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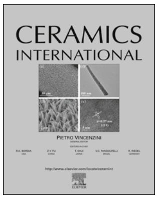

Calcium phosphate cements based on alpha-tricalcium phosphate obtained by wet method: Synthesis and milling effects

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ABSTRACT

Calcium phosphate cements present many advantages for their use as bone substitute, among which biocompatibility and bioactivity. However, these cements generally have low mechanical strength compared to the bones of human body. This work aims to develop a method to produce calcium phosphate cements based on alpha-tricalcium phosphate and to evaluate the influence of milling time (0–16 h) on their particle size and mechanical properties. The obtained powder was characterized by particle size analysis and X-ray diffraction. The proposed method allowed to obtain highly pure alpha-tricalcium phosphate. The milling resulted in different average particle size, showing a decrease of around 83% with 16 h of milling. Specimens were prepared and evaluated by apparent density, microstructure by scanning electron microscopy and compressive strength. The variation of the average particle size influenced the compressive strength whose best result was obtained for the sample without additional milling.

1. Introduction

Advances in many specialty bioceramics such as alumina, zirconia, hydroxyapatite, tricalcium phosphates and bioactive glasses have made important contributions to improving the quality of human life and to the development of the modern healthcare industry. These ceramics can be used inside the body without any inflammatory reaction, and to augment or replace various diseased or damaged parts of the musculoskeletal system [1]. They present biocompatibility, low density, chemical stability, high wear resistance, and for calcium phosphates, due to their compositional similarity to the mineral phase of bone, they are chiefly used as bone substitutes in the biomedical industry.

However, the use of any ceramic material as an implant in vivo depends upon its ability to withstand stresses at the site of application and its compatibility with the biological environment. Calcium phosphates are the chosen materials in both dentistry and medicine. They have been used in biomedical engineering and in clinical usage extensively, due to the range of properties they offer, such as tricalcium phosphate being resorbable and hydroxyapatite being bioactive [1–3]. They exhibit considerably improved biological affinity and activity compared to other bioceramics.

There are many systems of calcium phosphate cements (CFC) that have been studied; however, those based on α-tricalcium phosphate (α-TCP) are of particular interest due to the formation, during the setting reaction, of calcium deficient hydroxyapatite, similar to bone hydroxyapatite. This material, known as α-TCP bone cement, shows chemical and morphological similarities between the biomaterial and the mineral part of bone tissues, enabling osteoconduction to take place [4]. After some time, new bone tissue replaces the cement, preventing complications such as inflammatory processes or foreign body reactions. This material also establishes links of a chemical nature between hydroxyapatite and the bone (i.e. bioactivity), promoting bone growth where implanted and the proliferation of fibroblasts, osteoblasts and other bone cells [5–7]. It has been reported that α-TCP is a metastable phase and can only be obtained by rapid cooling after attaining a temperature above 1200 °C for several hours [8].

α-tricalcium phosphate is commonly produced by thermal transition of a precursor with Ca/P ratio ≈ 1.5 [9–11] or by solid state reaction of a mixture of solid precursors [12–15]. The preparation of alpha-tricalcium phosphate by solid state reaction was also developed by our research group [16–18]. However, it is important to find new alternative routes of synthesis aiming at developing of new methodologies in order to synthesize materials with improved properties and/or lower cost. Recently, Kolmas et al. [19] produced α-tricalcium phosphate by a wet chemical method, just as we do here. However, different to our research, the authors used $Ca(OH)_2$ and H_3PO_4 as reagents and thus obtained a powder that is not a monophasic, presenting an additional amorphous phase. According to these authors, by crushing this sample in a rotary-vibratory mill followed by two-stage heat

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treatment at 800 °C and 1300 °C, it was possible to obtain reflections with a width similar to commercial pure α-TCP.

Generally, by milling the solid phase in wet or dry conditions, it is possible to modify the particle size and hence the specific surface area of cement reactants and to control the mechanical properties of cement. By prolonged milling, crystalline salts can become amorphous [20], hence increasing both the kinetic and thermodynamic solubility of the material rendering the powder more reactive [20–22]. Alpha-tricalcium phosphate (α-TCP) is widely used in tissue engineering for the regeneration of bone tissue, due to its biocompatibility and biodegradability [23,24]. However, the low mechanical resistance of α-TCP still restricts clinical application.

