Synthesis and fabrication of β-tricalcium phosphate (whitlockite) ceramics for potential prosthetic applications

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A novel process is described for preparing dense, polycrystalline tricalcium phosphates. Single β-phase compositional integrity is achieved by introducing catalytic amounts of sulphate ion and this pore free material has close to theoretical density. Preliminary mechanical properties include a compression strength of 687 MN m^{-2} and a tensile strength of 154 MN m^{-2}. The relationship between processing variables and phase composition, microstructure, strength and translucence is described. The material has promise for bone implant applications.

1. Introduction

Recently there has been considerable interest in the development of calcium phosphate ceramics as potential hard tissue implants because of the close resemblance of these materials to vertebrate tooth and bone mineral. A variety of ceramic forms of hydroxylapatite [1—4] (Ca$_{10}$(PO$_4$)$_6$(OH)$_2$) and β-tricalcium phosphate [5, 6] [(Ca$_3$(PO$_4$)$_2$; whitlockite)] have been reported. Recent experience has indicated that ceramic forms of hydroxylapatite are inert as implant materials [7, 8] while those of tricalcium phosphate are bioresorbable [5, 6, 9].

The principal difficulties encountered during the preparation of calcium phosphate ceramics are achievement of high-strength and single phase compositional integrity. We have recently reported a novel precipitation method for producing a ceramic form of 100% hydroxylapatite, durapatite, which is substantially stronger than previously reported hydroxylapatite ceramics [4]. The present paper describes a novel catalytic method for the production of high-strength pure β-whitlockite ceramics.

2. Experimental methods
2.1. X-ray diffraction
The X-ray diffraction technique used for deter-mining various phases in the fired sample has been described previously [4]. The recorded peaks were compared with ASTM diffraction files. Peaks used for calculation of the composition of the various phases were (0.2.10) for β-whitlockite and (3 0 0) for hydroxylapatite.

The average particle size in the green cake was calculated from the line broadening of the (0.2.10) peak of β-whitlockite at half the maximum intensity using the Debye—Scherrer formula

$$t = \frac{0.9\lambda}{(B_M^2 - B_S^2)^{1/2}\cos\theta} \qquad (1)$$

where

t = the diameter of the particle,
λ = wavelength of copper K$_\alpha$ line,
B_M = the measured width of diffraction line at half its maximum intensity,
B_S = the measured width of the same diffraction line from a standard,
θ = the Bragg angle of the line.

2.2. Chemical analysis
Calcium was determined by standard EDTA techniques, and phosphate was determined spectrophotometrically by the method of Murphy and Riley [10]. The estimated accuracy in the Ca/P mole ratios is about ±2%. Analysis for sulphate utilized the standard barium gravimetric method.

2.3. Differential thermal analysis

The crystal–chemical transformations of the green cake during heating were studied by differential thermal analysis (DTA) using a Mettler recording vacuum thermoanalyser. The green cake was powdered and placed in platinum crucibles and the sample was heated from room temperature to $1100°C$ at a rate of $4°C min^{-1}$ in an argon atmosphere. Powdered Al_2O_3 was used as the reference and a Pt–Pt 10% Rh thermocouple was used for measuring temperature differences. DTA, expanded weight loss and differential thermal gravimetry (DTG) curves were recorded during the run.

2.4. Scanning electron microsopy

Small pieces of the sintered samples were fractured and then thermally etched for 1.5 h at a temperature $50°C$ below the sintering temperature. This heat treatment did not produce any appreciable grain growth, however, grain structure was clearly revealed. The samples were then coated with gold and observed in an AMR 1000 scanning electron microscope at 20 kV.

2.5. Mechanical testing

Fracture strength was determined by a three-point bend test. Samples of approximate dimensions 0.2 cm × 0.15 cm × 1.5 cm were cut from the sintered plates with a diamond saw, mounted on a polishing jig and all the four sides were ground and polished to a $1 \mu m$ finish using diamond paste. Fracture tests were conducted with an Instron unit using a test jig of 0.381 in. span at a cross-head speed of 0.05 in. min^{-1}. Compression tests were made on polished (600 grit) cylinders approximately 1.6 mm high and 4.6 mm in diameter.

Hardness tests were made on a Kentron Knoop hardness tester with a diamond indentor. Samples were embedded in epoxy and surfaces were ground flat and polished to a $1 \mu m$ finish with diamond paste. Each sample was indented 10 times with 200 g and 300 g loads. No effect of load on hardness values was noticed at these loads.

