

Formation of Calcium Phosphate Whiskers in Hydrogen Peroxide (H₂O₂) Solutions at 90°C

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A novel, one-pot technique of synthesizing calcium phosphate whiskers was developed. Commercially available β -tricalcium phosphate (β -Ca₃(PO₄)₂) powders were aged in unstirred 30% H₂O₂ solutions at 90°C for 48 h in ordinary glass media bottles. Resultant samples consisted of whiskers (200 nm wide and 5 μ m-long) of a biphasic mixture of octacalcium phosphate (OCP: Ca₈H₂(PO₄)₆·5H₂O) and carbonated apatitic (apatite-like) calcium phosphate (Ap-CaP). As-formed whiskers possessed a Ca/P molar ratio of 1.46 and a BET surface area of 8 m²/g. Upon soaking these whiskers in a Tris-HCl-buffered SBF solution of 27 mM HCO₃⁻ for 6 days, Ca/P molar ratio and surface area values were increased to 1.60 and 52 m²/g, respectively. The technique, owing to its simplicity, may prove useful in providing large amounts of biocompatible short whiskers for numerous technology sectors.

I. Introduction

SKELTONS and the hard tissues of mammals possess calcium phosphate (CaP) as the only biological inorganic phase. The human body uses the carbonated (5.8 wt%), alkali (Na⁺ and K⁺, totalling 0.73 wt%) and alkaline earth (Mg²⁺, 0.55 wt%) ion-doped, apatitic (*apatite-like*) calcium phosphate (Ap-CaP) as the sole inorganic phase, where and when it needs to exploit the load-bearing ability of such strong materials.¹ Owing to the presence of the above dopants and their unique stoichiometry, the apatitic human bone mineral deviates from the oversimplified formula of calcium hydroxyapatite (Ca₁₀(PO₄)₆(OH)₂).^{1,2} Whiskers of Ap-CaP were considered to be non-toxic and compatible with the human body.^{3–7} The economical and effortless production of biocompatible whiskers still remains an ardent task. CaP whiskers were mainly thought of as toughening additives for CaP bioceramic matrices or as fillers for biopolymer-based composites.^{8–10} CaP-whisker-reinforced composites are expected to achieve fracture toughness values much closer to those of human bones.¹¹

Yoshimura *et al.*^{12,13} laid the foundation for the hydrothermal synthesis of hydroxyapatite whiskers. The hydrothermal whisker synthesis procedures required aqueous solutions to be heated to 160–200°C in autoclaves to produce whiskers.^{14,15} Molten salt synthesis techniques,¹⁶ on the other hand, were suitable for the synthesis of hydroxyapatite and β -tricalcium phosphate (or biphasic mixtures of the two) whiskers.^{17,18}

The present paper reports a simple, one-pot technique to synthesize CaP whiskers, with a Ca/P molar ratio ≤ 1.50 , in 30% hydrogen peroxide solutions at 90°C. The only starting material of the proposed method is single-phase, commercially available β -tricalcium phosphate (β -Ca₃(PO₄)₂) powders (used without any further treatment whatsoever). To the best of our knowledge, the utilization of H₂O₂, by Toriyama *et al.*,¹⁹ together with

Na-EDTA in synthesizing hydroxyapatite powders by using Ca(NO₃)₂·4H₂O and (NH₄)₂HPO₄ was the only appearance of hydrogen peroxide in CaP powder production. Produced whiskers were also tested for their Ap-CaP-inducing ability by soaking them in synthetic body fluid (SBF) solutions^{20–22} at 37°C for 6 days.

