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Research Article

Effect of pH and Ageing Time in the Preparation of A Ceramic Drug Delivery Carrier

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ABSTRACT
Hydroxyapatite is the inorganic constituent present in the bone and it is used as a drug delivery carrier in hard tissue regeneration applications. Hydroxyapatite was prepared by simple precipitation technique and the effect of experimental parameters on the phase formation was studied. Calcium nitrate tetra hydrate and diammonium hydrogen phosphate were taken as the calcium and phosphate source. The calcined powders were characterized by Fourier - Transform Infrared spectroscopy to identify the functional groups present in the product and also analyzed by powder X-ray diffraction to identify the phases present in the product. Results showed that the product formed is pure hydroxyapatite and it confirms that aging time and pH of the system plays a significant role in the phase formation.

Keywords: Hydroxyapatite, Aging time, pH, Precipitation technique, Powder XRD; Ceramic Drug Delivery Carrier.

INTRODUCTION

Bone is a well-known natural composite material, which contains about 60% hydroxyapatite, 30% Type I collagen along with 10% water[1]. Synthetic hydroxyapatite is highly used in the hard tissue regeneration process either in the pure form or in combination with other ceramics or polymers. The chemical composition and other physical characteristics such as structure, specific surface area, porosity and particle size decides the in-vivo performance of the hydroxyapatite as a bone substitute[2].

Out of several calcium phosphate bioceramics, hydroxyapatite is the most commonly used constituent for bone replacement due to its less solubility in physiological environment and it shows very low inflammatory response with a better bonding ability to the bone directly[3]. Precipitated hydroxyapatites (Ca_{10-x} $(HPO_4)_x$ $(PO_4)_{6-x}(OH)_{2-x}$) possess a Ca:P molar ratio from 1.50 to 1.67 and sometimes even outside this range. Generally the precipitated hydroxyapatite shows poor crystallinity with particles in the submicron size. But the specific surface area will be very high and it will be in the range of 25-1000 m^2/g which almost mimics the apatite present in bone. The main difference between the hydroxyapatite present in the natural bone and precipitated hydroxyapatite is the absence of carbonate and magnesium ions substituted in the structure of natural hydroxyapatite. With a decrease in Ca:P molar ratio, crystallinity, crystal size and the solubility of precipitated hydroxyapatite will increase[4].

Hydroxyapatite is prepared by various preparatory techniques and from various starting materials[5-9]. The precipitation process is the most reported method for preparing hydroxyapatite powder, which is simple, low cost and suitable for large scale production. But the disadvantage of the method is it produces low quality powder with a large particle size, wide particle size distribution and a lot of hard agglomerates. Hydroxyapatite nanoparticles prepared by precipitation technique from calcium nitrate and diammonium hydrogen phosphate solution shows gradual increase in the size of hydroxyapatite grains when temperature increased from 100 to 1200 °C. Stoichiometric hydroxyapatite powder prepared by wet precipitation method by using ortho phosphoric acid and calcium hydroxide as raw materials results in needle-shaped particles which get transformed to spheroidal shape particles with the increase in precipitation temperature[10-11].

Several researchers investigated the correlation between the precipitation conditions and properties of the powder and concluded that the aging and precipitation kinetics are critical for the purity of the hydroxyapatite and its crystallographic characteristics[12]. Porosity of the hydroxyapatite powders plays a major role in the drug release kinetics when it is used as a ceramic drug delivery system for the controlled release of drug[13].

Based on the available reports, in the present study, we reported the preparation of hydroxyapatite by precipitation method in aqueous solution by varying the synthesis parameters like pH of the solution and aging time.

MATERIALS AND METHOD

Stoichiometric amount of powders of $Ca(NO_3)_24H_2O$ (99+%, AR, Rankem) and $(NH_4)_2HPO_4$ (99%, AR, Merck) were dissolved in demineralized water at room temperature to yield 1M stock solutions.

The pH of $Ca(NO_3)_{2.}4H_2O$ solution was adjusted to 10 by means of adding 1:1 solution of ammonium hydroxide and water. Stoichiometric amount of diammonium hydrogen phosphate solution was added drop wise to the solution of

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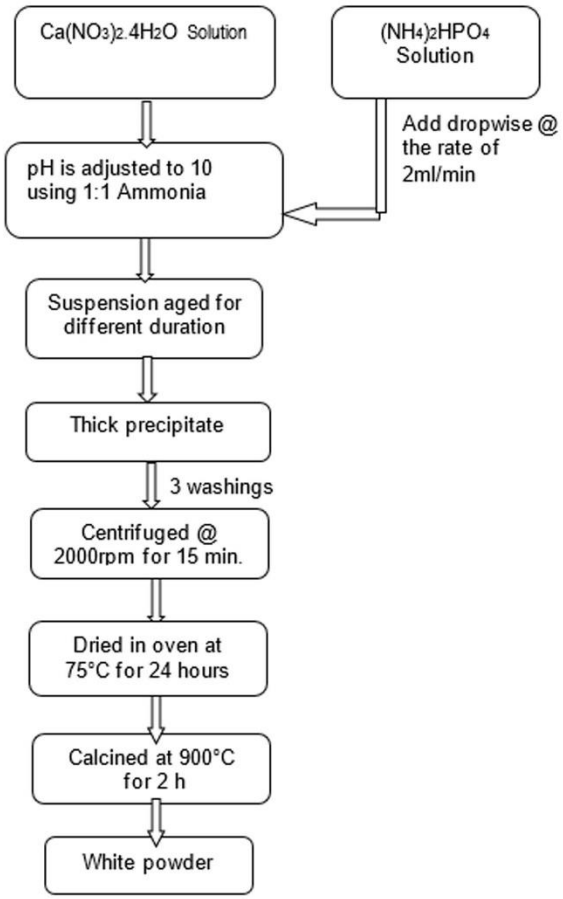