3. Synthesis and forming of tricalcium phosphate (β-whitlockite)

3.1. Precipitation and $(NH_4)_2SO_4$ doping of tricalcium phosphate

The method of precipitation was similar to the method used for precipitation of hydroxylapatite

[4]. Reagent grade $Ca(NO_3)_2 \cdot 4H_2O$ and $(NH_4)_2HPO_4$ were dispensed from concentrated stock solutions which had been doubly analysed for Ca^{2+} and PO_4^{3-}.

A solution of $Ca(NO_3)_2$ (1.40 moles) in 900 ml distilled water was brought to pH 11 to 12 with concentrated NH_4OH and thereafter diluted to 1800 ml. A solution of $(NH_4)_2HPO_4$ (1.00 moles) in 1500 ml distilled water was brought to pH 11 to 12 with concentrated NH_4OH and thereafter diluted to 3200 ml to dissolve the resulting precipitate. The pH was again checked and additional concentrated NH_4OH was added if necessary.

The calcium solution was vigorously stirred at room temperature and the phosphate solution was added in drops over 30 to 40 minutes to produce a milky, somewhat gelatinous precipitate which was then stirred overnight (more than 12 h). The reaction mixture was then centrifuged (2000 r.p.m. for 10 min) and the clear supernatant fluid decanted. The resulting mineral sludge was homogeneously resuspended in distilled water and served as a feedstock for subsequent studies.

In order to produce green states which ultimately afforded mixed hydroxylapatite-whitlockite ceramics, aliquots of the feedstock suspension were recentrifuged, homogeneously suspended in two volumes of distilled water, and filtered on a Buchner funnel with application of mild suction and a rubber dam. After filtration for several hours, the compact clay-like cake was dried intact at $90°C$ for 15 h to produce directly the green state [4].

To produce green states which afforded 100% β-whitlockite ceramics, aliquots of the feedstock suspension were recentrifuged, homogeneously suspended in to volumes of dilute aqueous ammonium sulphate (1 to 2%; see Section 4) and then filtered and dried as detailed above.

Modifications of the above representative synthesis and forming process were also investigated and are detailed in Section 4.

3.2. Mode of action of $(NH_4)_2SO_4$

To further assess the role of sulphate ion, green cakes which had previously served as precursors to 100% hydroxylapatite ceramics [4] (Ca/P = 1.67) were powdered and admixed with 20% by weight of powdered $(NH_4)_2SO_4$. The loose powder mixture was then heated at 900 to $1300°C$ for 1 h and examined by X-ray and elemental analyses. Additionally, green cakes which normally

TABLE I Effect of processing variables on the composition of tricalcium phosphate ceramics fired at 1150° C for 1 h

Initial mixing Ca/P mole ratio	SO_4^{2-} doping (% soln)	Composition of fired ceramic (wt%)			
		Ca/P mole ratio*	SO_4^{2-}*	β-whitlockite†	Apatite†
1.50	0	1.53	0	80	20
	1	1.54	0.67	100	0
1.40	0	1.48	0	84	16
	1	1.51	1.2	100	0
1.30	0	1.50	0	90	10
	1	1.51	1.76	100	0
1.20	0	1.49	0	90	10
	2	1.50	1.1	100	0

* Chemical analysis.
† X-ray diffraction.

produced highly translucent 100% hydroxylapatite ceramics [4] were sintered in a box furnace (volume 3400 cm³) in the presence of small quantities (4 mg) of remotely placed (10 cm) $(NH_4)_2SO_4$ or H_2SO_4. The surfaces of the fired ceramics were examined by direct X-ray diffraction.

In order to determine the accuracy of X-ray determinations on mixed whitlockite—calcium sulphate systems, presintered (1100° C for 1 h) pure β-whitlockite and presintered (1100° C for 1 h) pure calcium sulphate were mixed in known percentages and examined by X-ray diffraction.

3.3. Sintering conditions
Sintering was carried out in a box furnace. In general, the green cake was placed on an alumina dish and initially heated to 600° C over 0.5 h. The temperature was then raised quickly (~5 min) to the desired temperature (see Section 4) and sintered isothermally for 1 h, followed by a soak at 900° C for 4 h.

