

IRON SUBSTITUTED APATITES: A RESORBABLE BIOMATERIAL WITH POTENTIAL MAGNETIC PROPERTIES

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INTRODUCTION: Localized hyperthermia shows promise as a treatment modality for tumor eradication [1]. The most common approach, for difficult to access locations, in the body has been to manufacture a thermoseed that can be heated remotely. Ferri-magnetic materials are suitable thermoseeds that produce hysteresis heating by application of an alternating magnetic field. In addition to displaying magnetic properties for heating a material for hyperthermia also needs to be biocompatible.

Biocompatible ferri-magnetic glass ceramics have been identified as suitable candidates for hysteresis heating [2]. These glass ceramics have been based upon the ferric oxide - calcia - silica system [3-6]. Heat treatment of the glass in a reducing atmosphere nucleates the magnetite phase. Another approach has been to combine both a ferric and ferrous ions in the reactants to nucleate magnetite [7]. These glass ceramics have been optimized for hysteresis heating and are relatively stable in the body. Ideally, the most suitable thermoseed would be stable during heating and resorb at a later time. At present only biodegradable polymers have been utilized as soluble carrier materials for ferromagnetic materials [8].

The apatite structure is relatively flexible in the range of substitutional elements [9]. Previous work has indicated that the inclusion of ferrous ions during synthesis has produced an apatite structure [10]. While processing of sintered zinc, silicon, strontium substituted apatites have been investigated no information is available for iron containing apatites. This work will investigate synthesis and high temperature processing of an iron containing apatite to determine the suitability in production of a magnetite containing apatite ceramic.

METHODS: Apatites were synthesized at 37 °C by the drop-wise addition of di-ammonium hydrogen phosphate to a solution containing metal nitrate. As a reference, the first reaction employed a 1M calcium nitrate aqueous solution to produce hydroxyapatite, labeled as R1. In the second

reaction, iron was added at a concentration of 10 mol. % to partially replace the calcium in the apatite, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ resulting in a compound designated as R2. In the third reaction, iron was added at 10 mol. % in excess to produce R3. Metal nitrate solutions mixed to a volume of 1 liter were adjusted to a pH of 9.4 with ammonium hydroxide before addition of the phosphate.

During the course of the reaction a pH stat was used to maintain the set pH level by addition of 10 vol.% of ammonium hydroxide. The precipitate was allowed to mature for 24 hours, washed with 2 liters of deionized water, filtered in a Buchner funnel and then washed with 1 liter of ethanol before drying at 80 °C. The powder cake was heat treated at 1150 °C in either air or nitrogen in a tube furnace for 3 hours.

The specific surface area was determined on the synthesized powders using the BET method. The 5 point method with nitrogen was performed using a Micromeritics Gemini 2360 (Norcross GA, USA) to determine the specific surface area.

The powders were characterised by X-ray diffraction, Fourier transform infrared and Mossbauer spectroscopy. X-ray diffraction patterns were obtained using a Rigaku Geigerflex diffractometer, using copper K_α radiation at 22.5 mA and 40 kV passing through a 0.3° receiver and 0.5° divergence slit. A scan rate of 0.5° per minute and a step size of 0.05 degrees were selected over a two theta range of 20-60°. Fourier transform infrared spectra were recorded using the KBr pellet technique in a Perkin Elmer 1600 Series FTIR over a 400 – 4000 cm^{-1} range at a resolution of 4 cm^{-1} .

The samples were crushed with a pestle and mortar and 50 mg/cm^2 of each sample was sealed into perspex holders. The Mossbauer spectra were taken using a conventional constant acceleration waveform with calibration using α -iron.

RESULTS: The surface area of the dried hydroxyapatite, R1, was 50 m^2/g compared to a value of 70 m^2/g for the iron modified apatite powders, R2 and R3. The smaller ionic size of iron compared to calcium has aided the nucleation

process or prevented crystal growth, resulting in fine crystallites.

All apatite powders, (R1, R2 and R3) after drying indicated the same absorption peaks in the infrared spectra, Fig. 1. The presence of iron does not seem to have influenced the chemical bonding within the apatite structure.

After synthesis, both R2 and R3 appeared mud-brown compared to a white color for R1. Heating of the iron containing powders to 1150 °C resulted in a color change to red when heated in nitrogen and to gray when heated in nitrogen.

