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PREPARATION OF BIOMIMETIC HA PRECURSORS AT 37°C IN UREA- AND ENZYME UREASE-CONTAINING SYNTHETIC BODY FLUIDS

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ABSTRACT

An important inorganic phase of synthetic bone applications, calcium hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$), was prepared as a single-phase and sub-micron bioceramic precursor powder. Carbonated HA precursors were synthesized from calcium nitrate tetrahydrate and di-ammonium hydrogen phosphate salts dissolved in "synthetic body fluid" (SBF) solutions, containing urea (H_2NCONH_2) and enzyme urease, under the biomimetic conditions of 37°C and pH 7.4, by using a novel chemical precipitation technique. These powders were also found to contain trace amounts of Na and Mg ions in them, intentionally incorporated by using SBF solutions, instead of pure water, during their synthesis. The characterization and chemical analysis of the synthesized biomimetic HA precursors were performed by scanning electron microscopy (SEM), powder X-ray diffraction (XRD), Fourier-transformed infra-red spectroscopy (FT-IR), and inductively-coupled plasma atomic emission spectroscopy (ICP-AES).

INTRODUCTION

Calcium hydroxyapatite (HA: $Ca_{10}(PO_4)_6(OH)_2$), the main inorganic component of the hard tissues in bones, is a member of "apatite" family of compounds. Biological apatites, which comprise the mineral phases of calcified tissues (enamel, dentin, and bone), slightly differ from pure HA in stoichiometry, composition and crystallinity, and in other physical and mechanical properties. They were usually observed [1] to be carbonate-substituted and calcium-deficient.

Synthetic body fluids (SBF) prepared in accord with the chemical analysis of human body fluid, with ion concentrations nearly equal to those of the inorganic constituents of human blood plasma, were first used by Kokubo, *et al.* [2], to prove the similarity between in vitro and in vivo behavior of certain glass-ceramic compositions. In these studies, the glass-ceramic samples were soaked in SBF solutions, and their surfaces were observed to be coated with a poorly crystallized calcium deficient and carbonate containing apatite, which was similar to bone apatite [3].

HA powders for bioceramic applications have generally been synthesized by using aqueous solutions. It is known [4] that calcium hydroxyapatite is the least soluble and the most stable compound of calcium phosphate phases in aqueous solutions at pH values

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recognized by their relatively high thermal stability and phase purity even after high temperature (1100°-1300°C) sintering. Chemical synthesis of HA powders in neutral and/or slightly acidic aqueous media is known to be a more complicated and difficult task [7, 11]. This study [12] will focus on the determination of the experimental parameters of HA synthesis at the physiological pH (7.4) and temperature (37°C), in SBF solutions rich in urea and enzyme urease.

K. de Groot, *et al.* [8] studied the high-temperature characteristics of synthetic HA and reported that the synthetic HA with a Ca/P ratio near to 1.67 was only stable below 1200°C, when sintered in a dry or wet air atmosphere. It was claimed that beyond 1200°C, HA loses its OH^- groups gradually and transforms into oxyapatite ($Ca_{10}(PO_4)_6O$). When heated to 1450°C, oxyapatite was found [8] to dissociate into β-TCP, $Ca_2P_2O_7$ and $Ca_4P_2O_9$. On the other hand, Tas, *et. al.* [10] recently reported that pure HA powders prepared in distilled water may withstand, without decomposition, temperatures as high as 1300°C when heated for 6 h in a stagnant air atmosphere.

The surface properties and synthesis conditions of calcium hydroxyapatite, prepared by using pure water in highly alkaline medium, has previously been examined in different buffers [4, 6, 13] including the SBF; however, there is no published work, to our knowledge, on the "precipitation and formation" of calcium hydroxyapatite precursors in SBF solutions, containing urea and/or enzyme urease, at 37°C and pH of 7.4. The study presented here thus becomes the first systematic step taken in this specific field of "biomimetic" HA powder synthesis technology.

EXPERIMENTAL PROCEDURE

(1) Preparation of Synthetic Body Fluid (SBF)

SBF is known to be a metastable [3] buffer solution, and even a small, undesired variance in both of the preparation steps and the storage temperatures may drastically affect the phase purity and high-temperature stability of the produced HA powders, as well as the kinetics of the precipitation processes.

Merck (Darmstadt, Germany)-grade NaCl (99.5 %), $NaHCO_3$ (99.5 %), KCl (99.0 %), $Na_2HPO_4.2H_2O$ (99.5 %), $MgCl_2.6H_2O$ (98.0 %), Na_2SO_4, $(CH_2OH)_3CNH_2$ (99.2 %), $CaCl_2.2H_2O$ (99.0 %) and HCl (37 vol%, Carlo-Erba, Italy) were used in the preparation of the synthetic body fluids. SBF solutions were prepared [12] by dissolving appropriate quantities of the above chemicals in de-ionized water. Reagents were added, one by one after each was completely dissolved in 700 mL of water, in the order given in Table I.

