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Novel route for rapid sol-gel synthesis of hydroxyapatite, avoiding ageing and using fast drying with a 50-fold to 200-fold reduction in process time

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ABSTRACT

We have developed an innovative, rapid sol-gel method of producing hydroxyapatite nanopowders that avoids the conventional lengthy ageing and drying processes (over a week), being 200 times quicker in comparison to conventional aqueous sol-gel preparation, and 50 times quicker than ethanol based sol-gel synthesis. Two different sets of experimental conditions, in terms of pH value (5.5 and 7.5), synthesis temperature (45 and 90 °C), drying temperature (60 and 80 °C) and calcination temperature (400 and 700 °C) were explored. The products were characterised by X-ray diffraction (XRD) Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM) and specific surface area (SSA) measurements. Pure hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, HAp) was obtained for the powders synthesised at pH 7.5 and calcined at 400 °C, while biphasic mixtures of HAp/β-tricalcium phosphate (β-$Ca_3(PO_4)_2$, TCP) were produced at pH 5.5 and (pH 7.5 at elevated temperature). The novel rapid drying was up to 200 times faster than conventional drying, only needing 1 h with no prior ageing step, and favoured the formation of smaller/finer nanopowders, while producing pure HAp or phase mixtures virtually identical to those obtained from the slow conventional drying method, despite the absence of a slow ageing process. The products of this novel rapid process were actually shown to have smaller crystallite sizes and larger SSA, which should result in increased bioactivity.

1. Introduction

Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$; HAp) is the major constituent [1] (70–90 wt%) of biological apatite in natural bone [2], and it is therefore a useful bioceramic. The calcium phosphate ions are naturally metabolised during resorption, and do not induce abnormal calcium or phosphate levels in human organs [3]. Due to its chemical and structural properties being so similar to the bone mineral [4], along with a good osteoconductivity and biocompatibility, HAp is widely used as a biomaterial in the form of restorative, grafting, and coating materials [1]. HAp also has useful properties for the separation of proteins with activity in chromatography [5]. Human bones, and many HAp-based bioceramics, are actually a mixture of ~75% HAp and 25% beta-tricalcium phosphate (TCP, β-$Ca_3(PO_4)_2$), which also demonstrates superior bio-resorbability to pure HAp [6,7].

HAp can be synthesised by several methods: sol-gel approaches [1, 4], wet-chemical synthesis [8–11], mechanochemical synthesis [12], combustion synthesis [13], electrochemical deposition [14], hydrothermal synthesis [15], multiple emulsion technique [16], high gravity methods [17], etc.

Mechanochemical reactions occur by applying a strong mechanical energy that destroys the original materials and avails the atoms for the formation of different structures [18]. The electrochemical approach, often used to deposit HAp layers onto the surfaces of implant materials, is widely used as coating method [19]. Hydrothermal synthesis is a technique that involves reactions at elevated temperature and pressure of aqueous solutions/suspensions to directly crystallise ceramic materials [20].

Of the many available methods for HAp synthesis [5,21–25], the precipitation from suitable calcium (Ca) and phosphorous (P) precursor salt solutions is the most widely used, this being a convenient low cost method for obtaining HAp powder [26]. However, the precipitation from solution suffers several drawbacks, such as the necessity for high (non-acidic) pH to avoid the formation of Ca-deficient HAp, and relatively high calcination temperatures for the formation of crystalline HAp [1]. Also, the reaction time required for completing the formation of HAp is relatively long, and usually a slow ageing step is required for the precipitated sol-gel [27]. The low temperature required for the formation of HAp crystals, and a high degree of homogeneity, are the main advantages of the sol–gel process in comparison with conventional solid state methods for HAp powder synthesis [4]. Looking at the extensive literature on sol-gel synthesis and ageing of HAp powders, it is obvious that many protocols have been employed, and factors such as *total time of synthesis* investigated, to study their effect on the final HAp product, to achieve the optimum single or diphasic calcium phosphate end product for a predesigned function.