II. Experimental Procedure

Four grams of as-received β -tricalcium phosphate (β -TCP: β -Ca₃(PO₄)₂) powders (99.9%, Product No: 50 552, Fluka Chemie GmbH, Buchs, Switzerland) were placed in a 250 mL capacity Pyrex[®] glass media bottle (Catalog No: 215–1593, VWR International, West Chester, PA). 100 mL of 30% in water hydrogen peroxide (H₂O₂) solution (Catalog No: BP2633–500, Fisher Scientific Co., Fairlawn, NJ) of pH 3.50 (at 21° ± 1°C) was then added into the bottle. The bottle was tightly capped and manually shaken for 1 min, followed by keeping the bottle, for 48 h (undisturbed), in an electrically heated oven preheated to 90°C. Finally, the powdery contents of the bottle were filtered using a filter paper through a Buechner funnel, washed with 2 L of deionized water, and dried overnight at 90°C in a glass Petri dish to obtain the whiskers. pH of the mother liquor was measured to be 3.80 (at RT) before filtering. (It must be noted here that 30% H₂O₂ solutions may depress (by about 1.2 pH unit) the pH readings obtained when using a combination glass electrode, as we did. See: www.h2o2.com).

Whiskers were tested for their biomimetic CaP formation ability by soaking 1 g of those in 100 mL aliquots of an SBF solution of 27 mM HCO₃⁻^{20,21} at 37°C (in 250 mL glass media bottles) for 6 days. The composition of the SBF solutions used is given in Table I. Further procedural details of SBF solution preparation were previously described elsewhere.^{20–22} SBF solutions were totally replenished with freshly prepared SBF at every 48 h. Samples were removed from the bottles at the end of 6 days, and washed with plenty of deionized water, followed by overnight drying at 37°C.

Samples were characterized by powder X-ray diffraction, (XRD) (Model XDS 2000, Scintag, Sunnyvale, CA), scanning electron microscopy, (SEM) (Model S-4700, Hitachi Corporation, Tokyo, Japan), Fourier-transform infrared spectroscopy, (FTIR) (Model Nicolet 550, Thermo-Nicolet, Woburn, MA), BET surface area measurements (Model ASAP 2020, Micromeritics Corporation, Norcross, GA), and ICP-AES analysis (Model 61E, Thermo Electron, Madison, WI). Powder samples for XRD analyses were first ground in an agate mortar using an agate pestle and then sprinkled onto ethanol-damped single-crystal quartz sample holders as a thin and flat layer, followed by tapping to remove the excess of powder. The XRD was operated at 40 kV and 30 mA with monochromated CuK α radiation. XRD data were collected in the step mode over the two θ ranges of 20–40°, with an overall scanning speed corresponding to 0.01°/min. FTIR samples were first ground in a mortar, in a manner similar to that used in the preparation of XRD samples, and then placed onto the diamond ATR holder of the FTIR spectrometer. This spectrometer was equipped with an *Endurance Foundation Series* single-bounce diamond ATR (50°

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Table I. SBF Preparation

Order	Reagent	Gram per liter H ₂ O	Ions in SBF	Human plasma (mM)	SBF (mM)
1	NaCl	6.547	Na ⁺	142	142
2	NaHCO ₃	2.268	K ⁺	5	5
3	KCl	0.373	Ca ²⁺	2.5	2.5
4	Na ₂ HPO ₄	0.142	Mg ²⁺	1.5	1.5
5	MgCl ₂ ·6H ₂ O	0.305	Cl ⁻	103	125
6	1M HCl	10 mL	HCO ₃ ⁻	27	27
7	CaCl ₂ ·2H ₂ O	0.368	HPO ₄ ²⁻	1	1
8	Na ₂ SO ₄	0.071	SO ₄ ²⁻	0.5	0.5
9	Tris	6.057			
10	1M HCl	35–40 mL			

SBF, synthetic body fluid.

incidence angle), and 256 scans were performed at a resolution of 4 cm⁻¹. Powder samples examined with the SEM were sputter-coated with a thin Pt layer, just before imaging, to improve the conductivity of samples. The BET surface area of powder samples was determined by applying the standard Brunauer–Emmet–Teller method to the nitrogen adsorption isotherms obtained at -196°C using the Micromeritics ASAP 2020 instrument. During the ICP-AES analyses of whiskers, 50 mg portions of samples were dissolved in 5 mL of concentrated HNO₃ solution. Whisker sizes were evaluated using the linear intercept method on the SEM photomicrographs and the values reported here were the averages of 35 individual whisker measurements.