4. Experimental results
4.1. Effect of processing variables on the final ceramics
The effect of processing variables on the final composition of the fired ceramic is given in Table I. Reacting calcium and phosphate in the correct tricalcium phosphate stoichiometric ratio $(Ca_3(PO_4)_2$; Ca/P = 1.50) frequently resulted in the production of green cakes and ceramics with Ca/P > 1.50. Lower initial mixing ratios (Ca/P = 1.20 to 1.40) afforded ceramics with Ca/P closer to the theoretical value of 1.50.

The profound effect of introducing small amounts of sulphate ion into the mineral sludge, prior to final harvesting, is also shown in Table I.

All samples which had not been doped with dilute $(NH_4)_2SO_4$ produced ceramics containing whitlockite and hydroxylapatite phases, while $(NH_4)_2SO_4$ doped samples produced 100% β-whitlockite ceramics. Doping solutions containing less than 1% $(NH_4)_2SO_4$ were sometimes unsuccessful in completely converting the green cake to a 100% β-whitlockite ceramic and 3% solutions had a tendency to produce more friable green states. Some ceramic samples contained a small percentage of α-whitlockite which was completely converted to β-whitlockite by equilibration at 900° C for 4 h.

Although small amounts of sulphate ion were detected by chemical analysis in these doped ceramics (Table I), no secondary $CaSO_4$ crystalline phases were evident in their X-ray and microstructural analysis (see Section 4.5). It should be noted that no pH changes (versus distilled water) were observed during the wet chemical processes associated with the introduction of the dilute $(NH_4)_2SO_4$ doping solutions (see Section 3.1.).

4.2. Effects of sulphate ion
Green cakes which normally produced highly translucent 100% hydroxylapatite ceramics [4] (Ca/P = 1.67) were found to have thin (~50 to 100 μm) opaque coatings when sintered in the presence of remotely placed $(NH_4)_2SO_4$ or H_2SO_4 (Section 3.3). Concentrated hydrohalogen acids (HBr, HCl) had no such effect. Direct X-ray surface diffraction showed the opaque coatings contained 65% hydroxylapatite and 35% whitlockite.

Table II shows the results of admixing and then calcining hydroxylapatite and $(NH_4)_2SO_4$ powders (Section 3.2.). When heated at 900° C for 1 h, the apatite had completely reacted and

TABLE II The effect of heating (1 h) mixed hydroxyl-apatite (80%) and $(NH_4)_2SO_4$ (20%) powders

Temperature ($^\circ$ C)	SO_4^{2-}† (wt%)	Phase composition (wt%)‡		
		β-whitlockite	Apatite	$CaSO_4$
900	8.89	97	0	3
1000	8.74	98	0	2
1100	7.98	100	0	0
1200	6.13	80	20	0
1300	5.05	50	50	0
$3Ca_3(PO_4)_2$ + $CaSO_4$ *	8.90	0	87	13

* Preheated (1100° C for 1 h) individually and then mixed.
† Chemical analysis.
‡ X-ray analysis.

elemental analysis indicated the mixture contained an amount of sulphate ion equivalent to that which would be expected for the theoretical mixture $3Ca_3(PO_4)_2 + CaSO_4$ (%SO_4 = 8.90). Based on this same theoretical mixture, the $CaSO_4$ content (wt%), as revealed by X-ray analysis, should have been 12.75%, but only 3% $CaSO_4$ was observed. The sulphate ion content of the mixtures decreased as the temperature was raised, and increasing amounts of apatite began to reappear at higher temperatures (Table II). At and above 1100° C, no $CaSO_4$ was observed in the X-rays analysis even though significant amounts of sulphate ion were present. In contrast, when samples of β-whitlockite and calcium sulphate were preheated individually and then mixed in known proportions, predictable X-ray results were obtained, thus establishing the accuracy of the X-ray method (Table II).

4.3. Characteristics of green cakes and process of transformation to whitlockite

Both the ammonium sulphate doped and undoped green cakes were white coloured and fragile. There was no difficulty in handling the green cakes for sintering purposes. X-ray diffraction analysis on the green cakes showed only one broad peak near the strongest peak (0.2.10) of β-whitlockite. The average particle size determined from the peak broadening gave a value of approximately 75 Å for both the 1% ammonium sulphate doped and undoped green cakes. Because of the extremely small particle size, the green cakes can be considered to have an amorphous structure.

