

Synthesis of Ha by Various Sol-Gel Techniques and Their Comparison: A Review

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Abstract—Hydroxyapatite (HA) has become the first choice for coating of bioimplant in past decade due to its Ca/P ratio, which is almost similar to the human bone. It is used as a coating material for various body implants so that the implant get well adjusted and well tolerated by the body environment. In recent it was observed that there is continuous increase in the number of patients which undergoes bioimplant surgery, so there is a clear need of large production of effective HA coating on the bioimplant. During last two decades various methods were developed for HA synthesis. Due to inherent properties like low processing temperature, effective molecular mixing and suitability to generate nano sized particles sol-gel processes are preferred. In this article various sol-gel techniques developed earlier for HA synthesis has been discussed and their pictorial flow process and mutual comparison of each technique has been carried out.

Keywords: Hydroxyapatite, Bioimplant, Sol-gel, Biomaterials

INTRODUCTION

Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, HA) is an important inorganic biomaterial which has attracted the attention of researchers related to biomaterials field in recent years. Due to its chemical and structural similarity with the mineral phase of bone and teeth, is widely used for hard tissues repair. As a result, this inorganic phosphate has been studied extensively for medical applications in the form of powders, composites or even coatings [1–11]. It is also observed that dense sintered HA has many bone replacement applications and is used for repairing bone defects in dental and orthopaedic sites, immediate tooth replacement, augmentation of alveolar ridges, pulp capping material and maxillo facial reconstruction, etc [12]. For substituting or repairing the bone, the designed material must has the ability to create a bond with the host living bone [13]. Hence, it is always desirable to include a high degree of crystallinity and chemical stability among the desirable properties of an ideal hydroxyapatite [14, 15]. Furthermore, HA has also been studied for other non-medical applications, for example, as packing media for column chromatography, gas sensors, catalysts, etc. [2, 16]. However, poor mechanical properties, e.g. low strength and toughness, restrict monolithic HA applications to those that require little or no load-bearing parts [17]. Due to its diverse applications, the materials properties accordingly need to be tailored for real world application. Hence researchers have tried to customize its properties such as bioactivity, mechanical strength, solubility and sinterability by controlling its composition, morphology and particle size [9, 10].

The chemical, structural and morphological properties of synthetic HA can be modulated by varying the method and the conditions of synthesis. Classical methods for HA powder synthesis include direct precipitation, hydrothermal techniques, hydrolysis of other calcium phosphates, as well as solid-state reactions [18, 19] mechano-chemical methods [20, 21]. One of the

most widely used methods is wet precipitation, where chemical reactions take place between calcium and phosphorus ions under a controlled pH and temperature of the solution. The precipitated powder is typically calcined at 400-600°C or even at higher temperature in order to obtain a stoichiometric, apatitic structure. In some cases, a well-crystallized HA phase was only developed while approaching a sintering temperature of 1200°C. However, fast precipitation during phosphate solution titration (to calcium solution) leads to chemical inhomogeneity in the final product. Slow titration and diluted solutions must be used to improve chemical homogeneity and stoichiometry of the resulting HA. Careful control of the solution condition is critical in the wet precipitation. Otherwise, a decrease of solution pH below about 9 could lead to the formation of Ca-deficient HA structure [17]. Most of the wet methods are time-consuming because the formation of HA phase and the rinsing of unnecessary anions all take time. A method involving non-aqueous systems to synthesize HA has also been reported [22], in which a viscous solution was first obtained by hydrolysis and oxidation of a mixed acetone solution of calcium nitrate ($\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$) and phenyldichlorophosphine ($\text{C}_6\text{H}_5\text{PCl}_2$). After the viscous solution was dried and calcined at above 700°C, HA Powder was obtained. However, the method is usually not so simple due to the need of hydrolysis and oxidation steps.

