA mechanical properties is essential for its usage as bone graft replacement. In this regard, method of preparation and applied conditions have significant effect on HA properties.

Hydroxyapatite can be prepared using different methods such as hydrothermal method [8,9], solid-state reaction [10], precipitation [11,12], sol–gel [13,14], sputtering [15], mechanochemical [16], mechanochemical–hydrothermal [5,17], microemulsion [18] and others.

As proposed by Suchcanek et al. [5], synthesis of HA via the mechanochemical–hydrothermal method, using a zirconium ring mill, provides advantages in comparison to mechanochemical and hydrothermal processes. It poses more convenient method for synthesis than hydrothermal method because it has no need for high temperatures when forming the HA powder, thus lowering energy costs [5]. It is also more convenient than mechanochemical procedure since mechanochemical–hydrothermal method presents an aqueous phase that is not available in the mechanochemical method. This aqueous phase can accelerate kinetic processes that commonly limit the rate of reaction, such as dissolution, diffusion, adsorption, reaction, and crystallization [5]. The mechanochemical-hydrothermal method also offers variability in particle size by changing the controlled variables such as, milling time, speed, and amount of reactants.

Various research works used different conditions of preparation of HA nano-particles. Suchcanek et al. [5] milled the slurry at a rotation speed of 1500 rpm for 1 h and then at 800 rpm for 4 h at room temperature for preparation of carbonated HAp powders in the range of 0.35–1.6 μm with a specific surface area between 82 and 121 $m^2\,g^{-1}$. Scanning and transmission electron microscopy confirmed that the produced powders consisted of mostly submicron aggregates of nanosized, about 20 nm crystals. In addition, Nakamura et al. [17] milled a mixture comprising of $Ca(OH)_2$, an aqueous solution of H_3PO_4 and a dispersant, an ammonium salt of polyacrylic acid at 1250 rpm for 3 h. The average crystallite size of prepared HAp was below 20 nm.

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Table 1
Experimental Box–Behnken design with three levels and three variables utilized in the experiment

Run no.	Coded factor levels		
	Reaction and milling time	Milling speed	Surfactant
1	−1	−1	0
2	−1	+1	0
3	+1	−1	0
4	+1	+1	0
5	−1	0	−1
6	−1	0	+1
7	+1	0	−1
8	+1	0	+1
9	0	−1	−1
10	0	−1	+1
11	0	+1	−1
12	0	+1	+1
13	0	0	0
14	0	0	0
15	0	0	0

Variables	Levels		
	0	+1	−1
Milling speed (rpm)	2000	1000	1500
Milling time (h)	3	5	1
Surfactant (ppm)	100	0	50

2. Experimental

2.1. Materials

Calcium hydroxide powder ($Ca(OH)_2$), and solid diammonium hydrogen phosphate ($(NH_4)_2HPO_4$) (all analytical grade, Alfa Aesar, Ward Hill, MA) were used as reactants for synthesis of Hap.

2.2. Methods

HA was prepared using the mechanochemical–hydrothermal method according to the following chemical equation:

$$6(NH_4)_2HPO_4 + 10Ca(OH)_2 \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 12NH_4OH + 6H_2O \quad (1)$$

Ca/P ratio of 1.667 is kept constant so 5 M $Ca(OH)_2$ and 3 M $(NH_4)_2HPO_4$ are used. All the chemicals used are analytical grade from Fisher Scientific. 25 g of $Ca(OH)_2$ were added to 350 ml of de-ionized water. Then 26.756 g of $(NH_4)_2HPO_4$ were added gradually while magnetic stirring. The slurry was mixed for 1 h then it was transferred to MICROS reactor.

15 runs were carried out applying Experimental Box–Behnken Design with the three levels and three variables utilized in the experiment (Table 1). Each run was done independently while the amount of surfactant varied according to the design. Runs without surfactant, volume of de-ionized water was 350 ml. In the 50 ppm surfactant runs, volume of de-ionized water was 340 ml and mixed with 10 ml of Aminotris (methylenephosphonic acid) $[N(CH_2PO_3H_2)_3]$ surfactant from Pfaltz & Bauer Incorporation (NTMP) 0.18%. Also, in the 100 ppm surfactant runs, volume of de-ionized water was 330 ml and mixed with 20 ml of NTMP surfactant 0.18%.

The samples were reacted and milled using the MICROS MIC-O (NARA Machinery Co., Tokyo, Japan) laboratory-scale fine particle grinder under the specified conditions (Fig. 1).

The mill is a multi-ring media mill with a grinding mechanism that consists of a central rotating stainless-steel shaft that rotates other six sub-shafts that are sleeve lined with zirconia-toughened alumina [5]. The sub-shafts are connected symmetrically to the central shaft and contained 19 stacked zirconia rings that rotate eccentrically around each sub-shaft [5]. Rotation of the central shaft would cause the zirconia rings on the sub-shaft to rotate due to the centrifugal force acting on them [5]. This causes grinding of particles that are located between the rings. The mill has controllable speed rpm and can be time programmed.

After reaction and milling, the sample was poured into eight 50 ml centrifuge tubes to be centrifuged (Induction Drive Centrifuge, Model J2-21M, Beckman Instruments, Fullerton CA) at 15,000 rpm for 30 min. Measuring pH of the separated liquid was conducted and found to be in the range from 11.0 to 11.3. The solid precipitate particles were mixed six times with de-ionized water (Barnstead Nanopure Infinity distiller) and then were centrifuged at 2000 rpm for 10 min (the liquid phase appears clear). The pH of sixth wash liquor was measured and found to be in the range 9.2–9.8.

2.3. Characterization of the materials

X-ray crystallography (Phillips APD 3720, Cu Kα radiation) analysis was conducted for all prepared samples. Crystallite size (L_C) measurements included in this study were obtained by X-ray crystallography data and calculated with Scherrer's equation [16]:

$$L_C = \frac{k\lambda}{\beta \cos\theta} \quad (2)$$

where k is the shape coefficient (value between 0.9 and 1.0), λ is the wave length (1.54 A°), β is the full width at half maximum of each phase and θ is the diffraction angle [16].

2.4. Statistical analysis

A statistical design, Box–Behnken design [19], was used to study the effect of studied variables on the mean diameter of the produced hydroxyapatite particles. The design-matrix of different runs, 15 experiments, are shown in Table 1.

According to this design, the optimal conditions were estimated using a second-order polynomial function by which a correlation between studied factors and response (mean diameter) was generated. The general form of this equation is

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{33} X_3^2$$

where Y is the predicted response, X_1, X_2 and X_3 are studied variables; β_i are equation constant and coefficients. Software package, Design-Expert 6.1, Stat-Ease, Inc., MN, USA, was used for regression analysis of experimental data and to plot response

Fig. 1. MICROS MIC-O fine particle grinder and its interior part.