In order to understand the mechanism of transformation of the amorphous green cakes into strong polycrystalline ceramics during heat treatment, DTA and X-ray diffraction studies were carried out. Fig. 1 shows the DTA, DTG and expanded weight change curves for a green cake prepared by the ammonium sulphate doping procedure. On heating up to about 600° C, a gradual change in the DTA and weight loss curves was observed due to dehydration, then a sharp dip in the weight loss curve and a sharp peak in the DTA curve were seen at 725° C. Essentially identical DTA–DTG curves were obtained for undoped samples. The X-ray diffraction traces taken at different stages of heating are shown in Figs. 2a to c. The doped green material showed only a broad peak near the strongest β-whitlockite peak (0.2.10); on heating to 725° C a sharp peak
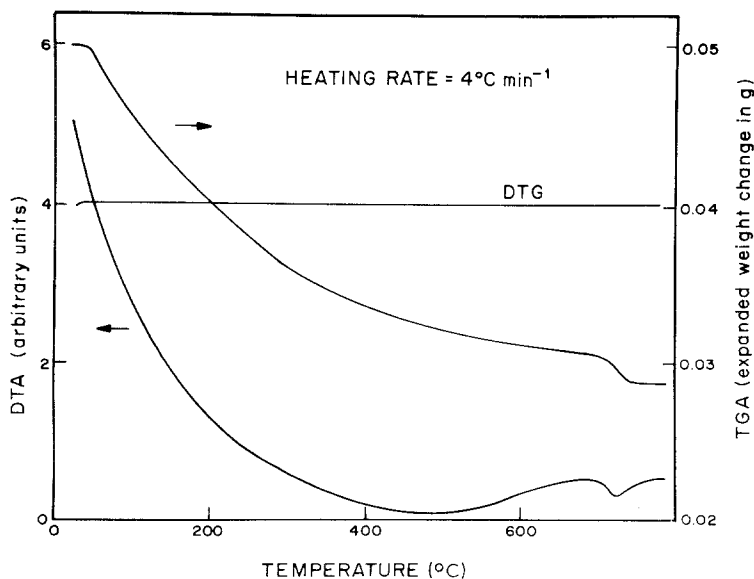

Figure 1 DTA, TGA (expanded weight change) and DTG curves for 1% ammonium sulphate doped β-whitlockite green cake.

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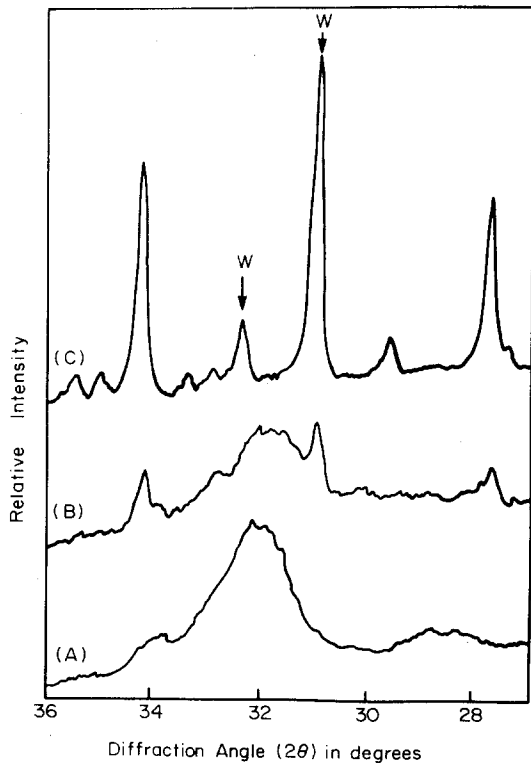*Figure 2* X-ray diffraction traces of 1% ammonium sulphate doped whitlockite green cakes: (A) Unheated material. (B) heated at 725° C for 20 min; β-whitlockite peaks (W) begin to appear. (C) Heated at 740° C for 1 h; 100% β-whitlockite.

Figure 3 Diffractometer trace of undoped green cakes: (A) Heated at 700° C for 20 min; hydroxylapatite peaks (H) begin to appear. (B) Heated at 750° C for 20 min; hydroxylapatite (H) and β-whitlockite (W) peaks are present. (C) Heated at 855° C for 1 h; sharp peaks of both phases are present.

started to appear at the (0.2.10) peak position and at 740° C all the β-whitlockite peaks appeared sharp indicating complete transformation to crystalline β-whitlockite. For comparison a green sample prepared without ammonium sulphate doping was heated in a similar manner and the corresponding X-ray diffraction patterns are shown in Figs. 3a to c. The green material showed the same broad peak as in the doped sample. On heating, only hydroxylapatite peaks started to appear at 700° C, at 755° C both β-whitlockite and hydroxylapatite peaks were seen and on heating above this temperature sharp peaks of both β-whitlockite and hydroxlyapatite were observed showing the complete transformation to a two phase polycrystalline structure from an amorphous structure.