A total of 40 mL of 1M HCl solution was consumed for pH adjustments during the preparation of SBF solutions. The 15 mL aliquot of this amount was added just before the addition of the 6th reagent, i.e., $CaCl_2.2H_2O$. The second portion of the HCl solution was used in the remainder of the titration process. Following the addition of the 8th

Order	Reagent	Amount (gpl)
1	NaCl	6.547
2	$NaHCO_3$	2.268
3	KCl	0.373
4	$Na_2HPO_4.2H_2O$	0.178
5	$MgCl_2.6H_2O$	0.305
6	$CaCl_2.2H_2O$	0.368
7	Na_2SO_4	0.071
8	$(CH_2OH)_3CNH_2$	6.057

* *Patent Pending*, Turkish Patent Institute, Turkey, Appl. No: 99/00037, January 11, 1999.

reagent (tris(hydroxymethyl)-aminomethane), solution temperature was raised from the ambient to 37°C. This solution was then appropriately titrated with 1M HCl to the pH value of 7.4. During the titration process, the solution was also continuously diluted with consecutive additions of de-ionized water to make the final volume equal to 1 L.

The nominal, starting ion concentrations of the SBF solutions used in this study were matched more closely with those of "human plasma" than the ones given by Kokubo and his co-workers [2, 3]. The most significant differences of this study, as compared to the previous workers, in terms of "SBF ion concentrations" can be stated as follows: *(a)* the nominal, initial HCO_3^- ion concentration of SBF was increased from 4.2 mM to 27.0 mM which, thus, acquired exactly the same value with that of human plasma, *(b)* Cl^- ion concentration was decreased from 147.8 mM to 125.0 mM in the preparation recipe, whereas the Cl^- ion concentration of human plasma is 103.0 mM. This has solely been achieved by changing the 4th reagent of SBF preparation recipe from K-phosphate [2, 3] to Na-phosphate. The differences between the ion concentrations of our SBF solutions and those of human plasma are compared in Table II.

Table II. Ion concentrations of SBF solutions and human plasma

Ion	Kokubo, *et al.*[2,3](mM)	Present work (mM)	Human plasma(mM)
Na^+	142.0	142.0	142.0
Cl^-	147.8	125.0	103.0
HCO_3^-	4.2	27.0	27.0
K^+	5.0	5.0	5.0
Mg^{2+}	1.5	1.5	1.5
Ca^{2+}	2.5	2.5	2.5
HPO_4^{2-}	1.0	1.0	1.0
SO_4^{2-}	0.5	0.5	0.5

0.4 M $Ca(NO_3)_2.4H_2O$ (Riedel de-Haen, 99%, Germany) and 0.16 M $(NH_4)_2HPO_4$ (Merck, 99%, Germany) stock solutions were used in the precipitation experiments as the calcium and phosphate ion sources. 8 to 9.5 M urea solutions were prepared (by dissolving the urea powder in SBF) and then aged at 85°C overnight in a sealed glass jar, to ensure the decomposition of urea. The pH values of 9.5 M, "aged urea" solutions were measured as 9.3 at 37°C, prior to their use in powder synthesis. The enzyme urease (Merck, Lot No: 108489, 5 units/mg, Germany) was added, within the concentration range of 2.5 to 10 units/mL, into the precipitation solutions to establish [14] and accelerate the complete decompositon of urea at 37°C.

The precipitation scheme developed during the HA precursor synthesis experiments was given in the flowchart of Figure 1. For a total volume of 205 mL of SBF, according to Fig. 1, 0.4 mL of 1 gpl methyl cellulose stock solution was used as a dispersant. 410 mg of enzyme urease was dissolved in the above urea-containing SBF solutions to keep its initial concentration at the level of 10 units/mL. The pH values of the solutions were maintained [12] at the physiological level of 7.4 during the entire chemical precipitation experiments. The synthesized powders were then calcined in air over the temperature range of 300°-1600°C for 6 to 17 hours, following their drying at 80°C.

(3) Powder Characterization

The phase purity and the levels of crystallinity of the calcined HA powders were studied by powder X-ray diffraction (Model: D-Max/B, Rigaku Co., Tokyo, Japan) at the typical step size of 0.05° 2 θ and a count time of 1 s. A monochromated Cu-K_α tube operated at 40 kV and 20 mA was used for the generation of X-rays. All of the collected X-ray spectra were corrected for the shifts in the d-spacings by using pure silicon (Starck Inc., Germany) as an external standard. A least-squares unit cell refinement program [15] was used for the precise determination of crystallographic parameters of the synthesized powders. The further details of XRD analysis were described elsewhere [16].

