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Optimization of process parameters for solution combustion synthesis of Strontium substituted Hydroxyapatite nanocrystals using Design of Experiments approach

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ABSTRACT

Combustion synthesis is energy efficient, cost effective and a single step process for producing high purity nanoceramics, compared to conventional multi-stage wet chemical processes. Strontium substituted Hydroxyapatite (Sr-HAp) is a bioceramic having beneficial effects on osteoporotic drug delivery, bone formation and regeneration. Limited research work has been reported on combustion synthesis of Sr-HAp with no detailed investigation on the influence of process parameters on powder quality. In the present study, a Design of Experiments based twenty seven trials for Sr-HAp synthesis and detailed characterization of as-synthesized powders using X-ray diffraction (XRD), Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) with Energy Dispersive Spectroscopy (EDS) were carried out to optimize the process parameters to obtain the desired powder characteristics. A hypothesis on the formation of one dimensional nanorods based on nucleation growth kinetics has been proposed. As-synthesized powders were found to exhibit better structural and chemical homogeneity with optimum crystallinity fulfilling the criteria for use in biomedical applications.

1. Introduction

Hydroxyapatite (HAp) is a widely used biomaterial in tissue engineering exhibiting excellent biocompatibility, osteoconductivity and stable bioresorption with no adverse physiological effects on human beings [1–11]. Synthetic HAp $\{Ca_{10}(PO_4)_6(OH)_2\}$ nanoparticles show crystal structure similar to that of natural bone and is considered as a promising implant (bone substitute) as well as dental enamel material [1–6]. However, synthetic pure HAp has certain shortcomings such as poor mechanical properties, higher degree of crystallinity and consequently higher structural stability. This results in a lower rate of biodegradation resulting in poor response as an orthopedic implant material [2,8,10,12,13]. Hence, it is essential to improve these properties for its use as a monolithic material in implant/tissue engineering applications. The objective of improving the HAp property may be achieved by (i) modifying the grain size and/or (ii) altering the surface morphology/topography and/or (iii) incorporating trace elements into HAp structure [9,10,12,14]. Several trace metal ions chemically related to Ca^{2+} such as Ag^{+}, Zn^{2+}, Cu^{2+}, Fe^{2+}, Ba^{2+}, Mg^{2+} and Sr^{2+} substitutions can modify its solubility, crystallinity, morphology and lattice parameters [3,4,9,10,12,14–16]. Modifications using these elements led to improvement, not only in mechanical strength but also in antibacterial property [14–17]. Strontium is one of the essential trace elements in human body (≈320 to 400 mg in bone and connective tissues) showing beneficial effects, under both normal and osteoporotic conditions by enhancing the strength and density of bone [4,9,10]. Ca and Sr share the same group in the periodic table of elements with the atomic radius of 0.99 Å and 1.13 Å respectively. Both elements can form complete solid solution in hydroxyapatite [18]. Zhang et al. reported that Sr content up to 40% showed steady increase in solubility resulting in higher proliferation without any toxicity, while no osteoblasts were found in 100% Sr-HAp indicating the toxicity of high Sr concentrations [7]. Renaudin et al. reported that an amorphous phase was observed while incorporating 40% of strontium in apatite lattice [16]. Hence, Sr substitution in HAp between 0–30% has been taken up for investigation in the present study. Through a proper selection of the process parameters, Sr-HAp powders with controlled characteristics suitable for biomedical applications can be obtained. This study involves an attempt to optimize the process parameters for synthesizing high purity 0–30% Sr-HAp nanocrystals with optimum crystallinity.

Although several methods such as precipitation [4,7,13,15,19,20], hydrothermal synthesis [4,9,20,21], sol–gel [5,12,16] and biosynthesis [10] have been reported for the synthesis of pure HAp, only few studies

Abbreviations: HAp $\{Ca_{10}(PO_4)_6(OH)_2\}$, Hydroxyapatite; Sr-HAp $\{Ca_{10-x}Sr_x(PO_4)_6(OH)_2\}$, Strontium substituted Hydroxyapatite; TCP, Tricalcium phosphate; Temp / T_{ig}, Ignition temperature; DoE, Design of Experiments; RSM, Response Surface Methodology; ANOVA, Analysis of Variance; Sub%, % Sr substitution; Time, Synthesis time; CrySz/D, Crystallite size; Pur%, Phase purity; Cry%/Xc, Crystallinity.

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have been devoted to the preparation of Sr-HAp nanoparticles. These processes are not only time consuming, energy intensive and expensive but also require a secondary, high temperature calcination treatment to achieve structural homogeneity in the powders [10]. These high temperature treatments may sometimes lead to adverse reactions including (i) phase decomposition, (ii) phase transformations and (iii) crystallite growth and agglomeration. Combustion synthesis is a simple highly exothermic, non-catalytic and self-propagating technique. This method could be a most suitable, cost effective alternative for the production of nanoSr-HAp powder involving ignition temperatures of around 500 °C [3,6,17]. In combustion synthesis, when heat energy is introduced into the system, the fuel gets ignited and releases energy required for completion of the combustion reaction. Simultaneously low melting point intermediate products and impurities volatilize at the adiabatic flame temperature (T_f) to produce a high purity product. Fuels normally used include urea, glycine, ammonium acetate, ammonium citrate, citric acid, hydrazine, malonic dihydrazide and tetra formal-tris-azine [6,21–24]. Combustion technique requires just a single step for the synthesis of advanced ceramics and is definitely advantageous compared to the traditional multi-step methods of synthesis. One interesting feature of this process is that combustion reactions result in micro/nanoporosity within the particle agglomerates preferred feature for bio applications [2,24]. These interconnected porous structures play an important role in biomaterials facilitating osteointegration, bone ingrowths and regeneration [1–3,9,23,24].