4.4. Effect of sintering temperature
The effects of sintering at different temperatures are given in Table III. Doped samples sintered at 1200° C displayed a density (displacement method) which was within experimental error of the theor-
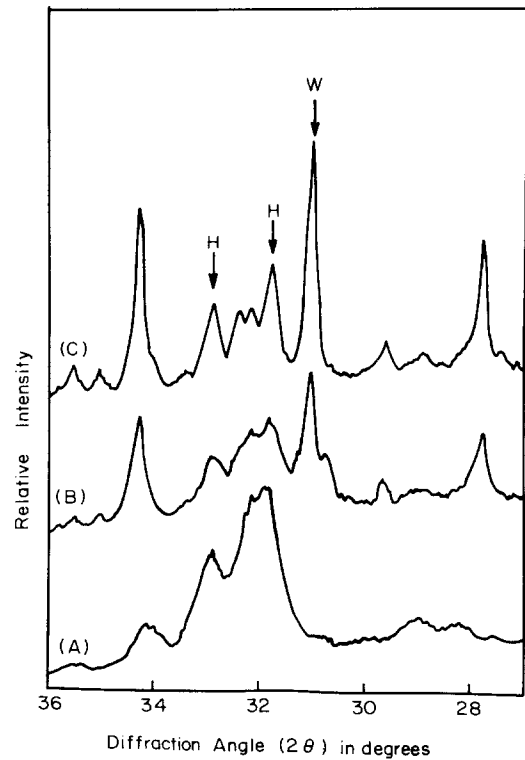
etical density of β-whitlockite (3.07). Based on the density and qualitative translucency ratings given in Table III, the optimal sintering temperature for the 100% β-whitlockite ceramic was approximately 1200° C. The mixed phase ceramics were also of high quality as evidenced by their translucency and microstructure (Section 4.5.).

TABLE III Effect of sintering temperature on sulphate doped 100% β-whitlockite ceramics

Temperature (1 h; ° C)	Density (% theoretical)	Average grain size μm	Translucence grading*
1000	—	—	opaque
1050	94.0	—	4
1100	98.3	0.295	2
1150	99.1	0.424	1
1200	99.7	0.483	1
1250	—	2.137	3
1100[†]	—	0.616	2

* 1 (almost translucent) to 4 (most opaque).
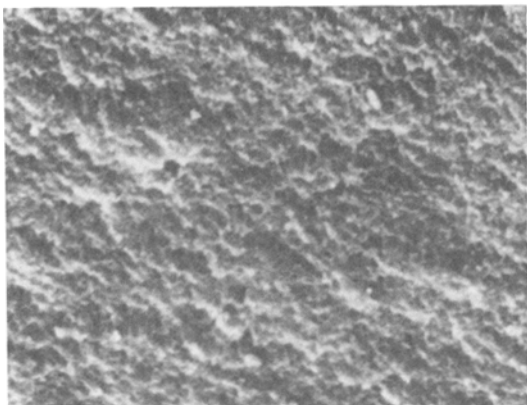
† Undoped mixed whitlockite–apatite ceramic.

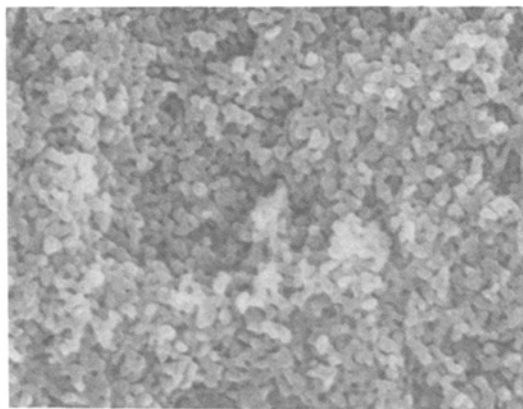Figure 4 Scanning electron micrograph of the fracture surface of 1% ammonium sulphate doped green cake (× 6200).