Fourier-transformed infra-red spectroscopy (FT-IR) (Model: DX-510, Nicolet Co., WI, USA) was used in the wave number range of 4000-400 cm^{-1}. Experimental spectra of solid samples were obtained by preparing KBr pellets with a 3:97 (wt%) sample-to-KBr proportions.

(4) Chemical Analysis

Inductively-coupled plasma atomic emission spectroscopy (ICP-AES) (Model Plasma-1000, Perkin Elmer Co., London, UK) was used for the accurate chemical analysis of Na and Mg ions in the SBF-synthesized HA precursors (after being dissolved in acid solutions) which were believed to originate from the use of synthetic body fluids during the synthesis experiments.

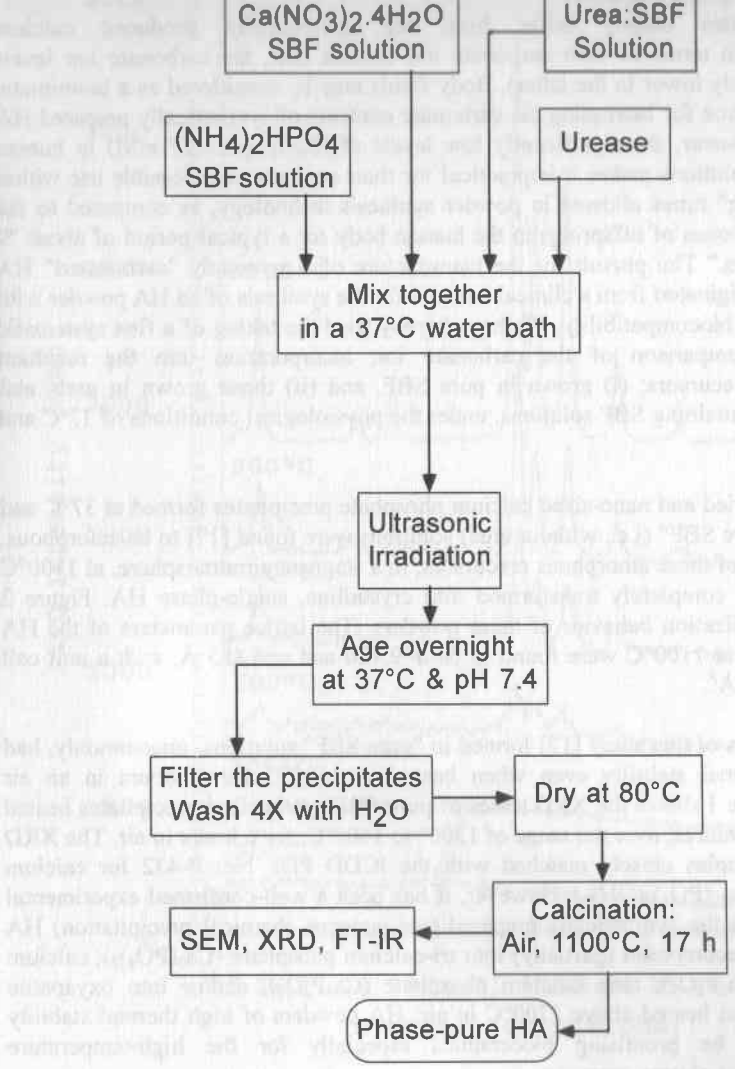

Fig. 1 Process flowchart of precipitation route used in biomimetic HA synthesis

Biological apatites mainly differ from the synthetically produced calcium hydroxyapatites in terms of their carbonate ion content (i.e., the carbonate ion levels being incomparably lower in the latter). Body fluids may be considered as a biomimetic and plausible source for increasing the carbonate contents of synthetically prepared HA bioceramics. However, the significantly low levels of HCO_3^- (i.e., 27 mM) in human plasma or SBF solutions makes it impractical for their economically feasible use within the shorter "aging" times allowed in powder synthesis technology, as compared to the aging of natural bones of offsprings in the human body for a typical period of about "9 months + 10 days." The pursuit for the manufacture of a genuinely "carbonated" HA powder mainly originated from a clinical demand for the synthesis of an HA powder with improved in vivo biocompatibility. We have hereby tried the taking of a first systematic step into the comparison of the carbonate ion incorporation into the resultant hydroxyapatite precursors; (i) grown in pure SBF, and (ii) those grown in urea- and enzyme urease-containing SBF solutions, under the physiological conditions of 37°C and pH of 7.4.