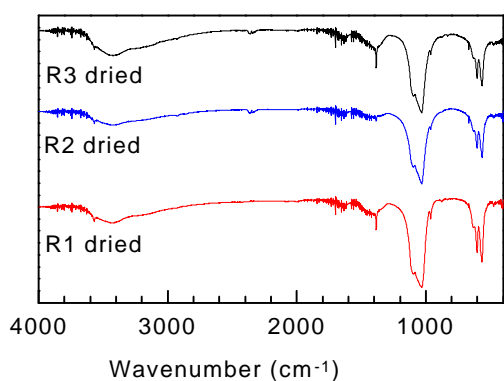


Fig. 1: Fourier transform infrared spectra of dried hydroxyapatite (R1), iron substituted hydroxyapatite (R2) and hydroxyapatite with excess iron (R3).

X-ray diffraction patterns revealed a change in phase composition. When heated in air, R2 formed both tricalcium phosphate and hematite, while in nitrogen no hematite was observed, Fig. 2.

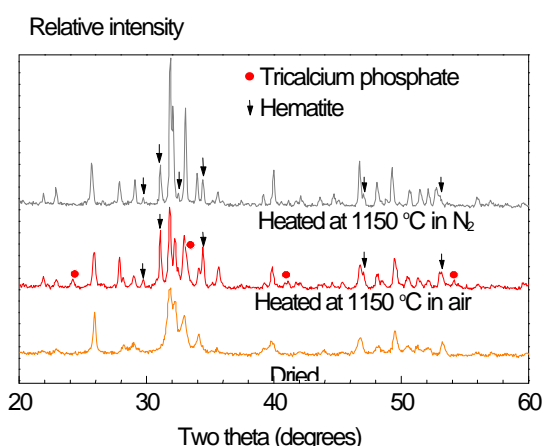


Fig. 2: Evolution of iron oxide in an iron substituted apatite (R2) upon heating in air & nitrogen.

R3 also showed the presence of hematite when heated in air and the absence of this phase when heat-treated in nitrogen, Fig. 3. A diffraction peak shift and a change in the relative peak intensities

has occurred. The absence of hematite in the sample heated in nitrogen, a shift in the apatite diffraction peaks and a change in relative peak intensities all suggest iron incorporation into the apatite lattice.

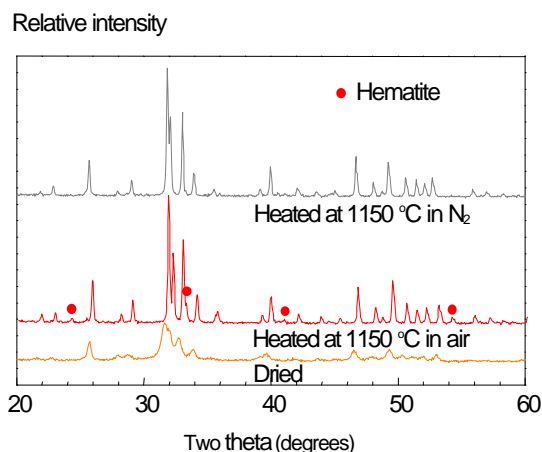


Fig. 3: Evolution of iron oxide in an apatite synthesized with excess iron (R3) and heat treated in air and nitrogen.

The room temperature spectra of R2 and R3 both showed two doublets. The dominant doublet has parameters isomer shift (IS) = 0.35(1) mm/s and quadrupole splitting (QS) = 0.74(2) mm/s with broad lines having a FWHM of nearly 0.50 mm/s. The second doublet had IS = 0.24(1) mm/s and QS = 0.30 mm/s with a good linewidth of 0.29 mm/s. The first doublet has the characteristic parameters of Fe³⁺ in octahedral coordination with oxygen and is very similar to that observed by Bauminger et al [11]. They ascribed the site to a compound similar to goethite α -FeOOH, which may be superparamagnetic since spectra taken by both groups at 85-100 K did not show any magnetic splitting. We would assign the second doublet to Fe³⁺ in the lattice and this accounted for 24% of the spectra area in R2 and 43% in R3.