III. Results and Discussion

The morphology of the as-received β-TCP powder used in this study is shown in the SEM photomicrographs of Fig. 1. These powders possessed a broad particle size distribution with individual particle sizes ranging from 5 to 30 μm. BET surface area of the powders was measured to be 0.9 m²/g. β-TCP is a calcium phosphate phase of high aqueous solubility, with a log *K*_{sp} value of -28 at 21°C.²³ It should be noted that the same solubility product for Ca-hydroxyapatite is -117.²³ Therefore, β-TCP particles were expected to readily dissolve without experiencing any significant difficulty in hot H₂O₂ solutions. In a study on investigating the dissolution behavior of intertubular and peritubular dentin samples by H₂O₂, Kawamoto and Tsujimoto²⁴ observed that while both dentin samples were significantly dissolved, hydroxyapatite samples were not influenced by hydrogen peroxide solutions at ambient temperature.

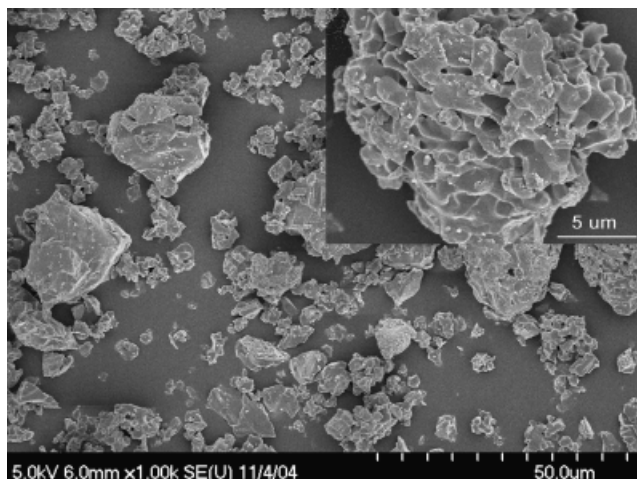


Fig. 1. Particle morphology of the starting β-TCP powders.

Experimental XRD traces (Fig. 2(a)) of the as-received powders confirmed that they were indeed single-phase β-Ca₃(PO₄)₂. Figure 2(b) showed the characteristic XRD data of the formed whiskers. Produced whiskers were found to be biphasic mixtures of apatitic CaP (ICDD PDF No. 46-905) and octacalcium phosphate (OCP: Ca₈H₂(PO₄)₆·5H₂O, ICDD PDF No. 26-1056), whereas OCP was only a minor phase (Fig. 2(b)). Whiskers had a BET surface area of 8 ± 0.2 m²/g. XRD runs were not able to detect any unreacted β-TCP. OCP and Ap-CaP biphasic deposits, for instance, are not uncommon on explanted intraocular lens surfaces.^{25,26} SBF soaking (6 days at 37°C) of the whiskers led to the disappearance of the OCP phase, and a poorly crystallized Ap-CaP was formed (Fig. 2(c)). SBF-soaked (6 days) whiskers were found to have a BET surface area of 52 ± 1 m²/g. The morphology of the biphasic whiskers were depicted in the SEM photomicrographs of Fig. 3. As shown in the low-magnification micrograph of Fig. 3(a), ellipsoidal nodules of whisker bundles (15–25 μm wide) were formed in hot H₂O₂ upon the dissolution of β-TCP powders. Individual whiskers in these nodules had mean width of 0.2 μm and an average length of 5 μm (Figs. 3(b) and (c)), resulting in an aspect ratio of about 25. SBF-soaked whiskers had nano-textured surface morphology (Fig. 3(d)), and this was characteristic SBF-soaked whiskers even when the synthesis method used was quite different.¹⁸

