Monocrystalline biocompatible whisker synthesis

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Ceramic Whisker: A short, thin filament comprised of a virtually defect-free single crystal (*i.e.*, monocrystalline); whiskers lack internal grain boundaries and have almost no crystalline defects, as a result of this, their strength may approach the theoretical fracture strength of the material they are made of.

Ceramic Fiber: While also single-crystalline (mostly) in nature, ceramic fibers are supposed to span longer continuous lengths compared to short, needle-like whiskers; ceramic fibers can also be polycrystalline or X-ray amorphous rather than single crystal. Whiskers are also categorized by their "**aspect ratio**," *i.e.*, length-to-diameter ratio.

Bioceramic: mostly calcium phosphates, such as hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$), pure or Zn-doped β- or α-tricalcium phosphate (TCP, $Ca_3(PO_4)_2$), tetracalcium phosphate (TTCP, $Ca_4(PO_4)_2O$), oxyapatite (OA, $Ca_{10}(PO_4)_6O$), which do not remain inert when they are brought in contact with human blood and saliva at the human body temperature (doubtful about naming "bioinert" Al_2O_3 and ZrO_2 as bioceramics)

This document summarizes the work I designed and executed on the synthesis of bioceramic whiskers in the form of several peer-reviewed publications. These publications serve to depict a significant decrease achieved in the bioceramic whisker synthesis temperature from 1190 to 90°C (in chronological order). There are three different synthesis procedures in them.

1.) **1190°C** / A. C. Tas, "Molten Salt Synthesis of Calcium Hydroxyapatite Whiskers," *Journal of The American Ceramic Society*, 84(2), 295-300 (2001)
2.) **1150°C** / A. C. Tas, "X-ray Diffraction Data for Flux-grown Calcium Hydroxyapatite Whiskers," *Powder Diffraction* (ICDD), 16(2), 102-106 (2001)
3.) **500°C** / S. Jalota, A. C. Tas, and S. B. Bhaduri, "Microwave-assisted Synthesis of Calcium Phosphate Nanowhiskers," *Journal of Materials Research*, 19(6), 1876-1881 (2004)
4.) **500°C** / S. Jalota, S. B. Bhaduri, and A. C. Tas, "*In vitro* Testing of Calcium Phosphate (HA, TCP, and bi-phasic HA-TCP) Whiskers," *Journal of Biomedical Materials Research*, 78A, 481-490 (2006)
5.) **90°C** / A. C. Tas, "Formation of Calcium Phosphate Whiskers in Hydrogen Peroxide (H_2O_2) Solutions at 90°C," *Journal of The American Ceramic Society*, 90(8), 2358-2362 (2007)

The high temperature (*i.e.*, molten salt synthesis, MSS) whisker synthesis method detailed in publications **1** and **2** determined K_2SO_4 (m.p. 1069°C) to be the best flux and the starting material could be any Ca/P material (finely ground) powder (not whisker) with a nominal Ca/P molar (atomic) ratio close to 1.67, when one wanted to synthesize monocrystalline whiskers of HA. The phase assemblage of the starting material is not important, it could be a mixture of ACP (amorphous calcium phosphate), TCP and/or HA. The work of publication 1 also tested the feasibility of using KCl (m.p. 775°C), KBr (m.p. 734°C), Na_2SO_4 (m.p. 884°C) or $CaCl_2$ (m.p. ~780°C) as the flux.

In brief, "K_2SO_4-to-starting powder" mass ratio was 1.6 (in publication-1), the K_2SO_4+starting powder dry mix was then placed into an inert crucible and heated in a muffle furnace (in an air atmosphere) to the maximum temperature of 1190°C (publication-1), which was about 120°C above the m.p. of the flux, K_2SO_4. First, K_2SO_4 melts and dissolved the starting material. With an increase in time at 1190°C, HA particles nucleate and grow in the melt. "K_2SO_4-to-starting powder" mass ratio in publication-2 was 3.0 and the temperature was 1150°C.