The as-filtered, dried and nano-sized calcium phosphate precipitates formed at 37°C and pH of 7.4 via "pure SBF" (i.e., without urea) solutions were found [17] to be amorphous. Upon calcination of these amorphous precursors, in a stagnant air atmosphere, at 1100°C for 6 hours, they completely transformed into crystalline, single-phase HA. Figure 2 shows the crystallization behavior of these powders. The lattice parameters of the HA powders calcined at 1100°C were found to be a=9.420 and c=6.885 Å, with a unit cell volume of 529.04 $Å^3$.

The HA precursors of this study [17] formed in "pure SBF" solutions, uncommonly, had an excellent thermal stability even when heated at 1600°C for 6 hours in an air atmosphere. Figure 3 shows the XRD traces of pure SBF-synthesized precipitates heated at different temperatures, over the range of 1300° to 1600°C, for 6 hours in air. The XRD spectra of all samples closely matched with the ICDD PDF No: 9-432 for calcium hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). However, it has been a well-confirmed experimental fact [6, 8, 10] that the synthetically prepared (via aqueous chemical precipitation) HA powders usually decomposed (partially) into tri-calcium phosphate ($Ca_3(PO_4)_2$), calcium pyrophosphate ($Ca_2P_2O_7$), tetra calcium phosphate ($Ca_4P_2O_9$), and/or into oxyapatite ($Ca_{10}(PO_4)_6O$) when heated above 1200°C in air. HA powders of high thermal stability are expected to be promising bioceramics especially for the high-temperature applications, such as plasma-spraying.

Biomimetic HA powders of the present study also contained trace amounts of other inorganic ions, provided by SBF. ICP-AES analysis performed on representative 1200°C-calcined samples indicated that these HA powders had 1500 ppm Mg and 160 ppm Na. Na^+ and Mg^{2+} ions, originated from the use of SBF solutions during precipitation, were believed to incorporate themselves in the crystal structure of calcium hydroxyapatite. The CO_3^{2-} ions are known [1] to substitute, in part, the OH^- sites, and again, in part the PO_4^{3-} groups of the HA structure. On the other hand, Mg^{2+} ions were claimed [1] to replace the Ca^{2+} sites of the HA structure. We also believe that the Na^+ ions might have

