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Formation of nanosized strontium substituted hydroxyapatites

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Abstract. Incorporation of specific elements into calcium phosphates offers the combination of a bioactive material and a therapeutic effect. This is important for improving the integration of implants as well as treating medical conditions. Strontium is a suitable candidate and displays the ability to stimulate bone growth and reducing bone resorption. This study investigated the formation of strontium carbonated hydroxyapatite nanoparticles from an amorphous phase. Crystallization of carbonated hydroxyapatite occurred at 585 °C, but samples with an intended 25% and 75% replacement of calcium with strontium crystallized at 624 °C. Heat treatment at the crystallization temperature revealed that strontium free apatite does not crystallize in 5 minutes, but an increasing strontium concentration leads to a higher rate of crystallization. X-ray diffraction patterns suggest that it may be difficult to include strontium, but higher strontium concentrations are possibly included with ease in the lattice. This work has produced a nanosized apatite accompanied by an amorphous phase after a short heat-treatment time. This offers a range of features that collectively show great promise for significantly enhancing the release of strontium for improved bone therapeutic effects.

1. Introduction

Hydroxyapatite (HAp) is a widely used biomaterial for bone regeneration and provides a surface for bone attachment to implants. The crystal lattice of hydroxyapatite $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$ can accommodate many divalent cation substitutions such as strontium (Sr), magnesium (Mg), barium (Ba), zinc (Zn), etc. These influence the processability of hydroxyapatite and also impact the biological properties. The osteoconductive properties of Sr make it a very interesting candidate for inclusion in the lattice for the preparation of nanosized apatite. Research will be directed towards the production of a nanosized Sr HAp.

Strontium increases bone formation and reduces bone resorption, and therefore dose control is important. Strontium may be administered orally as strontium renelate or included in the structure of apatite where a complete substitution for calcium is possible [1]. In

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hydroxyapatite, it is thought to favour the osteogenic differentiation of mesenchymal stem cells [2]. Studies in rats have shown that Sr improves the microarchitecture of bone, but is not as effective as bisphosphonate at improving the bone bonding to polymethylmethacrylate implants [3]. Another study with hydroxyapatite coated implants in osteoporotic rats has shown that Sr does however improve bone bonding to the implant [4]. A combination of Sr and hydroxyapatite could thus provide a synergistic effect in promoting bone growth and providing a good surface for attachment. The release of Sr may need to be increased and this can be provided by the more soluble carbonated apatite [5].

Previous work has shown the use of Sr enriched hydroxyapatites as powder [6], bone cements [7] and coatings made by plasma spraying [8] or laser ablation [9] for stimulating cell response. This work will prepare nanosized Sr substituted carbonated hydroxyapatite that can further increase the solubility, and determine whether it is possible to also include an accompanying amorphous phase. This is the first attempt to change the chemistry, decrease the crystal size and use an amorphous phase of the same composition as the basis for increasing the solubility.

The objective of this work is to a) produce strontium apatites with a different degree of calcium replacement, b) determine the influence of Sr on the crystallization of an amorphous precursor, and c) determine conditions for producing nanosized Sr carbonated hydroxyapatites. As an explorative study, the focus will be placed on 0% Sr, 25% Sr and 75% Sr replacement of calcium in apatite.

2. Materials and Methods

Strontium substituted carbonated hydroxyapatites were crystallized from an amorphous calcium phosphate precursor. The amorphous calcium phosphate was prepared from reagent grade $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ and $(\text{NH}_4)_2\text{HPO}_4$ and $(\text{NH}_4)_2\text{CO}_3$. Strontium nitrate was substituted for calcium nitrate to adjust the concentration for a 25% and a 75% replacement of calcium ions. Reactants were dissolved in deionized water at room temperature and the pH of the calcium containing solution was adjusted to 9.4. Both solutions were mixed for 10 minutes. And then washed with deionized water before filtration. Water was removed by freeze drying for 2 days.

The crystallization temperature was determined within a differential thermal analyzer (DTA), an EXSTAR TGA/DTA 6300. Heating was conducted in air from 30 °C to 900 °C at a heating rate of 10 °C min⁻¹ with the samples in zirconia crucibles. A cylindrical furnace was then heated to 5 °C higher than the crystallization temperature and a powder placed on a platinum foil for 5 mins, 15 mins, 30 mins and 60 minutes.