Sol-gel technique have attracted much attention recently [5, 6, 9-11] due to its well-known inherent advantages to generate glass, glass-ceramic and ceramics powders. These include homogeneous molecular mixing, low processing temperature, the ability to generate nanosized particles, the tremendous flexibility to generate nanocrystalline powders, bulk amorphous monolithic solids and thin films [23]. The sol-gel process is easily applicable to surface coating and it allows the preparation of high-quality HA thin films on metal substrates [7-10]. Thus, the sol-gel process can

be usefully utilized to synthesize both nanocrystalline HA powders and HA films under significantly mild conditions. The versatility of the sol-gel method opens a great opportunity to form thin film coatings in a rather simple process, an alternative to thermal spraying which is currently widely used for biomedical applications [24, 25]. Thermal spraying of HA coatings is a violent process which is difficult to control. The powder experiences extremely high temperatures (6000-10,000°C) which are required to melt the fast-moving HA granules before impacting them onto the metallic substrate. Special techniques are required to preserve the chemistry of the thermal-sprayed HA particles melted in plasmas. Finally, the particles experience an extremely fast cooling rate during solidification from the melt, once deposited on the coating. These factors when combined cause significant instability of the plasma-sprayed HA structure. Numerous reports [26-28] indicated decomposition of the sprayed HA to form other phases, such as tetracalcium phosphate, tricalcium phosphate, calcium oxide, and amorphous calcium phosphate. These phases are amorphous in nature which is prone to dissolution in vivo. Additionally, severe cracking of the plasma-sprayed layer (an inherent feature of plasma-sprayed ceramics) frequently leads to accelerated implant failure. The sol-gel approach provides significantly milder conditions for the synthesis of HA films. This result in a much better structural integrity whereas the defects that originated from plasma spraying can be largely avoided [25]. Furthermore, the lower temperature synthesis particularly benefits the metal substrates where the mechanical degradation or phase transition of the underlying Ti or Ti alloy (i.e. α β phase transition, occurring at 883°C and 960°C, respectively) can be prevented. However, thermal treatment of HA sol-gel films under vacuum environment is frequently required to avoid metal oxidation. This leads to structural instability of the HA coating (i.e. evolution of structural water under vacuum environment) during thermal treatment. Therefore, from both the economic and practical points of view, thermal treatment of the HA coating should be performed in air, and below the transition temperature of the substrate. In this paper the different method for synthesis of HA powder are discussed.

EXPERIMENTAL PROCEDURES

Different methods to synthesize HA powder from the sol-gel technique have been critically reviewed from the previous literature. The brief detail of selected methods can be illustrated one by one.

Formation of HA Powder by the Use of $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and P_2O_5 [29]

In this method two different chemical reagents

(precursors) were used i.e. $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ (0.01M) and P_2O_5 (0.003M). These reagents were used in a molar ratio of 10:3, to obtain the desired Ca/P ratio which is observed in hydroxyapatite. The reagents were dissolved in 5, 10, and 15 ml of ethyl alcohol. It was noticed that sequence of the dissolution of the reagents did not affect the process, but rapid addition of any one reagent to another reagent can cause precipitation. After dissolving the reagents in the ethyl alcohol, the solution was stirred slowly for 30 min-12 h. until the formation of a gel. Further the gel was dried in oven at 120°C in air for 15 h, followed by heat treatment in stagnant air at 900°C for 12 h, which finally results in HA powder. The whole procedure was as shown in the flow diagram given below.

Formation of HA Powder by the Use of $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and $(\text{NH}_4)_2\text{PO}_4$ [30]

In this method 0.5M $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and 0.5M $(\text{NH}_4)_2\text{PO}_4$ was used. The concentration of both precursors was taken up to 0.5M. Initially a mixture of $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and ethanol was taken. The pH value of the solution is 10.5. This solution was then added slowly at a rate of 5 ml/min. to the mixture of 0.5M $(\text{NH}_4)_2\text{PO}_4$ & ethanol having same pH value of 10.5. A constant temperature was maintained at 85°C supported by vigorous stirring. As a result of this a gel was formed which was continuously stirred at a constant pH of 10, maintained at a constant temperature of 85°C through a heating device for 4 h. It must be noticed that to maintain the pH value constant $\text{Ca}(\text{OH})_2$ solution was added. After that it was kept inside the oven at 40°C overnight. Then the product was sintered for 2 h at 400°C, and repeatedly at 750°C and 1200°C for the same time period. The procedure was as shown in the form of flow diagram given below.

Formation of HA Powder by the use of $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, P_2O_5 and Citric Acid [6]

$\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ was taken & mixed it with ethanol to form a 2 M solution 1. Solution 2 was prepared by using another gradient P_2O_5 and mixed with ethanol, this solution 2 was then allowed to refluxed for 24 h to form a 4M $\text{PO}(\text{OH})_3-x(\text{OEt})_x$ solution [31]. In this solution the amount of different phosphor species in the form of fractions were observed as:-

- 0.043 for H_3PO_4 ,
- 0.58 for $\text{PO}(\text{OH})_2(\text{OEt})$ and
- 0.377 for $\text{PO}(\text{OH})(\text{OEt})_2$, respectively [32].