After heat treatment in air, the dominant contribution to both spectra was due to hematite, α -Fe₂O₃ with a hyperfine field of 51.2(2) T. This accounted for 85% and 65% respectively of the spectral areas from the two samples. Although this is higher than the original goethite-like contribution, it does not necessarily imply that some has come from the other site since the narrower linewidth of approximately 0.30 mm/s indicates that the hematite is of much better crystallinity, and possibly larger particle size, which could lead to a higher recoilless fraction. The remainder of the area required three doublets with the best characterized one having an IS = 0.16(3) mm/s and QS = 1.6(1) mm/s. The low IS indicates that this is probably still structural but the site has been considerably

distorted from its arrangement prior to the heat treatment.

DISCUSSION: Other workers have synthesized γ - Fe_2O_3 using ferric nitrate in an aqueous solution. This involves a similar sequence of events comparable to the reaction route described in this paper. Initially, a precipitated $\text{Fe}(\text{OH})_3$ was reported after addition of ammonium hydroxide. Calcination at 250 °C produced a maghemite [12]. Such low temperature processing of powder applied to the synthesized powder reported in this paper may possibly produce the magnetic maghemite phase. Despite the attractiveness of obtaining a magnetic phase, the practicality is limited since the low temperatures would not be suitable in establishing a strong, coherent body. Maghemite (γ - Fe_2O_3) is transformed to α - Fe_2O_3 between 350 and 600 °C [13,14]. Sintering of apatites requires a temperature of at least 1100 °C.

From the two compositions chosen involving ferric ions, it can be observed that a replacement of calcium with a ferric ion has resulted in decomposition to beta tricalcium phosphate. The higher solubility of tricalcium phosphate compared to hydroxyapatite unnecessarily modifies the solubility characteristic of the resulting ceramic. On this basis, an addition of iron oxide during the synthesis stage, in line with the procedure chosen to produce R3, would be the most desired. Heat treatment could then be focused on transforming the iron oxide to the desired condition while maintaining a homogeneous matrix phase.

The ability of iron to remain in the lattice depends upon the heat treatment schedule. This property is confirmed by the diffraction peak shift that suggests that the iron is not adsorbed on the surface of the crystals, but enters the crystalline structure. This can be used to an advantage whereby an initial heat treatment is conducted in nitrogen to produce a sintered body and then the atmosphere is changed to crystallize an iron oxide phase. Since hysteresis heating depends on the amount of magnetic phase in the material, it would be necessary to increase the amount of magnetite. Further work would need to experiment with higher amounts of iron addition during the synthesis stage to ascertain the influence on the stability of the apatite lattice. The oxidation state of iron could be a key factor that influences the amount of iron that can fit into the apatite lattice.

This work has shown the formation of hematite, formed in neutral or oxidizing heating conditions. The use of a reducing gas such as 10% hydrogen in

carbon dioxide chosen by Kawashita et al [6] or pure hydrogen as discussed by Atalay [4], for forming magnetite in glasses, could also be selected for controlling the state of the iron oxide phase. It is believed that this would produce a magnetite containing hydroxyapatite.

The color of the heated apatite may be used to identify the type of apatite. A red has been produced from hematite and a change to gray occurs when the iron is accommodated in the lattice. This feature can be used to an advantage in determining the location of iron oxide even at the low concentrations.

A combination of ferrous and ferric ions has been used in producing magnetite in glass ceramics as described by Ebizawa et al [7]. This approach presents the correct proportion of ferrous and ferric ions required for formation of magnetite upon heating.

The resorption of hydroxyapatite is well established and it is predicted that magnetite containing apatite will dissolve at a rate dependent upon the amount of iron in the apatite lattice. For sintered hydroxyapatite, the dissolution at 37 °C produces about 5 ppm over a period of one hour. Heating the ceramic at temperatures required for hyperthermia will increase the solubility due to the increase in temperature and also due to the internal stress from the temperature gradient within the ceramic. These factors need to be determined as well as the relative solubility of the magnetite relative to the apatite.

CONCLUSIONS: It can be concluded that the transportability of iron is dictated by the atmosphere chosen for heat treatment. While nitrogen favours the formation of iron containing apatite, heating in air produces a hematite. Selection of a reducing atmosphere will be able to produce a finely dispersed magnetite in a biocompatible hydroxyapatite phase.

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