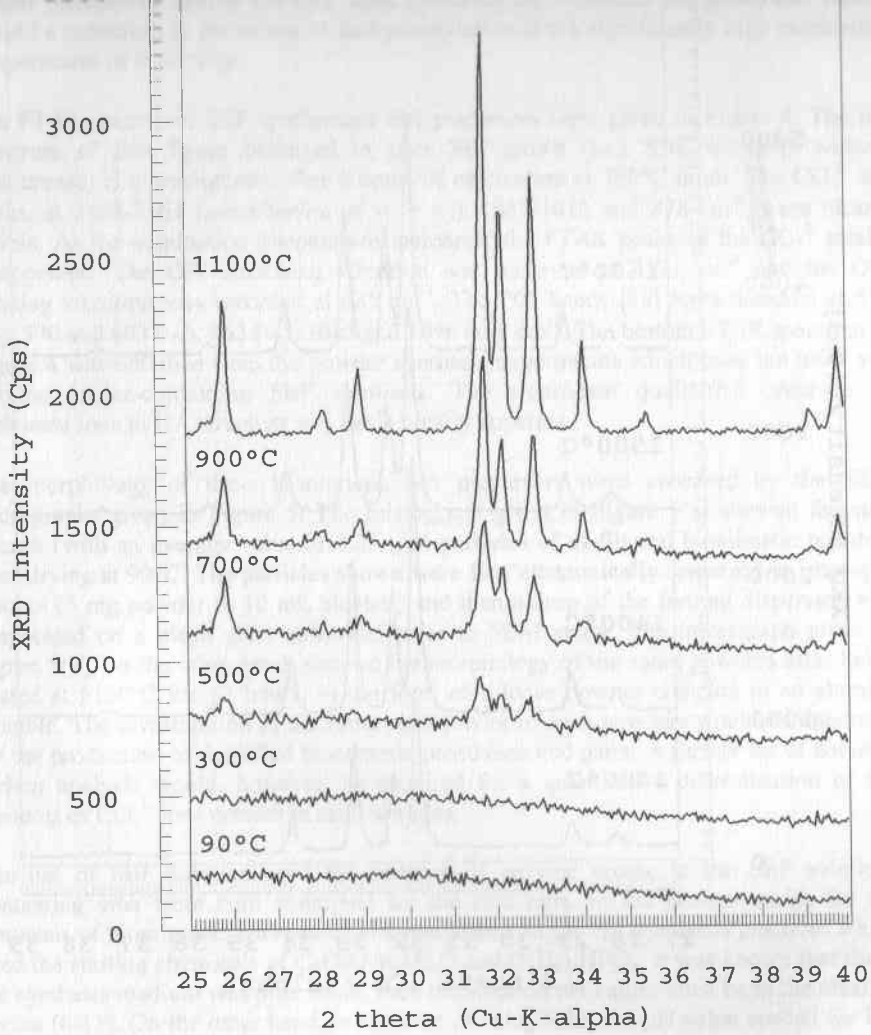

Fig. 2 Crystallization behavior of SBF-synthesized amorphous HA precursors

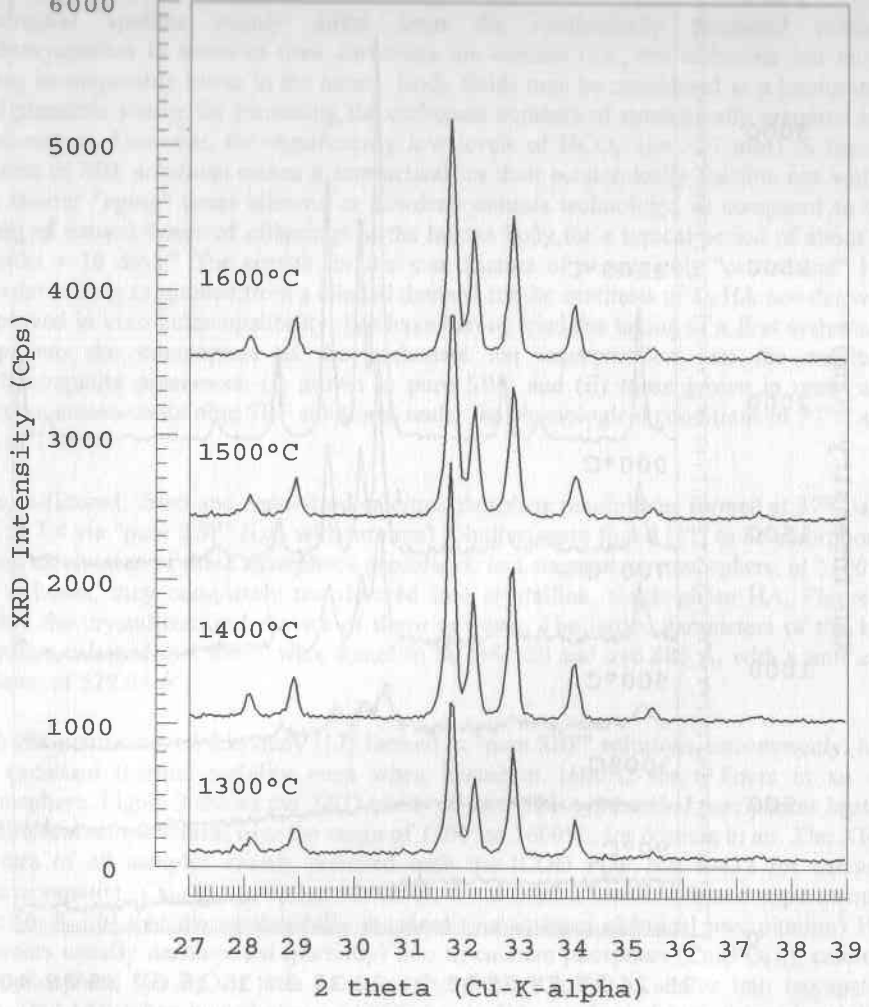

Fig. 3 XRD spectra of SBF-synthesized HA precursors after heating at different temperatures (1300°-1600°C, 6 h, air)

placed themselves nearby the OH^- sites (close to the P-bonded oxygens), and hence, caused a reduction in the extent of de-hydroxylation at the significantly high calcination temperatures of this study.

The FT-IR spectra of SBF-synthesized HA precursors were given in Figure 4. The top spectrum of this figure belonged to pure SBF-grown (i.e., SBF solutions without urea/urease) HA precipitates, after 6 hours of calcination at 700°C in air. The CO_3^{2-} ion peaks, at 2368-2361 (combination of $\nu_2 + \nu_3$), 1467-1412 and 878 cm^{-1}, were clearly visible. As the calcination temperature increased, the FT-IR peaks of the CO_3^{2-} totally disappeared. The OH^- stretching vibration was observed at 3571 cm^{-1} and the OH^- bending vibration was recorded at 635 cm^{-1}. The PO_4 bands [18] were detected at 470 (ν_2), 570 and 603 (ν_4), 962 (ν_1), 1045 and 1096 (ν_3) cm^{-1}. The bottom FT-IR spectrum of Figure 4 was obtained from the powder synthesis experiments which used the urea- and enzyme urease-containing SBF solutions. The significant qualitative presence of carbonate ions in HA structure was again clearly apparent.