In a typical aqueous sol-gel synthesis of HAp, the gel is aged at room temperature and then slowly dried at low temperatures below 100 °C, over a total period of a week or more. Lui et al. [28] obtained a calcium

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phosphate powder after ageing the sol at room temperature for 16 h followed by drying at 60 °C for at least 5 days (a minimum of 136 h). This produced single phase HAp at 350 °C, which then partially developed into TCP when heated to 600–800 °C. Padmanabhan et al. [29] aged an aqueous precipitate at room temperature for 48 h, followed by filtering, repeated washing, and then drying in an oven at 60 °C for 24 h (>72 h total), to produce a highly amorphous but single phase HAp, which did not crystallise until 500 °C. Sanosh et al. [30] aged their precipitated slurry for 24 h at room temperature before they dried at 65 °C for a further 24 h (48 h in total), but they did not form quality crystalline HAp until heating this product to over 600 °C, and it always had a significant amount of CaO as an impurity, so was never truly single phase. A relatively rapid synthesis method using freeze drying was reported by Pretto et al., [8] using two different ripening times; 2 h for low crystallinity and 24 h for high crystallinity powders, and they then dried these powders via freeze drying. However, even this more rapid method required 24 h ageing for a highly crystalline product. Zhu et al. [31] aged an aqueous HAp sol at temperatures between 25 and 100 °C for times of 24, 48, 72, and 300 h, followed by drying at 75 °C for 24 h, to make nano HAp. Increased ageing times lead to increased HAp crystallinity, and after ageing for 48 h at 50 °C (72 h total process) a poorly crystalline single phase HAp had formed. Correia et al. [32] used a complex aqueous basic precipitation process which required ageing whilst stirring for 4–6 days, all while under reflux at 75 °C, followed by washing and drying overnight at 100 °C, but the dried product was already well-crystalline HAp. To form a silica-HAp composite material, Ribeiro et al. [33] stirred a sol made by dissolving triethylphosphate in water for 24 h, followed by adding calcium nitrate in water and stirring for a further 24 h, followed by the addition of tetraethyl-ortho-silicate in ethanol and more string for a week, all at room temperature, to form and age. Drying details were not given, but this was a process lasting at least 216 h.

Non-aqueous sol gel routes can be significantly quicker, but still require ageing and drying periods of several days. A typical non-aqueous, ethanol based process mixes calcium nitrate and P_2O_5, each individually dissolved in ethanol, which instantly coprecipitate on addition. This is aged while stirring for 24 h at room temperature, and then dried at 80 °C for another 24 h, the gel consisting of poorly crystalline single phase HAp [4]. Agrawal et al. [34] used a mixture of calcium nitrate and P_2O_5 in ethanol to form a gel in 90 min, then followed by ageing for 24 h and drying at 80 °C for 24 h (49.5 h in total). Feng et al. [1] used calcium nitrate and P_2O_5 in ethanol, and compared ageing the gel for 4 h, 48 h and 72 h at room temperature, followed by drying for 24 h at 80 °C (totalling between 28 and 76 h). When heated to 600 °C, these all crystallised as HAp with a small amount of CaO as a secondary phase, but formed pure HAp at 700 °C, and TCP began to appear from 800 °C and upwards. Using calcium nitrate and P_2O_5 in ethanol, Costescu et al. [35] ageing the gel while stirring for 24 h at 80 °C, followed by drying at 80 °C for 96 h (120 h in total). This produced pure crystalline HAp after drying at only 80 °C, remaining so at 600 °C, and at 1000 °C TCP and a small amount of CaO had formed. Yasukawa et al. [21] combined calcium nitrate and P_2O_5 in ethanol, aged the precipitates with stirring for 10–15 h, then dried the gel at 80 °C for 20 h (a total of 30–35 h). This formed poorly crystalline single phase HAp at 400 °C, becoming much more crystalline but remaining single phase at 750 °C.