Figure 5 Scanning electron micrograph of the fracture surface of sulphate doped 100% β-whitlockite fired at 1000° C for 1 h (× 6200).
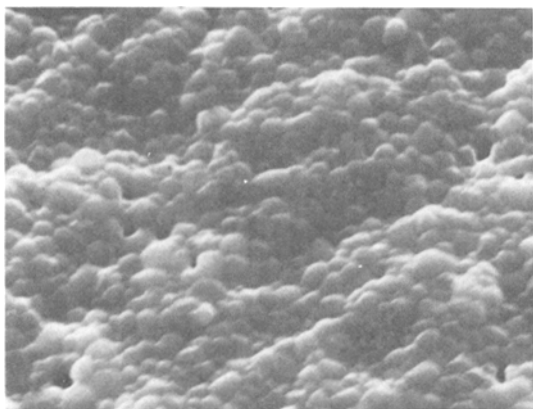

Figure 6 Scanning electron micrograph of thermally etched fracture surface of β-whitlockite fired at 1100° C for 1 h (× 6200).
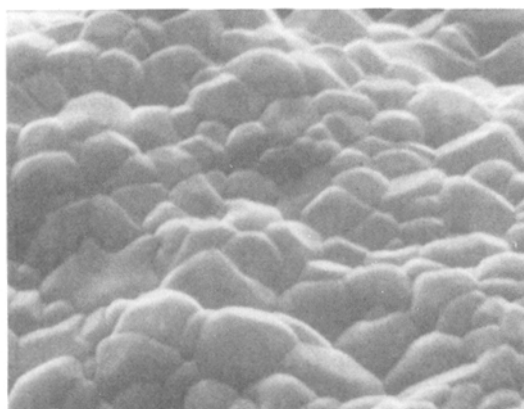

Figure 7 Scanning electron micrograph of β-whitlockite fired at 1150° C for 1 h (× 12400).

4.5. Microstructure

The microstructure of the green cakes was observed with the SEM. Since the green samples contained an appreciable amount of water, the SEM samples were heated to 600° C for complete dehydration. The particle structure remained unchanged after the heat treatment, as evidenced by the negligible shrinkage of the sample and the unchanged X-ray diffraction pattern. The SEM micrograph of the fracture surface of a green cake prepared by the ammonium sulphate doping procedure is shown in Fig. 4. Spherical agglomerates of crystals approximately 500 Å in diameter can be seen, but at 20×10^3 magnification the individual crystals cannot be resolved. The microstructure of the undoped green cake was identical.

A fracture surface of a doped sample fired at 1000° C is shown in Fig. 5. The highly reactive spherical particles in the green cake were joined by neck growth and a continuous pore channel was formed, as is clearly seen in the micrograph. The particles in the green cake have lost their identity and considerable grain growth has occurred; the sample appears to be in the intermediate stage of sintering and the particles were approximately cylindrical with dimensions $0.23 \, \mu m \times 0.51 \, \mu m$. The fracture surface of a sample sintered at 1100° C, after thermal etching, is shown in Fig. 6. The grain boundaries and isolated pores are visible. The average grain size was $0.295 \, \mu m$. Fig. 7 shows the thermally etched microstructure of a sample sintered at 1150° C. Porosity was completely eliminated and the average grain size was $0.42 \, \mu m$. During the intermediate and final stages of sintering, pore elimination has occurred without considerable grain growth. The
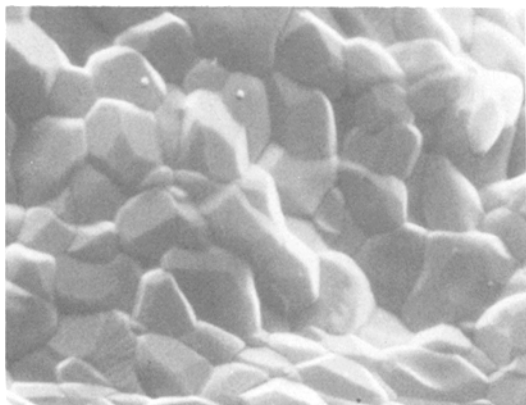
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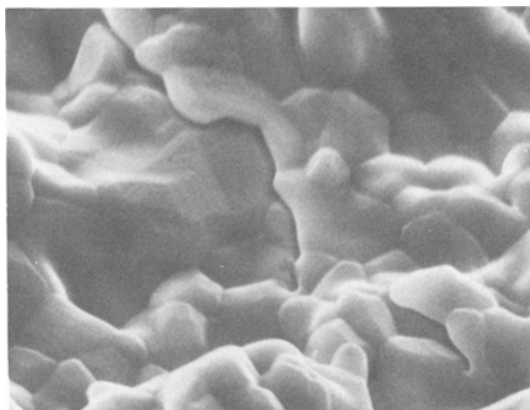*Figure 8* Scanning electron micrograph of β-whitlockite fired at 1200° C for 1 h (× 12400).