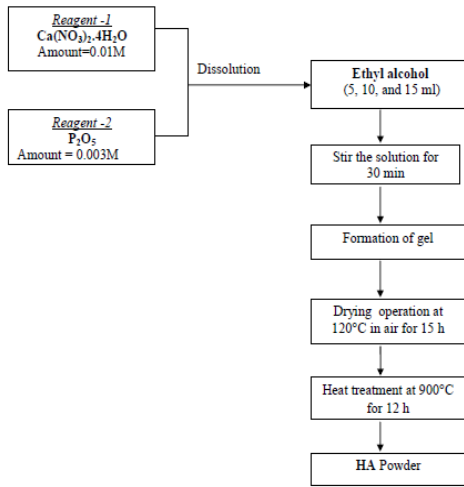


Fig. 1: Schematic Flow Process Chart for The Synthesis of HA by the Use of $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and P_2O_5 [Chart is Plotted on the Basis of Process Setup Reported in Ref. 29]

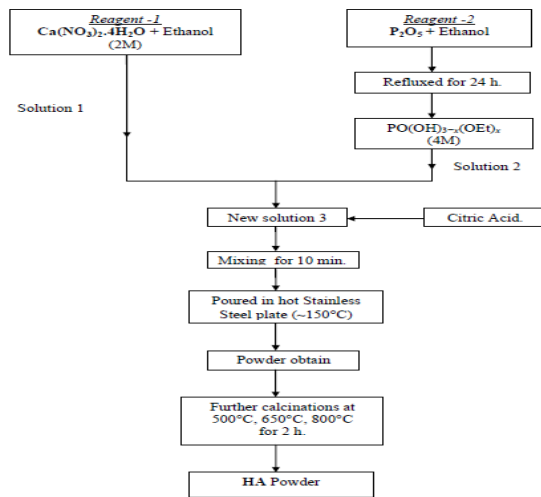


Fig. 3: Schematic Flow Process Chart for the Synthesis of HA by the Use of $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, P_2O_5 and Citric Acid [Chart is Plotted on the Basis of Process Setup Reported in Ref. 6]

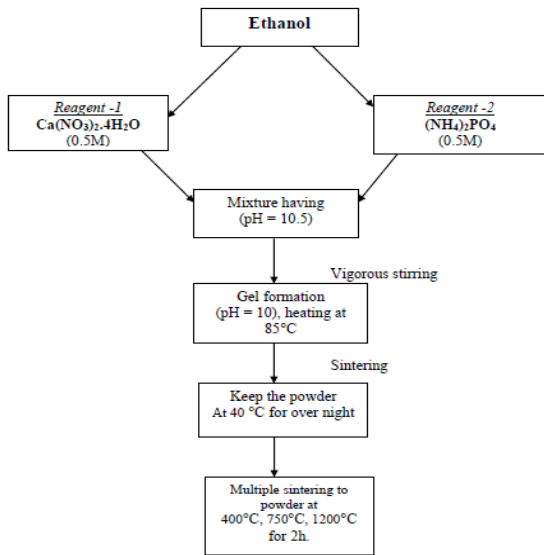


Fig. 2: Schematic Flow Process Chart for the Synthesis of HA by the Use of $(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and $(\text{NH}_4)_2\text{HPO}_4$ [Chart is Plotted on the Basis of Process Setup Reported in Ref. 30]

The two solutions were then mixed having a Ca/P molar ratio of 1.67. The different amounts of citric acid were added & allowed for mixing for 10 min. Now this final solution was poured on to a hot stainless steel plate operating nearly at 150°C to evaporate the solvent and to get the HA powder. The as-prepared powders were allowed to calcined in furnace at 500°C, 650°C and 800°C for 2 h, respectively. The following flow diagram shows the above procedure.