In this paper, we evaluate three different conditions to synthesize alpha-tricalcium phosphate powders by a wet precipitation process, two of them not previously reported in the literature, and also test the obtained and milled powder as calcium phosphate cement. Previous studies was conducted using different reagents concentration and different calcination temperature [25,26]. Therefore, this work aims to complement previous work in order to consolidate the best methodology to obtain alpha-tricalcium phosphate with high purity by wet precipitation process. The wet process was selected according to the reagents used, calcium nitrate and phosphoric acid, with Mg in trace quantities. The presence of magnesium has been reported to stabilizing beta-TCP phase [15,27,28], which does not react with water, reducing the mechanical properties of the cement. Thus, the absence of β-TCP should have the advantage of discarding the need for prolonged residence time at high temperatures of calcination and the use of quenching to obtain pure alpha-TCP phase, as typically described in the literature [11,14,27]. This study also describes the milling influence of α-TCP on the particle size and mechanical properties of calcium phosphate cements. In order to prepare calcium phosphate cement, the powders were mixed with an accelerator in an aqueous solution, for making specimens. The specimens were soaked in SBF (Simulated Body Fluid) for seven days before assessing the mechanical properties.

2. Experimental procedure

This work is divided into two parts. First, we evaluate the synthesis method that allowed us to obtain the α-TCP; then we examine the milling time effect for the properties of the cement.

2.1. Alpha-TCP synthesis

Calcium nitrate ($Ca(NO_3)_2 \cdot 4H_2O$) (Sigma-Aldrich, Germany) and phosphoric acid (H_3PO_4) (Dinâmica, Brazil), were used as reagents to obtain tricalcium phosphate powders, according to the following reaction:

$$9\ Ca(NO_3)_2 \cdot 4H_2O + 6H_3PO_4 \rightarrow 3\ Ca_3(PO_4)_2 + 36H_2O + 18\ HNO_3$$

In this stage we evaluated the influence of the addition order of the reagents and the calcination temperature in the obtained powder. The methodology, temperature and nomenclature adopted are shown in Table 1. The reagent concentration was maintained at 0.5 M. The powders were synthesized by wet reaction and the Ca/P ratio was maintained in 1.5.

The initial pH of the solutions was about 2.0. Thus, method 2 evaluated the influence of a pH correction to 4.0, thus seeking to prevent the formation of hydroxyapatite. According to Ferreira et al. [29] in experiments performed in pH values greater than 4.2, it is expected that the precipitated phase is hydroxyapatite.

The solutions obtained by mixing the reagents were maintained at a temperature of 90 ± 2 °C for 24 h. After this period, the solution was dried at 120 ± 2 °C for 24 h and then calcined at different temperatures for 1 h, according to Table 1. After the calcination, the reaction product was crushed using a pestle and mortar to obtain a fine powder, which was sieved using a # 325 sieve (< 45 μm).

Was also evaluated the influence of the concentration of the reagents in obtaining the α-TCP, using method 1. Thus, the concentration of the reagents was increased to 2.0 M, in order to obtain higher yield reaction. The selected calcination temperature was 1500 °C.

2.2. Milling time influence on calcium phosphate cement properties

The alpha-TCP synthesized by method 1, with a calcination temperature of 1500 °C and concentration of reagents of 2.0 M, was used to evaluate the influence of different milling times on the cement properties.

Milling was performed in a ball mill with a 100 mL polyethylene jar, using alumina balls of 10.80 mm diameter. Each gram of powder was milled with four alumina balls and using 2 mL of anhydrous ethyl alcohol (Dinâmica, Brazil). The alpha-TCP powder was milled for different time periods. The milling time and the identification of the samples are summarized in the Table 2.

The resulting solution (alpha-TCP + alcohol) was sieved only to keep apart the milling media and remained for 72 h in an oven at 70° C to promote the complete evaporation of the alcohol, leaving only the powder obtained for further characterization.

2.3. Characterization

Evaluation of the phase composition of powders after calcination and without mill in ball milling was performed using X-ray diffraction. Phillips X'Pert MPD diffractometer with a copper tube (Kα radiation = 1.5418 Å) was used for this analysis. The voltage and current used in the tube were 40 kV and 40 mA, respectively. The scanning speed of the goniometer was 0.05°/s, and the scan interval (i.e. 2θ) from 10 to 40°.

Particle size distribution was performed using laser particle size analysis. The detection range of the instrument is from 0.04 to

Table 1
Description of samples prepared by different methodologies.

	Titrant	Titrated	pH correction	Calcination temperature (°C)	Sample
Method 1	H_3PO_4	$Ca(NO_3)_2 \cdot 4H_2O$	–	1300	M1/1300
				1400	M1/1400
				1500	M1/1500
Method 2	H_3PO_4	$Ca(NO_3)_2 \cdot 4H_2O$	NH_4OH	1300	M2/1300
				1400	M2/1400
				1500	M2/1500
Method 3	$Ca(NO_3)_2 \cdot 4H_2O$	H_3PO_4	–	1300	M3/1300
				1400	M3/1400
				1500	M3/1500