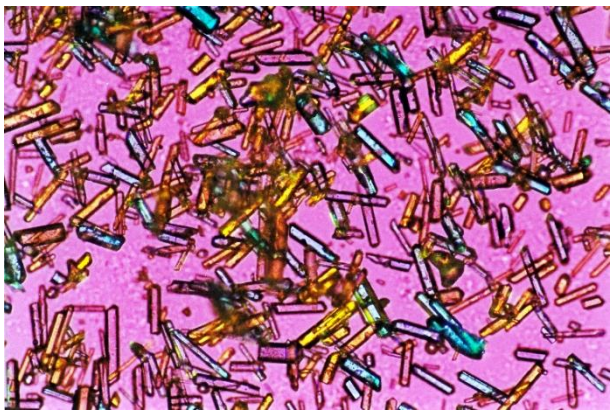
Whisker formation and growth (along the preferred growth axes of the bioceramic, HA) occurs during cooling from the peak temperature down to RT. The entire sequence of whisker formation can be summarized as "dissolution in molten flux - nucleation of embryo crystals - whisker growth." Dissolution and crystal nucleation are occurring at the peak temperature, while whisker growth takes place during cooling. Whisker are recovered from the glassy flux phase (which is soluble in water) by washing it in water, and that washing is continued until all the molten flux of K_2SO_4 is dissolved. The monocrystalline HA (calcium phosphate) whiskers do not have the cytotoxicity of, for instance, carbon nanotubes. The skeletal and maxillofacial hard tissues (except the pathological crystallizations in the urinary tract system) of the human body are made of calcium phosphates.

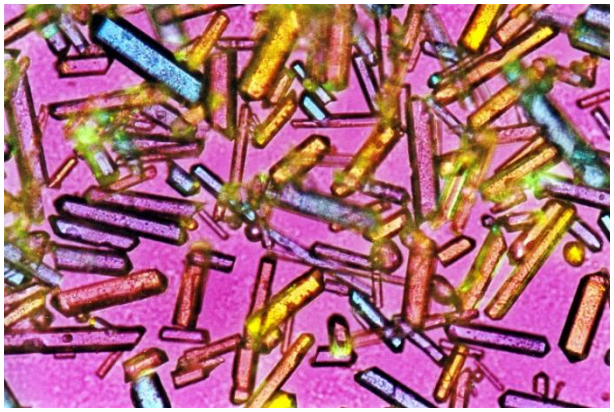
The monocrystalline HA whiskers produced by our molten salt synthesis method are monodisperse (non-agglomerated) and have their unique fingerprint, *i.e.*, their aspect ratio and their morphology.

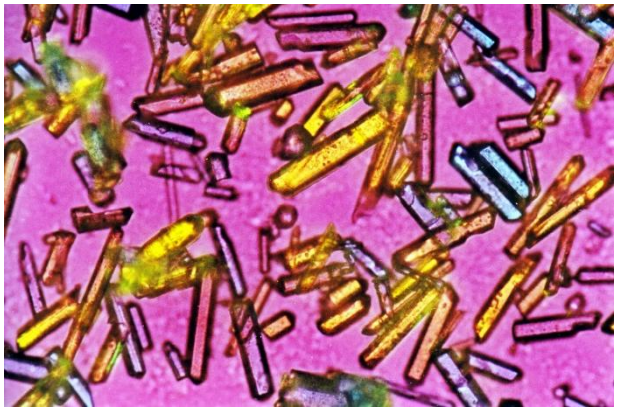
A company reproduced my molten salt-based HA whiskers and turned them into one of their commercial products much later than my publications 1 and 2, without my knowledge and without even asking my opinion; however, the "fingerprint" (their thickness, their lengths, their average aspect ratio, their monodisperse character and the morphology of the whisker surfaces) of my HA whiskers shine themselves in the micrographs of their website. *Alas*, things happen!

Third parties can freely reproduce what they read in an open article, this is why scientists make publications in the first place – simply to share the know-how they develop with

others; but any replicating parties should not hesitate giving a reference/citation to the original work, *i.e.*, to the work they learned from.







The above images of polarized microscopy (with crossed polarizers) are from publication-2. Different colors seen above are called interference colors. The images show that the molten salt-synthesized HA whiskers are monodisperse and "optically transparent."