Formation of HA Powder by the Use of $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and $(\text{NH}_4)_2\text{HPO}_4$ [33]

Synthesis in Alcoholic Medium

In this method two analytic grade reagents i.e. $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and $(\text{NH}_4)_2\text{HPO}_4$ were taken for the synthesis of HA powder. The concentrations of both the reagents were varied in order to obtain a Ca/P molar ratio in solution of 1.00, 1.67, and 2.55. Initially $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ was dissolved in 25 ml of deionised H2O to form a solution 1. Similarly the second reagent $(\text{NH}_4)_2\text{HPO}_4$ was dissolved in 25 ml of ethanol to form solution 2. The pH value of both solutions 1 & 2 must be greater than 9 and it was adjusted by the addition of NH_4OH . After that both solutions 1 & 2 was mixed and stirred at 37°C for 3 min.

The powder products were obtained by filtering the solutions after 3 min of stirring at 37°C. The filtered products were repeatedly washed and dried at 37°C overnight. Gels were obtained by drying the sols after 3 min of stirring at 37°C. A part of the sol was dried at 37°C, whereas a second part was oven-dried at 80°C overnight.

Synthesis in Aqueous Medium

The syntheses in aqueous medium were carried out following the same procedure as for alcoholic medium, but in this case $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ was dissolved in 50ml of deionised water and then added rapidly to 50 ml solution containing $(\text{NH}_4)_2\text{HPO}_4$.

Formation of HA Powder by the Use of $P(OCH_2CH_3)_3$, $Ca(NO_3)_2$ and Anhydrous Ethanol [17]

In this method Triethyl phosphite $P(OCH_2CH_3)_3$ acts as one of the precursor. It was diluted in anhydrous ethanol. Initially a small amount of distilled H_2O was added in the previous mixture for hydrolysis. The mixture was then sealed in a glass beaker after addition of H_2O followed by vigorous stirring. Opaque appearance of mixture was observed. But after 30 min. of mixing the visibility of the solution became clear to ensure the complete hydrolyzation of phosphite. A 3M calcium nitrate $Ca(NO_3)_2$ was dissolved in anhydrous ethanol and subsequently added drop wise into the hydrolyzed phosphorus solution. Vigorous stirring was continued for an additional 10 min after the addition. A clear solution was obtained and aged at room temperature for 16 h before drying. The solvents were then driven off at $60^\circ C$ until a viscous liquid was obtained. Further drying of the viscous liquid at $60^\circ C$ resulted in a white gel. The gel was ground with a mortar and pestle into fine powder and subjected to different calcinations temperatures, from 300 to $800^\circ C$ with 25- $50^\circ C$ intervals, for 2 h [17]. The procedure was as shown in the form of flow diagram given below.

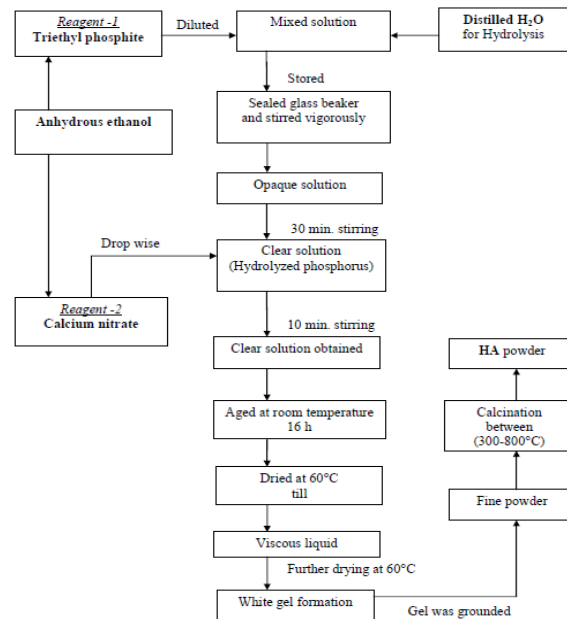


Fig. 5: Schematic Flow Process Chart for the Synthesis of HA by the Use of $P(OCH_2CH_3)_3$, $Ca(NO_3)_2$, and Anhydrous Ethanol [Chart is Plotted on the Basis of Process Setup Reported in Ref. 17]