The morphology of these biomimetic HA precursors were observed by the SEM micrographs given in Figure 5. The micrograph given in Figure 5(a) showed the sub-micron (with an average value of 0.25 μm) particles of as-filtered biomimetic powders after drying at 90°C. The particles shown were first ultrasonically dispersed in isopropyl alcohol (5 mg powder in 10 mL alcohol) and then a drop of the formed dispersion was evaporated on a clean glass substrate, prior to SEM study. The micrograph given in Figure 5(b), on the other hand, showed the morphology of the same powders after being heated at 1150°C for 12 hours, in the form of a loose powder compact in an alumina crucible. The investigation of the sintering behavior of such powders would be important for the production of densified bioceramic prostheses and parts. A further set of decisive carbon analysis would, however, be required for a quantitative determination of the amounts of CO_3^{2-} ions present in such samples.

The use of SBF solutions and the addition of enzyme urease to the SBF solutions containing urea were both attempted for the first time, in the present study, for the synthesis of biomimetic, carbonated HA precursors. In the HA synthesis practices which used the starting chemicals of $Ca(NO_3)_2.4H_2O$ and $(NH_4)_2HPO_4$, it was known that the if the synthesis medium was pure water, then the solution pH values must be in the alkaline region [6-11]. On the other hand, in the case of using SBF, the pH value needed for HA synthesis decreases [12, 17, 19] considerably. In combination with the initial presence of spontaneously formed seed crystals [12, 17, 19] in precipitation solutions, the high ionic strength of the precipitation medium (provided by SBF) played an important role in inducing the formation of pure calcium hydroxyapatite precursor phase that would otherwise, normally, not nucleate at such a low pH value of 7.4. Following the addition of the enzyme urease into the precipitation solutions, the pH values have changed as shown in Figure 6. (Without the addition of enzyme urease into the same solutions, the plots would look like horizontal, straight lines.) When the enzyme concentration was kept at the initial, nominal level of 2.5 units/mL, the synthesized powders were consisted of two phases, i.e., a mixture of HA (20%) and $Ca_3(PO_4)_2$ (20%). However, when the enzyme concentration was increased to 10 units/mL, the solution pH value was observed