$n_\omega = 1.651, \quad n_\varepsilon = 1.644$, birefringence = 0.007

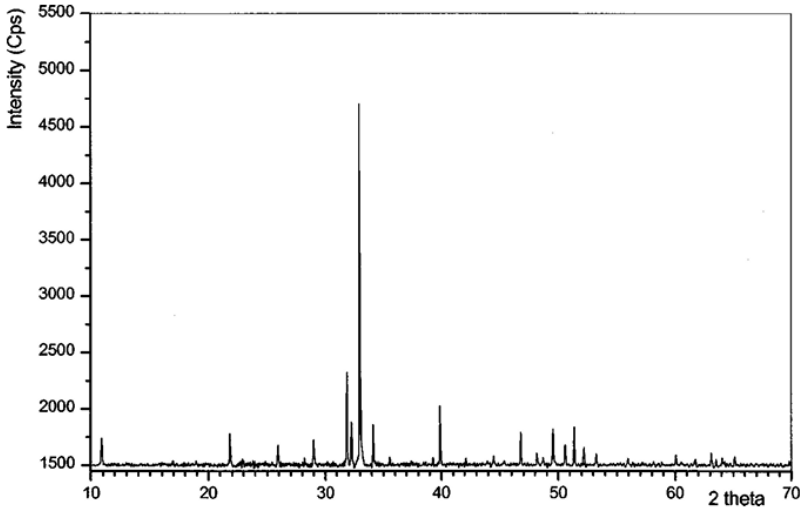
• Omega (ordinary ray) → the refractive index for light vibrating perpendicular to the crystal's main optic axis (the *c*-axis)

• Epsilon (extraordinary ray) → the extreme refractive index for light vibrating parallel to the crystal's optic axis



This is the typical SEM photomicrograph of the HA whiskers produced by the molten salt method of publications 1 and 2. Prior to both of these publications, there were no mention of such monocrystalline and monodisperse HA whiskers.

The below X-ray diffraction pattern of the single-crystal molten salt whiskers was from publication-2 and the XRD data table of publication 2 was later accepted to the ICDD-PDF (International Centre for Diffraction Data – Powder Diffraction File, Pennsylvania, U.S.A.) database. Click here to reach at the ICDD-PDF card (No: 00-055-0592) of these molten salt-synthesized monodisperse whiskers. Below is the XRD pattern (w/ Cu K_α radiation) of the single-crystal whiskers shown above from publication-2, and the (300) reflection had the highest intensity (due to the preferred orientation of whiskers).

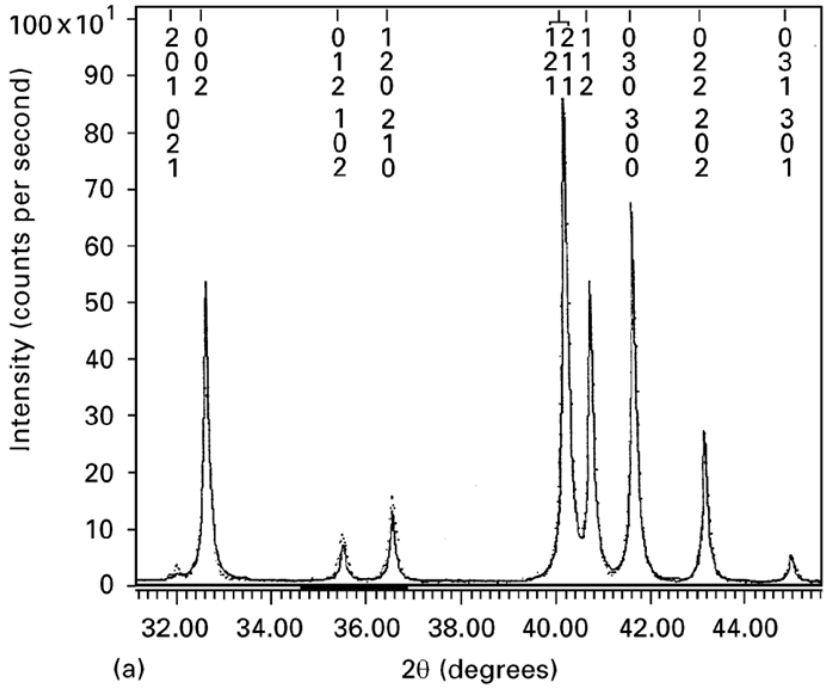


Hexagonal monocrystalline whiskers of publication-2 had the lattice parameters of a=b=9.4189, c=6.8827 Å, α=β=90°, γ=120°, space group=$P6_3/m$ (H-M No: 176), V=528.80 Å^3 and Dx=3.155 g/cm^3. On the other hand, the lattice parameters of polycrystalline and single-phase hexagonal HA powders we synthesized (by heating at 1200°C) back in 1994 were a=b=9.4147 Å and c=6.8777 Å. The positional (unit cell) parameters (determined by Rietveld analysis) of these polycrystalline HA powders and their XRD pattern (w/ Fe K_α radiation) are reproduced below.