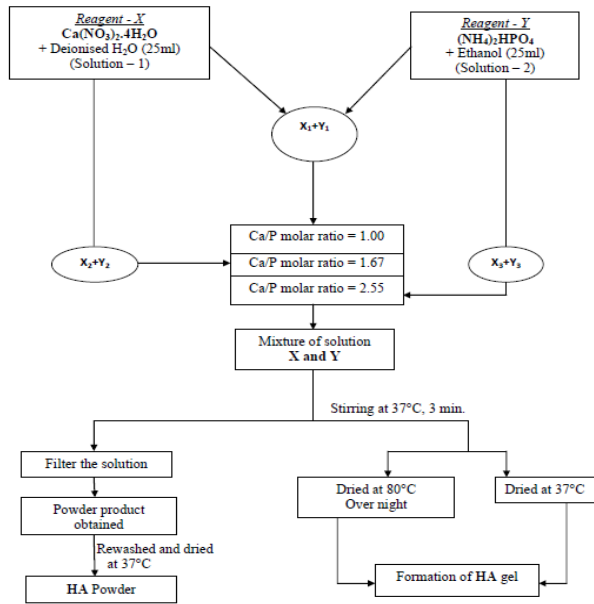


Fig. 4: Schematic Flow Process Chart for the Synthesis of HA by the Use of $Ca(NO_3)_2 \cdot 4H_2O$ and $(NH_4)_2HPO_4$ [Chart is Plotted on the basis of Process Setup Reported in Ref. 33]

COMPARISON OF VARIOUS SOL-GEL TECHNIQUES USED FOR THE SYNTHESIS OF HA POWDER

Summary of as discussed sol-gel techniques are given in Table I with comparison in relation to powder properties, advantages and limitation of synthesized powder

CONCLUDING REMARK

It is thought that by studying the review work done in this literature give easy understanding to future researchers for getting knowledge regarding various sol-gel techniques developed earlier for HA synthesis. The mutual comparison of the sol-gel techniques, give ease to understand the effect of change of reagent or precursor solution, subsequent drying and sintering at different temperatures on the end product. Also the approach can easily be extended for generation of HA coating on various substrates for biomedical applications. But after reviewing of this literature it is quite clear that the appropriate method is still awaiting for synthesis of most effective HA Powder.

Table 1

Method	Powder Properties	Advantages	Limitations
Method-1[29] Ca(NO ₃) ₂ ·4H ₂ O +P ₂ O ₅ HA	<ul style="list-style-type: none"> Resultant Gel was transparent or translucent. Single phase of HA powder was obtained. Size of HA powder particles lies in the range of 50–150 nm. 	Formation of nano structure HA with the low processing temperature & it was easily deposited on various substrate.	<ul style="list-style-type: none"> This process result the presence of amorphous HA powder in the as prepared precursor. Heat treatment at 900°C for 12 hr in stagnant air is required to convert the amorphous phase into pure crystalline HA.
Method-2[30] Ca(NO ₃) ₂ ·4H ₂ O + (NH ₄) ₂ PO ₄ HA	<ul style="list-style-type: none"> Nano crystalline powder having particle size in the range of 1.3 nm in radius was produced. No by-products up to 1200°C 	<ul style="list-style-type: none"> The powder produced by this method is having porous crystalline structure. (b) porosity in the powder exhibits good biocompatibility that enable the circulation of physiologic-al fluid. In this method synthesis is carried out in the presence of alcohol which provides thermally stable powder. 	<ul style="list-style-type: none"> For the pure crystalline HA powder as final product we have to heat at or above 750°C
Method- 3[6] Ca(NO ₃) ₂ ·4H ₂ O +P ₂ O ₅ +Citric Acid HA	<ul style="list-style-type: none"> Multiple phases of HA powder (hydroxyapatite, carbonated hydroxyapatite and a small amount of β-tricalcium phosphate) was formed at 650°C. Single phase of oxy hydroxyapatite at 800 °C. 	<ul style="list-style-type: none"> Citric acid provides good gelation. Easy availability of citric acid. 	<ul style="list-style-type: none"> Amorphous HA having multiple phases like β-tricalcium phosphate, oxy-HA are present with HA.
Method- 4[33] Ca(NO ₃) ₂ ·4H ₂ O + (NH ₄) ₂ HPO ₄ HA	<ul style="list-style-type: none"> Nano size powder was synthesized by this process. 	<ul style="list-style-type: none"> Pure crystalline powder was formed The powder synthesis by this method can be successfully applied to the coating of substrates with compact HA thin films The whole process is carried out at low temperature i.e. 300°C comparative to others. 	<ul style="list-style-type: none"> Synthesis method is larger and complicated

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