Using organic precursors and solvents at a basic pH, Vijayalakshmi et al. [36] obtained a gel after 24 h ageing, followed by 16 h drying at 120 °C (40 h total) to give a totally amorphous product, but upon heating this crystallised as a mixture of HAp and $CaCO_3$ even when heated to 900 °C. The dried gel was a mixture of a tiny amount of amorphous HAp with the mostly unreacted precursors, but this formed pure crystalline HAp upon heating to 550 °C. A highly complex "fast" route was developed by Hsieh et al., [37] using the costly and highly toxic, carcinogenic and teratogenic solvent 2-methoxy ethanol to form the gel, followed by ageing in a sealed container in an oil bath at 80–90 °C for 16 h. This was then followed by either "fast" gelation under reduced pressure, or gelation over 48 h, at ambient pressure. It should be noted that they never state precisely what time they mean by "fast", but at one point in the text they vaguely mention "short-time aging, for example 5–10 h", suggestion the total time for their process was between 21 and 64 h. Furthermore, the "fast" method resulted in a HAp sample heavily contaminated with CaO after HAp crystallised at 600 °C, and even the slower, 60 h aged sample contained some CaO.

It can clearly be seen that all of these precipitation sol-gel routes require many hours, in the order of several days, to complete the ageing and drying process. Moreover, the simple aqueous ones, which are the easiest, most economic and least environmentally harmful, are also the slowest. This investigation is focused on the rapid (no ageing, only 1 h drying) synthesis of nano-crystalline HAp using a simple aqueous sol-gel approach. A comparative feasibility study is also made between the conventional ageing and drying steps, which usually require long periods of over a week for the completion of synthesis, and a novel fast rotary evaporation that leads to virtually identical products, but in a time period that is up to 200 times shorter than traditional ageing and oven drying for aqueous gels, and 50 times quicker than that used for ethanol based sol-gel HAp synthesis.

2. Materials and methods

2.1. Experimental design

Two different sol-gel synthesis routes, designated as **1** and **2** in Table 1, were compared (see Section 2.2 below). To summarise, the conditions were:

1. Reaction at 45 °C, pH = 7.5, drying on rotary evaporator at 60 °C for **FD**
2. Reaction at 90 °C, pH = 5.5, drying on rotary evaporator at 80 °C for **FD**

The sol prepared from each synthesis was divided into two parts, to be aged and/or dried by two different protocols. One part was aged at room temperature for a week, and then the resulting slurry was filtered, and the filter cake dried at 80 °C for 48 h in air (conventional drying; **CD**). The other part was dried directly in only 1 h, without any ageing, using a rotary evaporator (fast drying; **FD**). Both types of *as*-dried powders from synthesis **1** were calcined at 400 °C and 700 °C, but the as-dried powders from synthesis **2** were calcined at 700 °C only, as shown in Table 1. It is well known that the more acidic pH of 5.5 used in route **2** favours the formation of biphasic of β-TCP along with HAp even at low temperatures, at the expense of the pure HAp phase [43]. Therefore, samples from route **2** were calcined at 700 °C only, as pure HAp would not be obtained at lower temperatures. When the reaction is carried out under highly basic conditions (pH = 9–10), it is known that a pure HAp phase can form at temperatures of 500 °C [32,38]. However, we suspected that pure HAp could be obtained at the intermediate, near-neutral pH of 7.5 and lower synthesis temperature used in route **1** after calcination at only 400 °C, so for that reason we also studied **FD1** and **CD1** after calcination at 400 °C, and we also used a slightly lower drying temperature of 60 °C for the **FD** process as well.

2.2. Synthesis procedure

Analytical grade calcium acetate monohydrate ($Ca(CH_3CO_2)_2 \cdot H_2O$) and orthophosphoric acid (H_3PO_4) were used as the starting precursors for calcium and phosphorous, respectively. The reactants were mixed according to the stoichiometric HAp molar ratio (Ca:P = 1.67). Ammonium hydroxide (NH_4OH) was used to set the required pH values of 7.5 for route **1**, and pH 5.5 for route **2**, and these were kept constant during the synthesis. All reagents were purchased from Sigma Aldrich, Germany, and were ACS grade. The reactants were added to distilled water at a fixed stirring rate of 500 rpm for both routes, and at a reaction temperature of 45 °C for route **1** and 90 °C for route **2**.