Most of the available literatures have been confined either to the synthesis and characterization of Sr-HAp or on influence of Sr^{2+} on the rate of bone formation from a clinical point of view. Only a limited number of studies have been devoted to optimization of the synthesis parameters and detailed characterization of Sr-HAp. In a previous study [3], the authors have reported solution combustion synthesis of Sr-HAp emphasizing the influence of fuel used, pH of the solution, synthesis time and ignition temperature on the Sr-HAp synthesis as well as its sintering kinetics and phase formation [3]. This knowledge of understanding the influence of process parameters such as synthesis temperature and time is insufficient for production of powders with different Sr concentrations with desired powder characteristics as well as also to scale up the process for bulk powder production.

This paper therefore, attempts optimization of solution combustion process parameters for synthesis of Sr-HAp using Design of Experiments (DoE) approach. In addition, DoE based models have been validated by the characteristics of powders synthesized under optimized conditions. This paper aims (i) to use statistical methods for systematic investigation of the influence of important process parameters for solution combustion synthesis of Sr-HAp and (ii) to optimize these process variables to yield desired powder characteristics with minimum energy requirement and lowest cost. A Response Surface Methodology (RSM) based DoE technique was employed to determine the correlation between three important process parameters to obtain single Sr-HAp phase with required characteristics. The synthesized powders should have nanocrystals with optimum crystallinity, chemical homogeneity and better purity. A hypothesis on formation of Sr-HAp one dimensional nanorods has been proposed.

2. Materials and methods

Precursors used for preparing the solution were analytical grades of calcium acetate ($Ca(C_2H_3O_2)_2$), strontium chloride ($SrCl_2$) and diammonium hydrogen phosphate ($(NH_4)_2HPO_4$). DoE was used to design the number of screening experiments to optimize the parameters.

2.1. Design of Experiments (DoE)

Design of Experiments offer powerful mathematical models which can be applied for chemical reactions in industrial chemical synthesis. Response Surface Methodology is a collection of statistical tools used in DoE to optimize the response surface that is influenced by various process parameters and to quantify the relationship between the controllable input parameters. RSM includes the following steps: (i) designing a series of experiments for adequate and reliable measurement of the responses of interest, (ii) developing a mathematical model of the second order response surface with the best fit, (iii) finding the optimal set of experimental parameters that produce a maximum or minimum value of response and (iv) representing the direct and interactive effects of process parameters through contour plots and pie charts [25]. Prior to applying the DoE, the first step in modeling is to identify the main factors influencing the solution combustion process and the limiting values for the levels to be varied. Based on the author's previous work [3,17], ignition temperature (B = 400–600 °C) and synthesis time (C = 20–40 min) for varying %Sr substitution (A = 0–30 mol%) were identified as the main factors influencing the resulting powder characteristics. These factors were investigated at three levels, namely, +1 (high), 0 (middle) and −1 (low), keeping the other parameters constant as shown in Table 1. The screening DoE experimental plan was based on the full factorial design (F^k, where F is number of factors and k is number of levels; F = k = 3; 3^3 = 27 trial experimental runs) developed by Frank Yates to investigate both the main and interaction effects of parameters in a consistent and logical manner. These twenty seven trial runs were designed to verify the relative significance of the combustion process variables and help to optimize the process parameters for single step synthesis of Sr-HAp nanocrystals.

2.2. Synthesis of Sr-HAp

Sr substituted HAp {$Ca_{10-x}Sr_x(PO_4)_6(OH)_2$, where x = 0, 1.5 and 3} were combustion synthesized using the starting aqueous solution reactants containing (Ca + Sr)/P in the ratio 1.66. Calcium acetate was used as the precursor, since it has the strongest phosphate binding ability and is used as drug to prevent high phosphate levels in the blood. Diammonium hydrogen phosphate easily reacts with acetates and chlorides, resulting in decomposition accompanied by a vigorous reaction in the solution. Starting pH of the solution was 7.4, close to the pH (7.35 to 7.45) of bone forming body fluid [8]. Higher and lower solution pH values led to the formation of secondary phases and impurities in the final product as reported studies [3]. 2 wt.% of urea was added to the solution as fuel. Prepared solutions were then ignited at three different temperatures (400, 500 and 600 °C) and three different time durations (20, 30 and 40 min) in a muffle furnace. Combustion initiated at high temperature at one point and propagates by exothermic heat throughout the entire solution. This ensures a homogeneous synthesis. The spongy mass obtained after combustion was taken out and crushed to obtain fine powders.

2.3. Characterization of as-synthesized Sr-HAp

As-synthesized powders were characterized by XRD (Shimadzu LabX-6000 model) using monochromatic Cobalt (Kα) radiation (λ = 1.79 Å). From the XRD patterns, the crystal structure, phases present, crystallite sizes and crystallinity were determined. Crystallite size, crystallinity and phase purity of the synthesized Sr-HAp powders were evaluated as a function of process parameters such as % Sr substitution,

Table 1
Important process parameters for Sr-HAp synthesis and their levels.

S. No.	Factors			Responses		
	Description	Symbol	Label	Low (−1)	Middle (0)	High (+1)
1	Sr substitution (%)	A	Sub%	0	15	30
2	Ignition temperature (°C)	B	Temp	400	500	600
3	Synthesis time (min)	C	Time	20	30	40