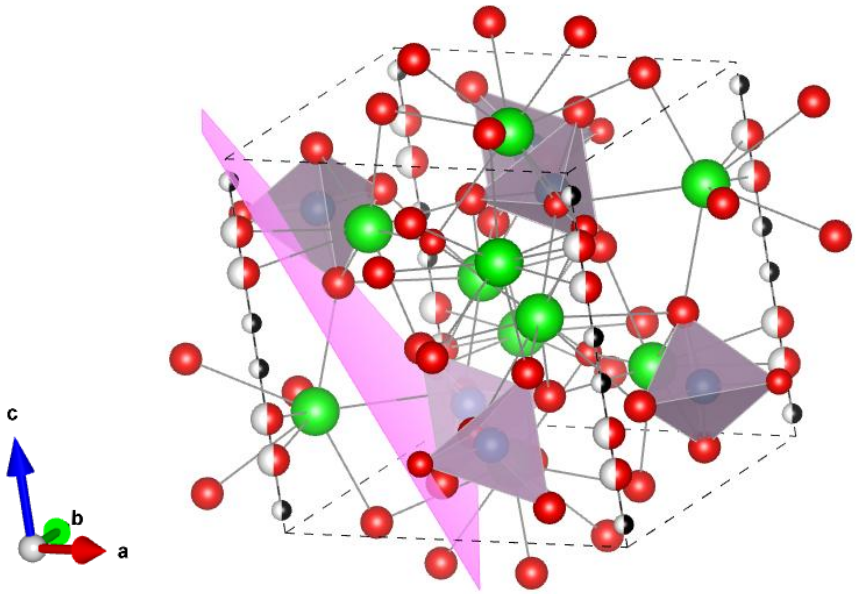
TABLE II Positional (unit cell) parameters of the HA powders (1200 °C)

Atom	*x*	*y*	*z*	Site occupancy
O(1)	0.3351(9)	0.4890(9)	0.2500	1.006(29)
O(2)	0.5875(8)	0.4606(9)	0.2500	1.009(42)
O(3)	0.3304(9)	0.2468(11)	0.0687(13)	1.017(79)
P	0.3982(6)	0.3696(6)	0.2500	1.002(4)
Ca(1)	0.3333(2)	0.6667(1)	0.0060(10)	0.6905(12)
Ca(2)	0.2473(6)	0.9914(8)	0.2500	0.9982(23)
O(H)	0	0	0.1767(5)	0.5067(121)
H	0	0	0.0673(5)	0.5032(129)

Estimated standard deviations (e.s.d) for the parameters varied are given in parentheses following the digits for which they are applicable.