ICP-AES analyses performed in triplicate revealed that the produced whiskers had a Ca/P molar ratio of 1.46 ± 0.1. SBF soaking for 6 days caused this ratio to rise to 1.60 ± 0.1. IR spectra of the starting TCP powders, produced whiskers, and SBF-soaked whiskers are given in Fig. 4(a) through (c). CO₃²⁻ ion absorption bands seen at 1470–1420 and 873 cm⁻¹, as well as the symmetric and anti-symmetric stretching of the PO₄ group (at 1090, 1024, 971, 603, and 560 cm⁻¹), confirmed the “bone apatite-like” mineral characteristics of the SBF-soaked whiskers (Fig. 4(c)). The bands observed at 537, 870, 945, 1133, and 1210 cm⁻¹ are known to occur in nonstoichiometric apatites containing HPO₄²⁻ ions.^{27–29} The β-TCP powders used in this study did not transform to Ap-CaP when heated in deionized water (of pH 6.7) at 90°C for 48 h. The XRD and IR spectra of the resultant samples (data not shown) still belonged to those of pure β-TCP.

H₂O₂-in-liquid water decomposes, and its decomposition rate is increased roughly two times by raising the temperature by 10°C (from room temperature).³⁰ This decomposition can be described by the following overall reaction

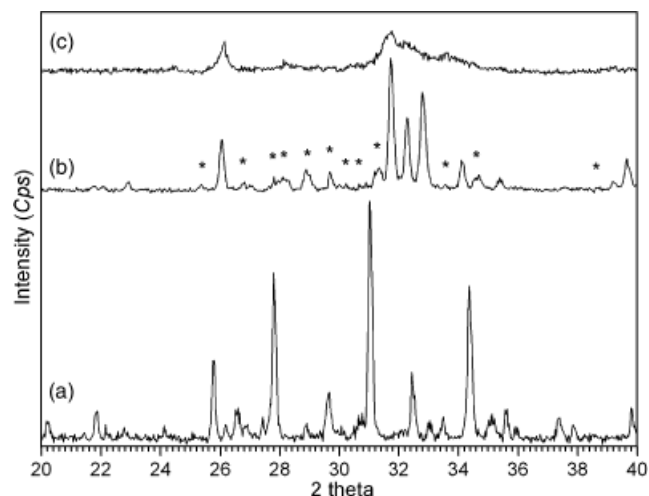
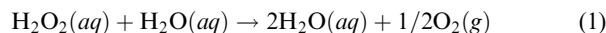


Fig. 2. X-ray diffraction traces of the samples of this study; (a) starting β-TCP powders (phase pure), (b) as-formed biphasic whiskers (*: OCP, rest: Ap-CaP peaks), (c) synthetic body fluid-soaked whiskers.

