

Investigation of calcium phosphate formation from calcium propionate and triethyl phosphate



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ABSTRACT

Synthetic calcium phosphates are used in for example bone cements and implant coatings to increase biocompatibility. The common method to produce tricalcium phosphate (TCP) uses high temperatures, which creates large crystals with low specific surface areas. In order to investigate new methods to produce TCP at lower temperatures, the reaction between calcium propionate and triethyl phosphate conducted at 220 °C was studied. The method had a near 100% conversion rate, the main synthesis products were calcium phosphate and ethyl propionate. The formed calcium phosphate polymorph could be controlled depending on the water content of the precursor mixture. Anhydrous conditions created amorphous calcium phosphate. As the concentration of water increased, β-TCP was formed, followed by calcium deficient hydroxyapatite and monetite. The particle size increased with the water content, from 20 to 40 nm for amorphous calcium phosphate to tenths of micrometers for monetite. The specific surface areas varied between 209 m²/g for the amorphous product to 3.6 m²/g for the monetite product.

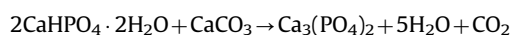
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1. Introduction

Calcium phosphates are well known for their ability to stimulate the growth of natural bone. Hydroxyapatite (HA), tricalcium phosphate (TCP) and tetracalcium phosphate (TTCP) are some examples of calcium phosphate compounds which have a beneficial effect on the growth of bone tissue. Among these, hydroxyapatite is chemically most similar to natural bone [1], but has a slow resorption time when used as a bone substitute material. TCP, with the chemical formula Ca₃(PO₄)₂, is a common ingredient in bone substitutes since it stimulates the growth of new bone, but also because it resorbs faster in the human body than HA. The effect of TCP on osteogenesis was studied as early as 1920 [2]. TCP exists in several polymorphs, where α-TCP and β-TCP are the most intensely studied. β-TCP is stable at room temperature whereas α-TCP is the high temperature polymorph and is stable between 1125 °C and 1430 °C [3]. β-TCP is for example used as blocks or granules for bone defects or spinal fusions [4,5]. α-TCP forms a self-setting cement with water and is therefore used in calcium phosphate cements [6,7].

Due to its ability to react with water, it is generally considered that TCP has to be synthesized under anhydrous conditions. One common method to produce TCP is to react a calcium compound

such as CaCO₃ with a phosphorous containing precursor such as CaHPO₄ at temperatures of above 800 °C [8,9]:



Another method works by calcining amorphous calcium phosphate (ACP) or calcium deficient HA (CDHA), heat treatment at 700–1300 °C is used to induce a phase transformation from ACP to TCP or from CDHA to TCP [10–12]. A more recent synthesis method for TCP is flame spray pyrolysis, where calcium phosphates are produced in a flame, and the products are subsequently crystallized to TCP at 900 °C [13,14].

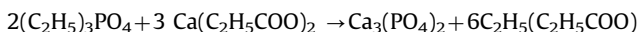
Synthesis of TCP at high temperatures may not be desirable in some cases. Calcination at high temperatures cause sintering effects which increase particle size and a decrease in the specific surface area. A small particle size creates stronger bone cements and small particles also resorb faster in the human body. A common method of decreasing the size of the particles and crystallites is by ball milling, either of the calcined product or before the heat treatment [15,16]. This is a slow process and may be expensive to scale up. Methods which create small particle sizes of TCP directly and at low temperatures are therefore of interest. There are a few reports in the literature which show that β-TCP can form at lower temperatures, these include precipitation in methanol [17], formation under hydrothermal conditions [18,19], and precipitation in ethylene glycol [20,21].

In this study we investigate the reaction between triethyl phosphate and calcium propionate. In theory, this synthesis should

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proceed as:



Thus, the synthesis products should be calcium phosphate and ethyl propionate. Using triethyl phosphate as a phosphorous precursor has the advantage that it is easy to control the water content of the reaction mixture and perform the synthesis under anhydrous conditions, as water is more easily removed from triethyl phosphate compared to other phosphorous compounds, such as for example phosphoric acid. Another purpose of the study was to investigate the formed calcium products from a reaction between a phosphate ester and a calcium carboxylate, since this reaction is a possible candidate to produce in situ polymerized calcium phosphate/polyester composites [22].

2. Experimental

2.1. Calcium phosphate synthesis

In a typical experiment, 9.31 g (0.05 mol) of calcium propionate (Fluka, 99%) was thoroughly mixed with 6.07 g (0.033 mol) of triethyl phosphate (Aldrich, 99.8%), and, for some of the experiments, with various amounts of water. Prior to the mixing, the calcium propionate was dried at 120 °C for 12 h to remove absorbed water. The triethyl phosphate was dried by using 4 Å molecular sieves (2–3 mm diameter, Scharlau). The mixture was placed in a glass vial in a PARR stainless steel autoclave with a PTFE inner vessel. The autoclave was placed in an oven at 220 °C for 24 h. The autoclave was allowed to cool to room temperature and the product was collected. The product consisted of a white solid substance and a liquid with a fruity odor. The liquid was collected for further analysis. The solid was split in two parts, one was calcined in an oven at 350 °C and the other part was washed repeatedly with a total volume of 500 ml of isopropanol and dried at 120 °C for 1 h.