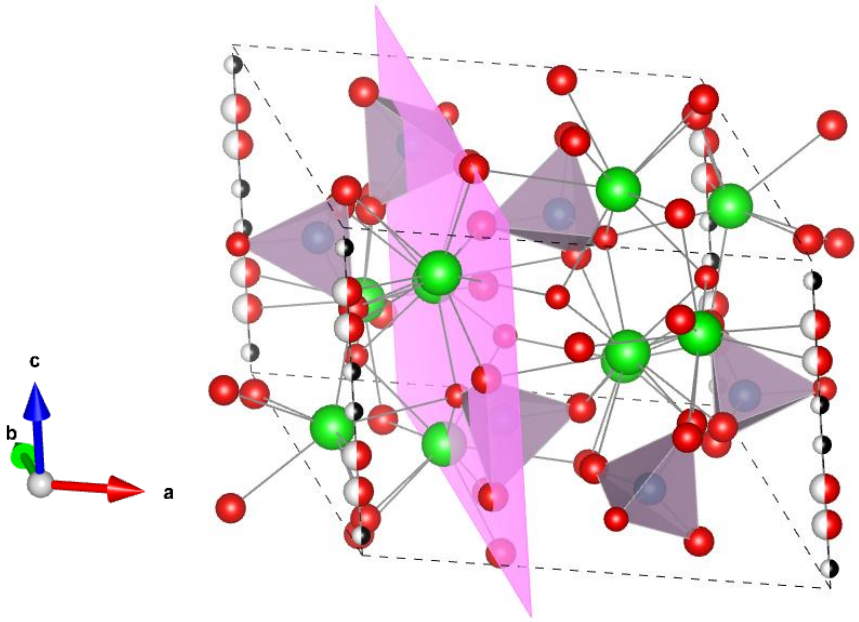


The (211) reflection has the highest intensity in polycrystalline HA powders and the (300) reflection would not dominate their XRD pattern; this is the eye-catching difference between the monocrystalline HA whiskers and the polycrystalline HA powders.



Polycrystalline HA unit cell with its maximum intensity *(211)* plane shown in pink

(black: H, green: Ca, red: O, blue: P)

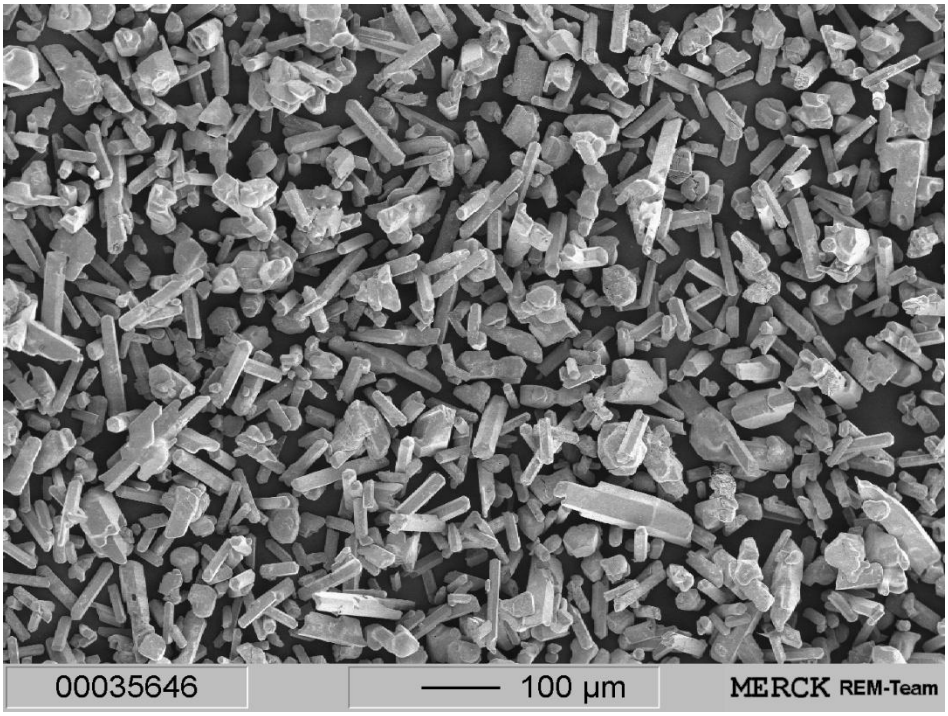


Single-crystal HA unit cell with its maximum intensity *(300)* plane shown in pink