Figure 9 Scanning electron micrograph of β-whitlockite fired at 1250° C for 1 h (× 3100).

Figure 10 Electron micrograph from two-stage replica of a mixed phase ceramic (80% β-whitlockite and 20% hydroxylapatite) fired at 1100° C for 1 h (× 11 780).

microstructure of the sample fired at 1200° C is shown in Fig. 8. Some grain growth has occurred and the sample was pore free.

Samples fired at 1150° C and 1200° C were translucent, in agreement with the pore free microstructure. Increasing the sintering temperature to 1250° C caused a decrease in translucency. At this temperature, considerable grain growth has occurred (grain size 2.14 μm; Fig. 9). Microcracks were introduced along the grain boundaries due to exaggerated grain growth and development of internal stresses. One grain, which grew as large as 8 μm, introduced a crack at the boundaries, as seen in the micrograph. Thus, the microstructures also clearly showed (cf. Table III) that the optimal sintering temperature was between 1150° C and 1200° C.

The mixed apatite—whitlockite phase ceramics were also pore free, as shown in Fig. 10. In general, the microstructure of the single phase or mixed phase ceramics was the same.
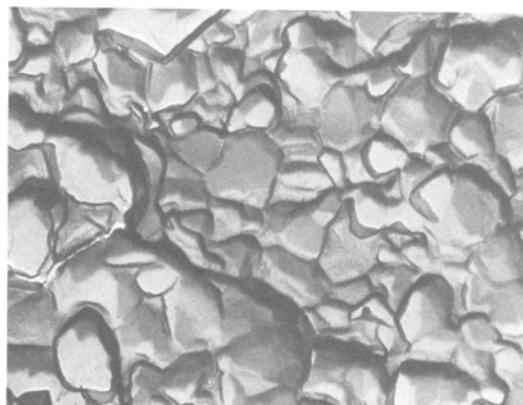
4.6. Mechanical properties

Since ammonium sulphate doped β-whitlockite samples fired at 1150° C and 1200° C appeared to be the best samples from observations of density, microstructure and translucence, only these samples were tested for fracture strength. The average fracture strength of samples fired at 1150° C was 141 MN m^{-2} ± 20% for 14 samples and that of samples fired at 1200° C was 154 MN m^{-2} ± 20% for 8 samples. The average compressive strength of samples fired at 1100° C was 687 MN m^{-2} ± 13% for 17 samples. The average modulus of elasticity in tension was 33 × 10^9 N m^{-2}.

The Knoop hardness of the samples fired at 1150° C was 473. This value compares with 480 for sintered hydroxylapatite [4], 430 for natural apatite and 560 for fused silica.
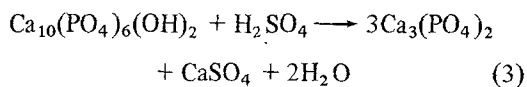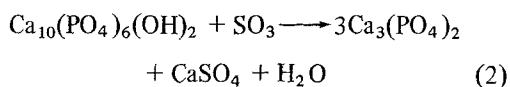
5. Discussion

The precipitation of tricalcium phosphate from aqueous solution has been the subject of previous studies. The initial phase that precipitates, sometimes called "amorphous" calcium phosphate, has a Ca/P ratio of 1.5 regardless of the initial mixing stoichiometry [11, 12]. When rapidly prepared and harvested (a process which is not amenable to large scale preparations) "amorphous" calcium phosphate serves as a thermochemical precursor to apatite-free whitlockites [11, 12]. When allowed to age in its reaction medium, as in the present case, the tricalcium phosphate shows a greater tendency to produce apatite--whitlockite mixtures [11]. Finally, the green state used in the present process contains a significant amount (~ 6%) of tightly bound

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water [4] and it has been shown the presence of water vapour during calcination of tricalcium phosphate promotes the formation of apatite [11]. Thus, the present study, wherein mixed whitlockite—apatite ceramics were obtained in undoped runs is consistent with previously reported observations.