Figure 1: Flow chart for the synthesis of hydroxyapatite by precipitation method

calcium nitrate at the rate of 2 ml/min at room temperature under continuous stirring. A suspension of the calcium phosphate solution was maintained as such and aged for different duration until it forms a viscous precipitate which was subjected to centrifugation at 2000 rpm. The thick precipitate obtained was washed thrice and dried in hot air oven at 75°C for 24 h. The resultant powder was finely grounded by using mortar and pestle and calcined at 900°C (fig. 1). Same procedure is followed for all the precipitation synthesis by varying the processing parameters like aging time of the precipitate formed and pH of calcium nitrate solution. Phase identification was done using RIKAKU X-Ray Diffractometer, using Cu Kα, Ni filtered radiation. The functional groups were identified using FTIR (Thermo Nicolet, Avatar 330 FTIR Spectrometer, USA) studies.

RESULTS AND DISCUSSION

Addition of ammonium hydroxide to calcium nitrate forms a milky white solution which indicates the formation of calcium hydroxide. To this solution when diammonium hydrogen phosphate was added it forms a white solution which on aging forms a thick white precipitate indicates the formation of calcium phosphate. Obtained precipitate was aged for the period of 1h, 1 day and 10 days. After aging process the left out water was removed by means of centrifugation and subsequent drying of the product in hot air oven at 75°C for 24 h. After the removal of water molecule the sample was calcined at 900°C for 2h.

Effect of aging time

The aging time plays a vital role on the thermal stability of the hydroxyapatite as the thermal stability increases with the aging time. It was reported that with the aging time of 8, 12 and 24 hours pure β-tricalcium phosphate, β-tricalcium phosphate and hydroxyapatite and pure hydroxyapatite were obtained as a product respectively. During calcination hydroxyapatite obtained at lower aging time was found to have lower thermal stability than the hydroxyapatite obtained with higher aging time[14]. The Ca and P precursors forms an unstable Octacalcium phosphate initially which gets transformed to hydroxyapatite over a period of 24 hours[15]. With the increase in aging time the product formed will be a stoichiometric hydroxyapatite with higher specific surface area as the stoichiometric hydroxyapatite possesses higher specific surface area than the nonstoichiometric hydroxyapatite[16].

The FT-IR spectra (Fig. 2) of the samples aged for 1 and 10 days shows the characteristic absorption peaks of pure hydroxyapatite corresponding to OH^- group at 631 cm^{-1} and 3571 cm^{-1} and PO_4^{3-} vibrations at 570 cm^{-1}, 602 cm^{-1}, 1045 cm^{-1} and 1089 cm^{-1}, together with the weak bands of the CO_3^{2-} group at 1550 cm^{-1}. Carbonate ion can substitute on two possible sites of hydroxyapatite either site A (OH-

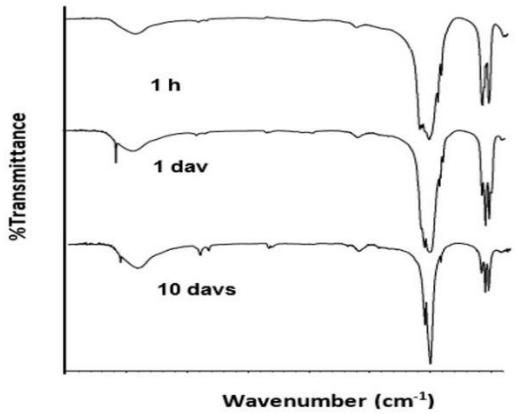

Figure 2: FTIR spectra of hydroxyapatite synthesized by precipitation technique with different aging time and calcined at 900 ° C.

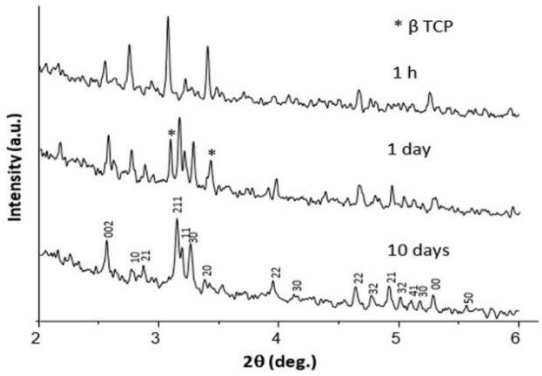

Figure 3: XRD pattern of hydroxyapatite synthesized by varying aging time.