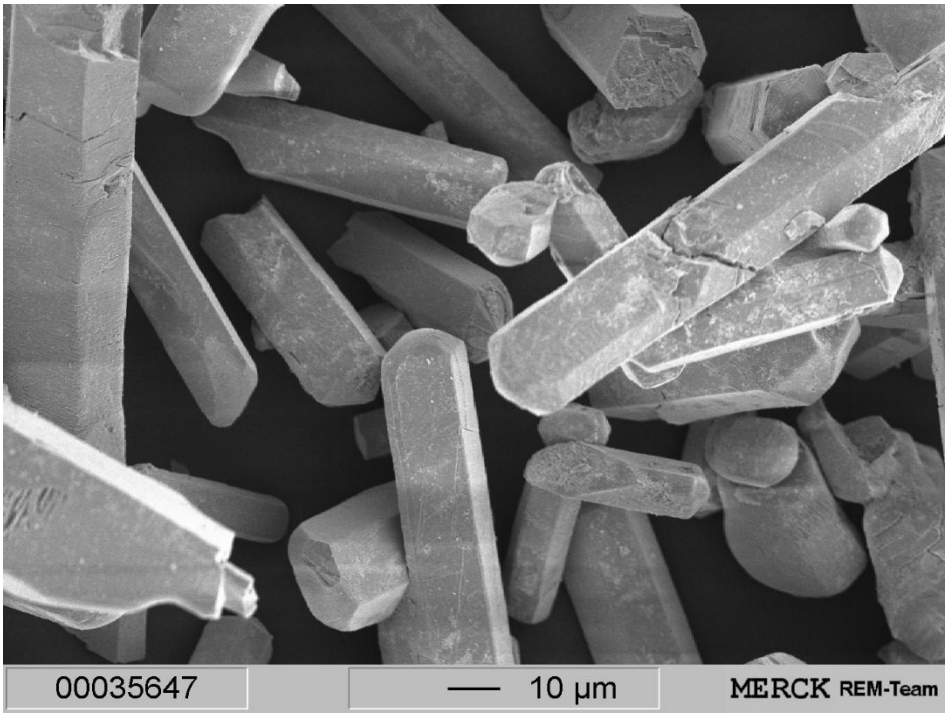
Whiskers, as seen in the above SEM photomicrograph, orient themselves along their long sides (preferred orientation), this is the reason why the highest intensity peak in their XRD pattern is from the (300) plane. The above structure drawings (prepared by us using

the shareware VESTA) will help the careful eyes to easily catch that the *(300)* plane of HA contains two Ca^{2+} ions, while its *(211)* plane does not. The *(300)* plane is apparently the preferred growth direction of the HA embryo first forming in molten K-sulphate and single-crystal HA is nucleating in Ca-rich domains. Calcium is the heaviest element of the HA formula, that also helps to understand why the *(300)* plane of single-crystal HA has an overwhelming intensity.

The below couple of SEM images show the β-TCP (β-$Ca_3(PO_4)_2$) monocrystalline whiskers we obtained (when I was working as a staff scientist at Merck Biomaterials GmbH, Darmstadt, Germany from 2001 to 2003) by using the molten salt synthesis method described in publications 1 and 2.



(patent protected)