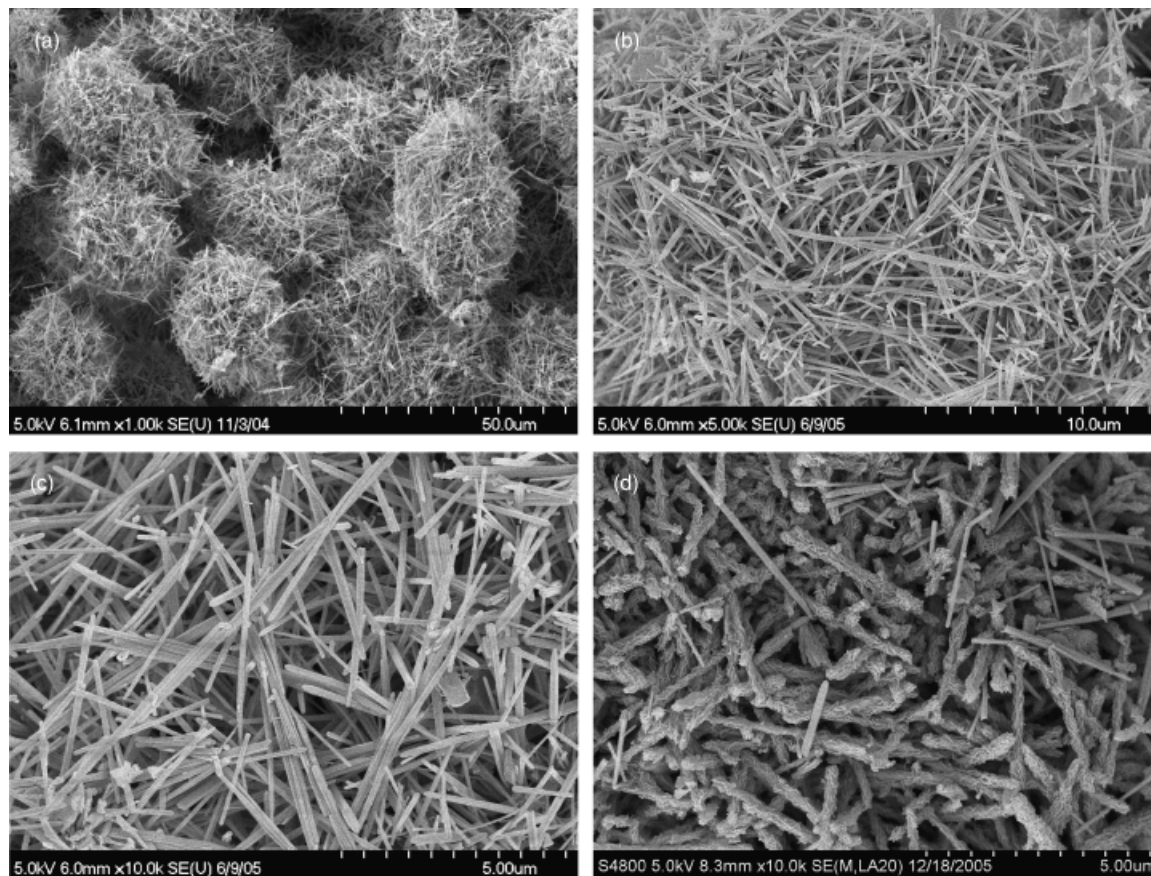
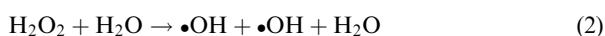
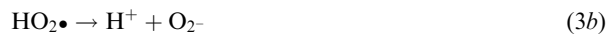
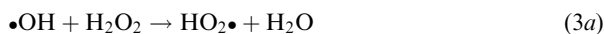


Fig. 3. Scanning electron microscopy photomicrographs of whiskers; (a) to (c) as-formed whiskers at different magnifications, (d) synthetic body fluid-soaked whiskers (6 days, 37°C).

The initial H_2O_2 decomposition step in water is assumed to be

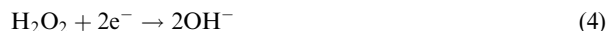


and this $\bullet\text{OH}$ radical may further react to form hydroperoxide (OOH or HO_2):



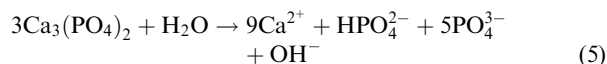
and the overall reaction is still represented by Eq. (1).^{31,32}

In electrochemical systems, on the other hand, the decomposition of H_2O_2 takes place according to the following equation:



and H_2O_2 is thus known to be an electrochemical hydroxide precursor, for instance, in synthesizing ZnO nanorods.³³

In the presence of β -TCP powders in H_2O_2 solutions at 90°C, much of the above decomposition reactions will occur on the surfaces of powder particles.³¹ H_2O_2 decomposition (epitomized by the above reactions) on the surfaces of β -TCP particles will give rise to its dissolution according to



and that a slight pH increase on particle surfaces will further catalyze the H_2O_2 decomposition. Ap-CaP cannot form at low pH values, instead the formation of OCP should precede its occurrence.³⁴ In consequence, OCP or Ap-CaP will crystallize as the following reactions take place:

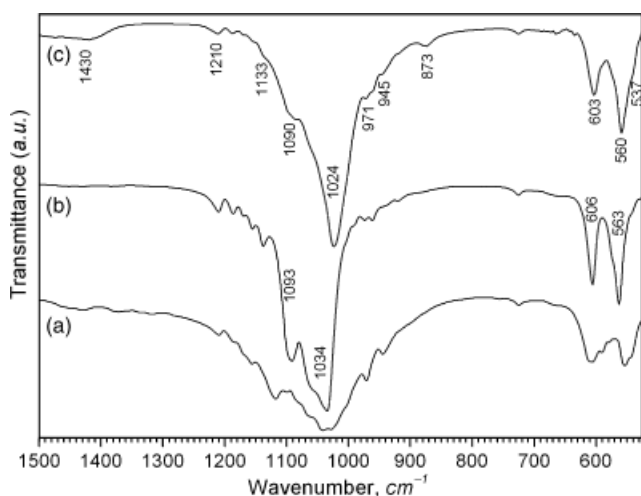
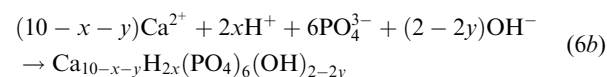
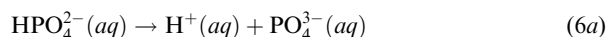
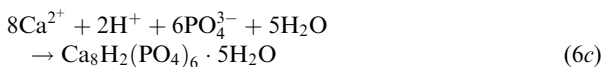


Fig. 4. Fourier-transform infrared spectroscopy traces of the samples of this study; (a) starting β -TCP powders (phase pure), (b) as-formed whiskers, (c) synthetic body fluid-soaked whiskers.



Instantaneous pH on the dissolving particle surfaces will then determine which phase to crystallize, i.e., OCP or Ap-CaP.³⁵ OCP is a precursor in the biomineralization of Ap-CaP or biological apatites.^{36–38} The presence of a good lattice match between the (001) plane of OCP and (0001) of apatite makes the epitaxial growth of the crystals of the two quite feasible.³⁶ This study simply captured the moment of the coexistence of whiskers of these two phases.

SBF solutions are supersaturated with respect to Ap-CaP nucleation because of their physiological pH (7.4) and Ca/P molar ratio (2.5), and therefore, even when they are optically transparent, they contain CaP clusters with sizes of around 10 Å.³⁹ These CaP clusters were first described by Betts and Posner⁴⁰ to have the $\text{Ca}_9(\text{PO}_4)_6$ stoichiometry, and are known as Posner clusters. These clusters present in the SBF solutions aggregate to produce the biomimetic CaP nanotexture, while filling the intercluster spaces with water and bicarbonate molecules.¹⁸ Original whiskers, when soaked in Tris-HCl buffered SBF of 27 mM HCO_3^- , behaved like a “guiding scaffold” for the formation or regeneration of nanotextured CaPs with a rod-like morphology (Fig. 3(d)). The significant increase achieved in the BET surface area of the whiskers (from 8 to 52 m²/g) upon SBF soaking was quite promising. Nanoroughness inscribed onto the surfaces of those whiskers (by SBF-soaking) can increase the whisker pullout forces in biopolymer composite applications, in comparison to smooth-surfaced CaP whiskers.

Concerning the biocompatibility of these H_2O_2 -synthesized CaP whiskers, it must be remembered that during the *in vivo* inflammatory response, activated phagocytic leukocytes are known to produce H_2O_2 .⁴¹ In other words, stimulated macrophages and other leukocytes are known to secrete peroxide and other free radicals, which exert a local bactericidal effect.⁴¹ Therefore, *in vitro* bone cell tests will soon be performed on these whiskers to quantify their cytotoxicity.

IV. Conclusions

(1) A simple technique for synthesizing biphasic whiskers of octacalcium phosphate and apatitic calcium phosphate was developed. Whiskers with an aspect ratio of about 25 were easily produced by aging β -tricalcium phosphate powders in 30% H_2O_2 solutions at 90°C.

(2) As-formed whiskers had a Ca/P molar ratio of 1.46 and a BET surface area of 8 m²/g.

(3) SBF soaking of the whiskers at 37°C for 6 days increased their Ca/P molar ratio to 1.60.

(4) SBF-soaked whiskers were found to have a BET surface area of 52 m²/g. SBF-soaked whiskers comprised only of the Ap-CaP phase.

(5) Such whiskers may be used as fillers in biopolymer composites.

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