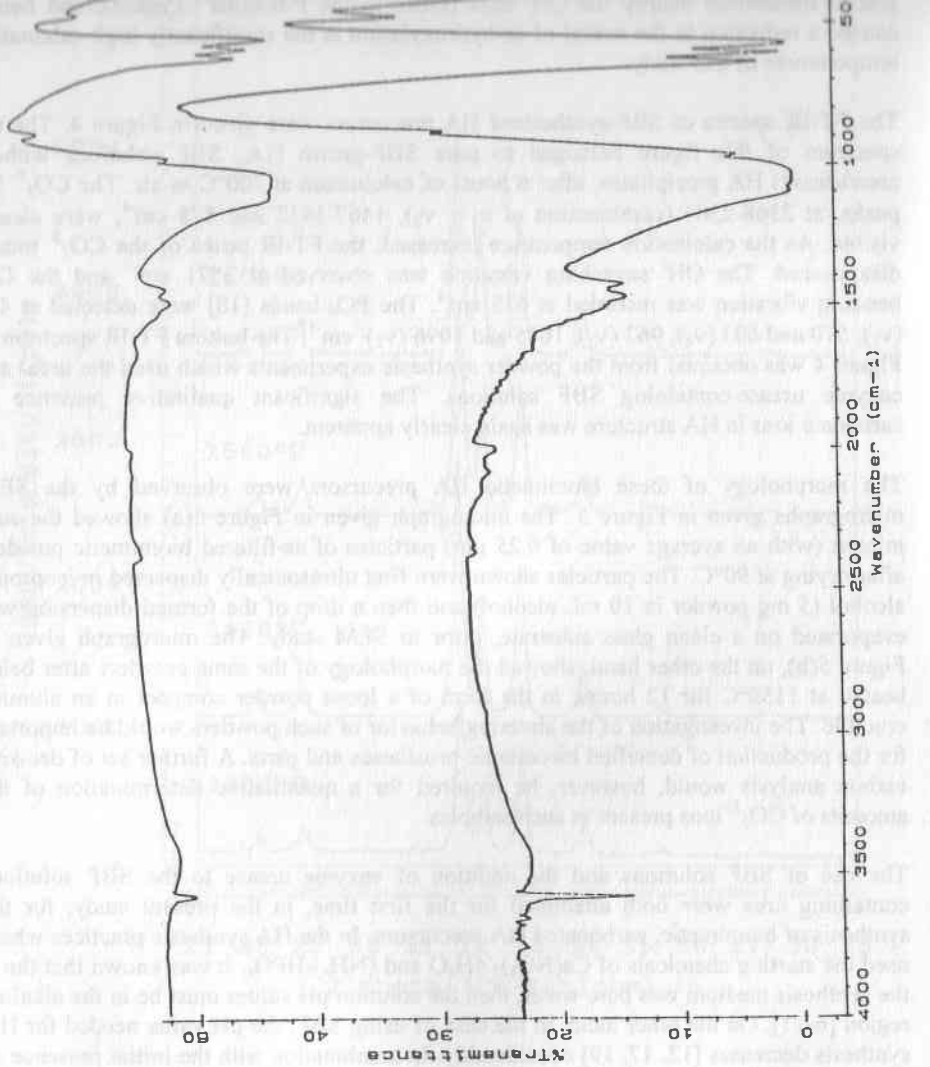

Fig. 4 FT-IR spectra of SBF-synthesized HA precursors (*Top*: in pure SBF, *Bottom*: in urea- and enzyme urease-containing SBF, samples heated at 700°C in air for 6 h)

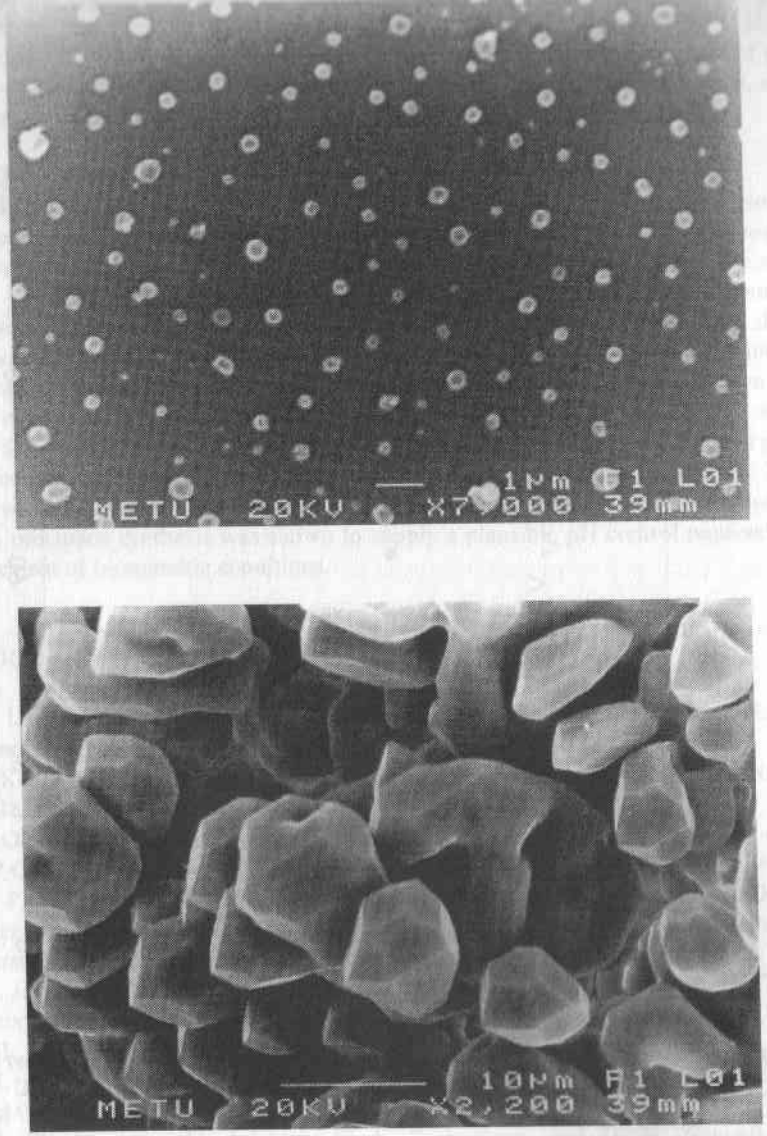

Fig. 5 SEM micrographs of SBF-synthesized (urea/urease) HA precursors, (*Top*: 90°C, *Bottom*: 1150°C)