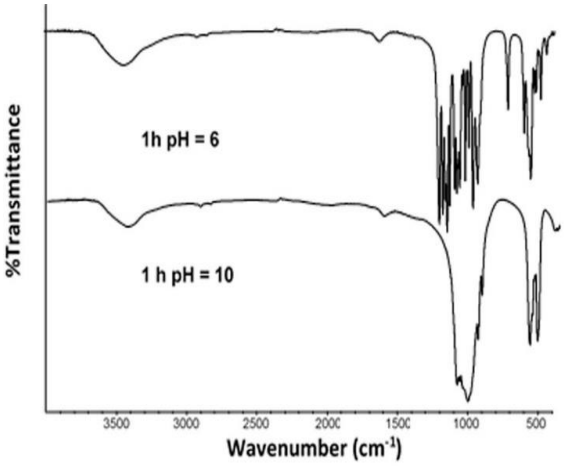

Figure 4: FTIR spectra of hydroxyapatite synthesized by varying pH.

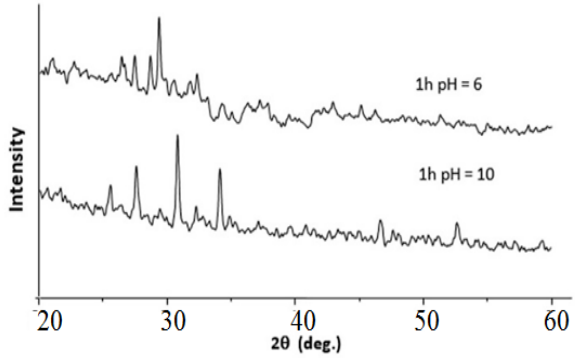

Figure 5: XRD pattern of hydroxyapatite synthesized using precipitation method.

site) or site B (PO_4^{3-} site) which can be distinguished by FT-IR spectroscopy. In the present studies intense peaks at 1550 cm^{-1} indicate the substitution of carbonate ions in OH- site (site A). Whereas the precipitate aged for 1 h shows the absence of both bending and stretching vibrations of OH^- indicates the absence of hydroxyapatite phase.

XRD patterns (Fig. 3) confirms the results obtained from FTIR spectra as it shows the pure phase for the precipitate aged for 10 days and composite consists of hydroxyapatite as major phase for the precipitate aged for 1 day. Whereas the precipitate aged for 1 h forms a pure β-TCP phase. From the above results the mechanism of hydroxyapatite formation is evident as it forms β-TCP initially and which on aging gets converted to hydroxyapatite over the period of time.

Effect of pH

Without the addition of ammonia solution pH of the as prepared calcium nitrate solution was found to be 6 and addition of diammonium hydrogen phosphate to this solution produces a white suspension. After aging for 1 h the solution is centrifuged and dried for 24 h in hot air oven and the resultant product is calcined at 900 °C for 2 h. FTIR spectra (Fig. 4) of this sample show the absence of characteristic hydroxyapatite peaks as well as tricalcium phosphate peaks which indicates the absence of both the phases. XRD patterns (Fig. 5) also confirms the result as it shows the presence of dicalcium phosphate phase.

When the pH of calcium nitrate solution was adjusted to 6 and aging time was maintained as 1h then the product formed is found to be $Ca_2P_2O_7$ and when the pH of calcium nitrate solution was adjusted to 10 and aging time was maintained as 1h then the product formed is β-tricalcium phosphate. FTIR and XRD pattern (Fig. 4 & Fig. 5) confirms that the product formed is pure β-tricalcium phosphate.

By varying the pH and molar proportion of calcium and phosphorus ions the particle size and phase composition can be controlled[17]. Present result is also in agreement with the reports as the ratio of Ca to P ions and aging time was kept constant and the pH of the solution was varied from 1 to 6 which resulted in two different products as calcium pyrophosphate was observed at the pH of 1 and β-tricalcium phosphate was observed at the pH of 6.

Also the obtained results confirm the established mechanism of hydroxyapatite formation. Octacalcium phosphate will be the phase formed by adding calcium and phosphorous precursors which immediately gets converted to amorphous calcium phosphate which results in the calcium-deficient hydroxyapatite and hydroxyapatite[15,18].

The pure hydroxyapatite formed after 10 days of ageing time can be used as a targeted drug delivery system for controlled release[19]. The release kinetics depends on the porosity of the hydroxyapatite particles when it is used in the pure form and it depends on the constituents present in the formulation when it is used as a composite[20,21].

CONCLUSION

The present study shows a simple route to synthesize pure hydroxyapatite. The effect of aging time is proved to be significant as the time taken for the conversion of tricalcium phosphate to hydroxyapatite is found to be high. The role of pH in phase formation is also confirmed as in acidic pH dicalcium phosphate and in alkaline pH tricalcium phosphate were the immediate products formed after mixing the calcium and phosphate sources.

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