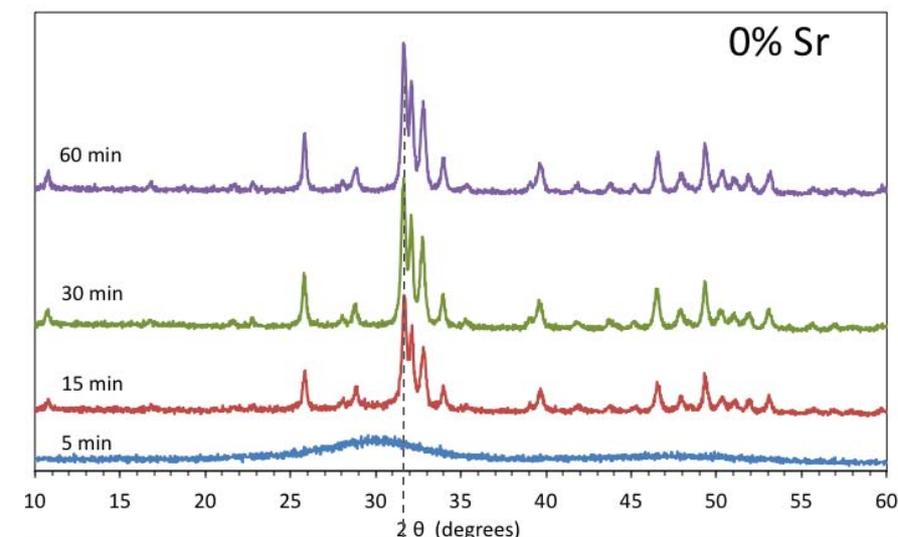
The phase of the heat treated powder was determined in an X-ray diffractometer (D8 Advance, Bruker) operated with $\text{Cu K}\alpha$ radiation ($\lambda=1.54056 \text{ \AA}$) generated at 40 kV and 40 mA and the diffracted intensity detected with a scintillation counter. Each sample was scanned from 10 to 60° 2 θ at a 0.02° step.

The chemical composition of Sr apatites was determined using wavelength dispersive X-ray spectrometry (S8 TIGER, Bruker) using a Rh lamp at 4 kW. Samples were analyzed in a

powder form under a 5 μm X-ray polypropylene film, using an 8 mm collimator in a helium atmosphere. Results are expressed in oxide formula units.

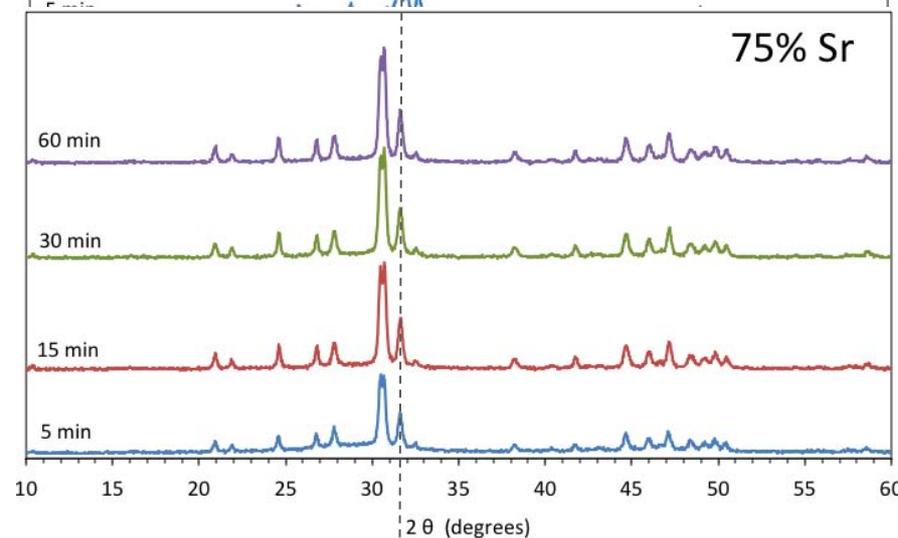
3. Results and Discussion

Three compositions for investigation included a 0% Sr, 25% Sr and 75% Sr where the percentage indicates the degree of intended calcium replacement with strontium, as set by the reactant concentrations. This allows comparison of a strontium depleted, a low substitution



and high substitution of strontium for the calcium. The exothermic peak on the DTA for 0% Sr extended over a range of 60 $^\circ\text{C}$, indicating slow ordering of calcium and phosphate for forming a crystalline state. A similar trend was observed for both Sr concentration samples.