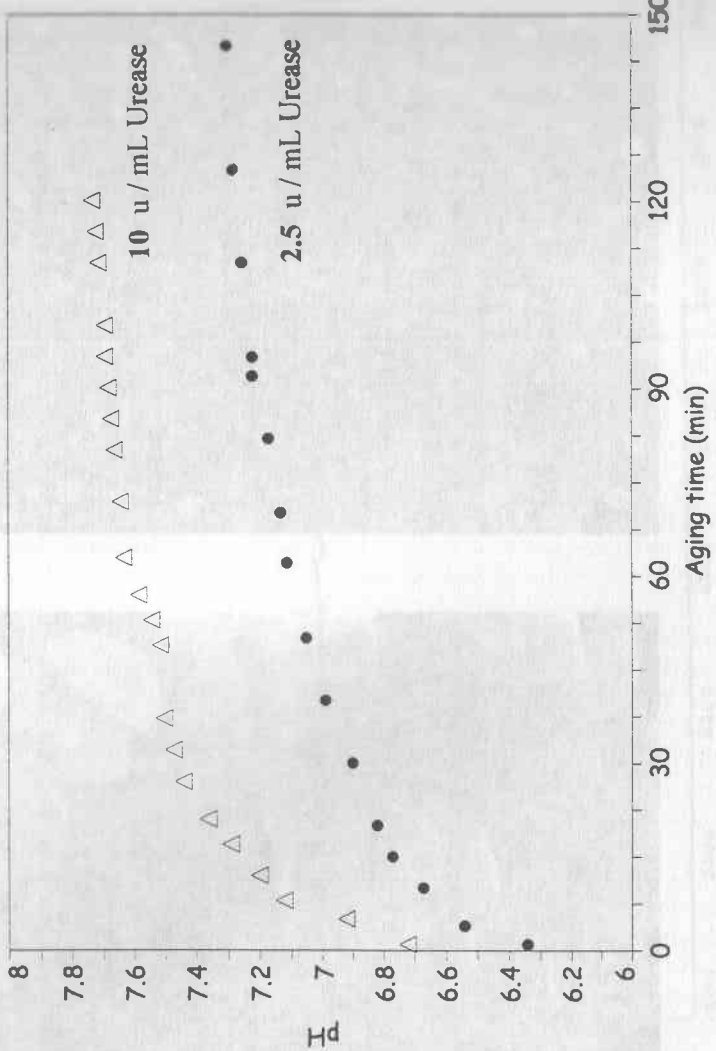

Fig. 6 pH control provided by the enzyme urease (at two different concentrations) in urea-ctg. SBF solutions during Ca-phosphate powder precipitation at 37°C

obtained at this concentration of urease were found to be single phase HA after calcination at 1100°C. The biomimetic pH control (around the neighborhood of pH 7.4) in urea-containing synthetic body fluids have thus been shown to be achievable, at 37°C, by the addition of the enzyme urease in appropriate amounts (8-10 units/mL).

CONCLUSIONS

Chemically homogeneous, single-phase calcium hydroxyapatite (HA) precursors have been synthesized by a novel chemical precipitation technique via synthetic body fluid solutions (either pure or urea/enzyme urease-containing), at the physiological conditions of pH 7.4 and 37°C, with dissolved calcium nitrate tetrahydrate and di-ammonium hydrogen phosphate salts in appropriate amounts. The produced powders were shown to be carbonated and to have unprecedented phase stability even when heated at 1600°C, for 6 hours, in a stagnant air atmosphere. Biomimetic HA powders were also shown to have small amounts of other inorganic ions, provided and incorporated into the HA structure by the SBF solutions used during synthesis. ICP analysis performed on calcined powders indicated that the HA powders of this study had 1500 ppm Mg and 160 ppm Na. Enzyme urease when added in proper amounts into the urea-containing synthetic body fluids used for HA precursor synthesis was shown to supply a plausible pH control required for the achievement of biomimetic conditions.

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PHYSICAL CHARACTERISTICS OF SINTERED HYDROXYAPATITE

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ABSTRACT

Hydroxyapatite is the principal inorganic component of bone, and is an implant material for skeletal reconstruction. Hydroxyapatite is a single phase ceramic with a reported large thermal expansion anisotropy. Large thermal expansion anisotropy is known to cause microcracking upon cooling in ceramics, and such microcracking is a strong function of the grain size. The discussion focuses on the relationship between microcracking in sintered hydroxyapatite and properties such as hardness and fracture toughness.

INTRODUCTION

Hydroxyapatite (HAP) is of considerable interest as a bio-implant material, either by itself or as part of a composite. However, for ceramics such as HAP, material properties, including the elastic modulus, thermal expansion, thermal conductivity, and thermal diffusivity are strongly affected by microcracking, and the values of these properties change significantly if microcracking exists [1]. In this context, microcracks are cracks with a very small aspect ratio (crack opening displacement/crack length).

Three mechanisms by which microcracks are induced in brittle materials are: (1) thermal expansion anisotropy or TEA, (2) thermal expansion mismatch between different crystallographic phases, and (3) rapid, displacive phase transitions [1]. TEA refers to the fact that for non-cubic crystalline lattices, the thermal expansion along different crystallographic axis differ from axis to axis. The thermal expansion anisotropy (TEA) causes the grains to shrink at different rates in different directions, for example, during cooling, and these differing rates of thermal contraction create stresses between adjacent grains. The greater the TEA, the greater the stress [1]. Stresses between adjacent grains arising from differing thermal expansion coefficients of differing phases and from a rapid