2.2. Characterization

For the X-ray diffraction (XRD) measurements, a Bruker D8 powder diffractometer with $\text{CuK}\alpha$ radiation (1.54 Å) was used. The scanning electron microscopy (SEM) analysis was done with a Zeiss Ultra 55 equipped with an Oxford INCA energy dispersive x-ray spectroscopy (EDX) system. Gas chromatography (GC) was performed with a Thermoquest Trace 2000 equipped with a Fisons MD800 mass spectrometer. Inductively coupled plasma atomic emission spectroscopy (ICP-AES) measurements were done with a Perkin Elmer Optima 5300DV. The specific surface area was measured with a Micromeritics Tristar instrument, using nitrogen adsorption and the BET algorithm for specific surface area calculation.

3. Results and discussion

In a series of experiments, the water content in the precursor mixture was successively increased, from anhydrous to 60 mmol. Fig. 1 shows XRD diffractograms for the synthesis with different concentrations of H_2O . Diffractogram (A) is for the product synthesized under anhydrous conditions. As seen, this diffractogram has a large hump around $2\theta=30^\circ$ and no distinct diffraction peaks, this indicates that the sample consisted of ACP. Above 15 mmol, crystalline β -TCP was formed (B). A water content of above 40 mmol yielded CDHA (D). A water content of 60 mmol gave monetite, with minor CDHA content (E). The XRD measurements

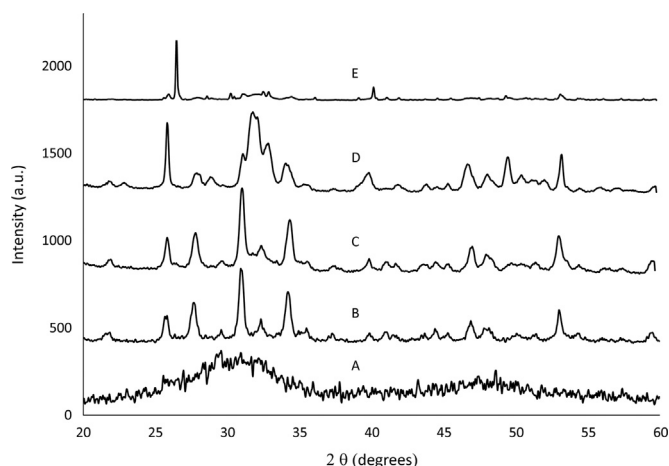


Fig. 1. XRD diffractogram of calcium phosphate formed with different quantities of water. A) anhydrous conditions; B) $\text{Ca}/\text{H}_2\text{O}=3.33$; C) $\text{Ca}/\text{H}_2\text{O}=1.67$; D) $\text{Ca}/\text{H}_2\text{O}=1.25$; E) $\text{Ca}/\text{H}_2\text{O}=0.83$.

Table 1

Overview of the calcium phosphates formed with different water contents.

Water amount	Molar ratio $\text{Ca}/\text{H}_2\text{O}$	Polymorph
0	–	Amorphous
5.5 mmol	9	Amorphous
10 mmol	5	Amorphous
15 mmol	3.33	β -TCP
30 mmol	1.67	β -TCP+CDHA
40 mmol	1.25	CDHA
60 mmol	0.83	Monetite

are summarized in Table 1. From the XRD analysis, no difference was seen between the samples which were calcined at 350 °C and the samples which were washed with isopropanol. The only difference between these cleaning methods was the color; calcined samples had a slight brownish tint whereas the isopropanol-washed were clear white, which indicates that the calcination procedure left small amounts of carbon in the sample.

SEM analysis was done on samples of the amorphous powder, crystalline β -TCP and the monetite sample. Fig. 2(a) and (b) shows images from the amorphous samples. At low magnification it can be seen that the amorphous samples formed irregular shaped particles with sharp edges and smooth surfaces, the size of the particles were approximately 100–200 μm . Higher magnifications reveal that these particles consisted of granules with sizes of 20–40 nm. The crystalline β -TCP samples formed similar structures on the micrometer level, and at higher magnifications it can be seen that these agglomerates also were composed of spherical granules (Fig. 3(a) and (b)). The main difference is that these granules are smaller compared with the amorphous samples. EDX measurements for the amorphous and β -TCP samples revealed a Ca/P ratio of 1.46, close to the theoretical ratio of 1.5.

At a H_2O content of above 40 mmol, monetite was formed instead of CDHA. SEM analysis of these samples show flake-like particles at low magnification (Fig. 4(a)), while higher magnifications reveal sharp-edged crystals with clearly visible growth steps (Fig. 4(b)). Each crystal was covered with a thin layer of irregular shaped particles, most probably this phase is CDHA, as seen in the diffractogram at around $2\theta=32^\circ$.

The nitrogen adsorption measurements showed a specific surface area for the amorphous sample of 209 m^2/g while the β -TCP sample had a surface area of 65 m^2/g . For the monetite samples, the specific surface area was 3.6 m^2/g .

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