The use of sulphate ion as a catalyst to promote the conversion of apatite to whitlockite is not apparent and in fact resulted from an initially annoying, but ultimately serendipitous observation. During the course of sintering pure hydroxylapatite ceramics [4], whitlockite-containing coatings were sporadically observed on these ceramics as a result of some volatile contaminant. This volatile contaminant ultimately proved to be sulphur trioxide, derived from sulphate ion which was present in minute amounts in some iron-containing ceramics which had been previously sintered in the same furnace. The catalytic effect of sulphate ion was confirmed as detailed in Section 4.2.

Although the exact mechanism whereby sulphate ion converts apatite to whitlockite in the present study is not known, several conclusions can be drawn from our results. In the case of admixing and reacting hydroxylapatite and ammonium sulphate powders, as detailed in Section 4.2., the elemental analysis suggests the reaction initially proceeds according to Equations 2 or 3; in Equation 3, the sulphuric acid is derived by the reaction of volatile SO_3 with water in the green cake.

$$Ca_{10}(PO_4)_6(OH)_2 + SO_3 \longrightarrow 3Ca_3(PO_4)_2$$
$$+ CaSO_4 + H_2O \qquad (2)$$

$$Ca_{10}(PO_4)_6(OH)_2 + H_2SO_4 \longrightarrow 3Ca_3(PO_4)_2$$
$$+ CaSO_4 + 2H_2O \qquad (3)$$

X-ray analysis, however, suggests the calcium sulphate is not present as a secondary crystalline phase but exists as a solid solution within the β-whitlockite structure. On further heating at higher temperatures (Table II), both the X-ray and elemental analysis suggest the sulphate-containing material begins to decompose, possibly producing a defect apatite:

$$3Ca_3(PO_4)_2 + CaSO_4 \longrightarrow Ca_{10}(PO_4)_6O + SO_3$$
$$(4)$$
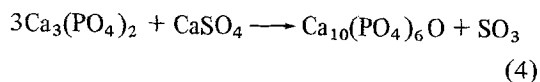
The above gross reaction between hydroxylapatite

and ammonium sulphate powders clearly demonstrates the ability of sulphate ion to decompose hydroxylapatite, scavenge the liberated calcium ion, and produce 100% β-phase whitlockite. In the case of the ammonium sulphate doped whitlockite ceramics, which contain only small amounts of sulphate ion, it is possible the sulphate has served to scavenge any excess calcium ion which would otherwise go on to produce hydroxylapatite. Alternatively, if excess calcium ion is not present, the sulphate ion may enter the hydroxylapatite lattice, an event for which there is a precedent [13], and destabilize it relative to whitlockite. In either case, differential thermal analysis can shed little light on the matter since the DTA and DTG traces of both the doped and undoped cakes were essentially identical, as were the microstructures of the green cakes.

The mechanisms controlling the sintering of both the doped and undoped green cakes to 100% density are believed to be similar to those reported for 100% dense hydroxylapatite prepared by the same precipitation process [4]. The very small initial particle size (~ 75 Å) in the green cakes and the peculiar way they are bound together by water molecules are two of the important factors contributing to the high activation energy for sintering and densification.

Previously reported dense β-whitlockite ceramics have been prepared by high-pressure powder compaction techniques and have had compression strengths in the order of $\sim 344 \, MN \, m^{-2}$ [14], or approximately one-half the strength of the present material. Bioresorbable β-whitlockite implants currently being investigated are not in dense form but instead have a high degree of purposefully introduced macroporosity (pore size ~ 100 to $300 \, \mu m$) [5, 6]; this allows for tissue infiltration and a more rapid and uniform resorption and replacement by bone. Thus, the next step in the development of bioresorbable implants, after maximizing the strength of dense materials, is to modify the forming process so that macroporous materials of maximum strength can be made. This has been previously accomplished, in conjunction with powder compaction techniques, by homogeneously incorporating sized naphthalene particles in the whitlockite powder [5, 6, 15]. The mixture is then pressed followed by removal of the naphthalene by sublimation, and the green piece is then sintered. In the present case, the slip-like mineral sludge has been found to be com-

patible with more or less standard ceramic foam producing techniques and the desired macroporous 100% β-whitlockite ceramics have been achieved [16].

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