Crystallization occurred at 585 $^\circ\text{C}$ for 0% Sr, but was higher at 624 $^\circ\text{C}$ for both 25% Sr and 75% Sr. The large size of the Sr ion must reduce the mobility necessary to form a denser assembly. Heat treatment was chosen at 5 $^\circ\text{C}$ higher than the crystallization peak. A comparison of all three compositions shows that 0% Sr does not crystallize after 5 minutes, but 25% Sr and 75% Sr reveal a combination of the starting amorphous phase and an apatite, Fig 1. The amount of apatite is higher for 75% Sr. No other calcium phosphate phases are present. Sr delays the onset of crystallization with a



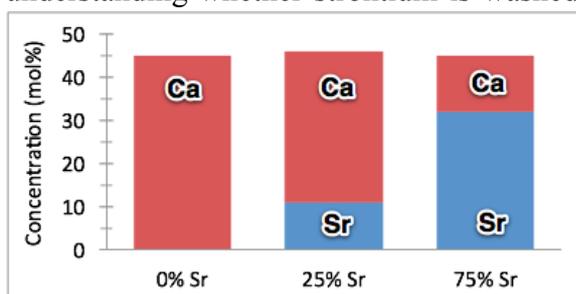
contribution from carbonate, but favours faster crystal growth.

Figure 1. X-ray diffraction patterns of 0% Sr, 25% Sr and 75% Sr heated for different periods.

A dashed line is included at $2\theta = 31.7^\circ$ to show the shift to lower angles for 75% Sr.

The characteristics of the crystallized carbonated hydroxyapatite is set by the heat treatment at 15 minutes. No substantial change is noted at longer heating times, Fig 1. The diffraction peaks for the 25% Sr seems very similar to 0% Sr, but a clear shift to lower angles is apparent for 75% Sr. An absence of a concurrent display of peaks from high and low strontium concentration apatites suggests a uniform solid solution for all compositions. The X-ray diffraction patterns validate the X-ray fluorescence results that show an absence of Sr for 0% Sr, a small concentration for 25% Sr and a large concentration for 75% Sr, Fig 2. It appears that less than the added strontium may have entered the lattice for the 25% Sr sample and more than 75% Sr has entered the lattice for the higher Sr containing carbonated hydroxyapatites. Further work is needed to determine the extent of incorporation in the lattice. This is more readily ascertained from a peak shift in samples heated treated at a higher temperature, to produce narrower X-ray diffraction peaks.

Further work needs to produce a more complete range of Sr containing samples. This could include a 50% Sr and a 100% Sr composition. These samples will facilitate a better understanding whether strontium is washed away during the rinsing stage and whether it is



possible to produce a pure Sr carbonated apatite using the new approach.

Further characterization could employ Fourier transform infra-red spectroscopy to analyze for the carbonate and hydroxyl groups. DTA/TGA could reveal the thermal stability and reveal the suitability of the powder for sintering or other thermal processing routes.

Figure 2. X-ray fluorescence of 0% Sr, 25% Sr and 75% Sr.

The inclusion of carbonate in the apatite lattice, the production of a small crystal size and the presence of an amorphous phase, as seen by heating for 5 minutes provides many factors to extend the apatite solubility and hence the strontium delivery to the surrounding tissue. Further work is necessary to measure the surface area and solubility of the nanopowders and the nanosized apatite together with the amorphous phase.

Conclusions

Crystallization of an amorphous phase has successfully led to the introduction of Sr inside the apatite lattice. While carbonated hydroxyapatite crystallizes at 585 °C, strontium containing compositions require further heating to 624 °C. Nanosized crystals can be obtained by heating between 5 and 10 minutes just above the crystallization temperature.

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