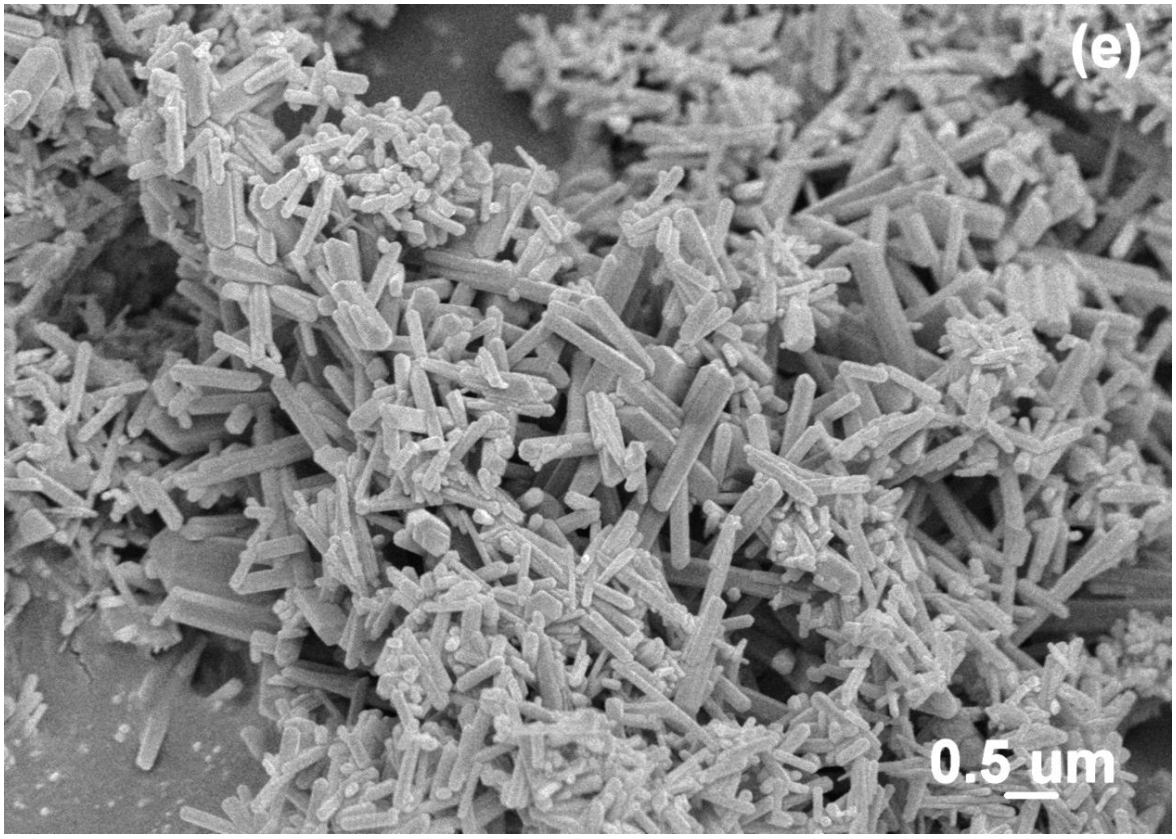


(patent protected)

Publications 1 and 2 both used the same molten salt synthesis (MSS) method and both used K_2SO_4 powder as the flux and a starting material in powder form (to dry mix with K_2SO_4 prior to heating) having a nominal Ca/P molar ratio of *ca* 1.67. In each of these publications temperature and the mass ratio of K_2SO_4-to-starting material were different, and publication 2 had the purpose of contributing the XRD data of the MSS-synthesized monocrystalline whiskers to the ICDD-PDF database.

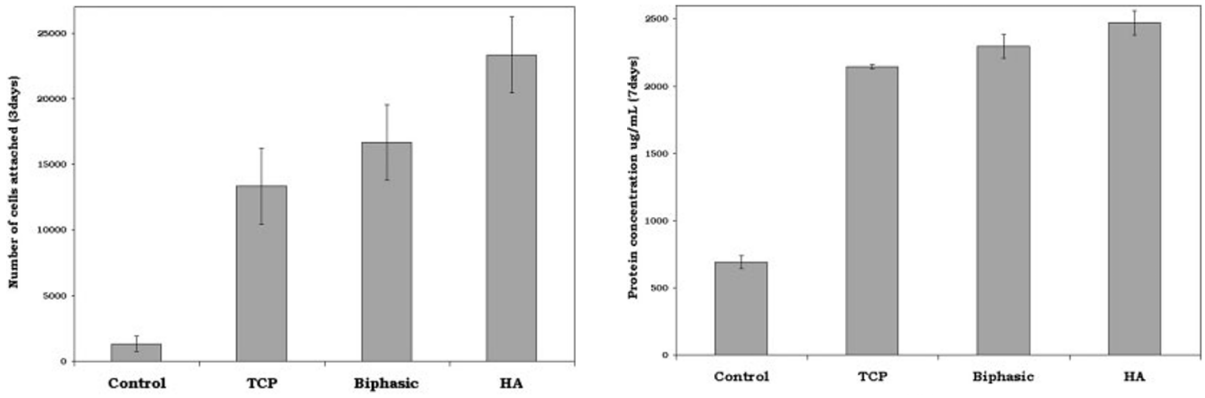
Publications 3 and 4, on the other hand, used a different HA whisker synthesis method; it was a hybrid of "molten salt" synthesis (MSS) and self-propagating "combustion synthesis" (SPCS) methods. (For my work with the SPCS method, see articles numbered as 51, 60, 62 in the weblink here and at this link.) Publication 4 had the purpose of testing the calcium phosphate whiskers (*i.e.*, whiskers of HA and biphasic HA - β-TCP) in osteoblast cell cultures to verify their biocompatibility. In publications 3 and 4, the starting material was a transparent (precipitate-free) liquid with dissolved $Ca(NO_3)_2{\cdot}4H_2O$, KH_2PO_4, $NaNO_3$, urea and a small aliquot of concentrated HNO_3. $NaNO_3$ has a melting point of 308°C and it served as the molten salt. Urea presence was for the combustion synthesis. This is how a hybrid molten salt & combustion synthesis process was designed in publications 3 and 4. 10 mL portions of the liquid starting material was placed in Pyrex glass beakers and heated to *ca* 500°C. The heating can be achieved either in a muffle furnace or in a microwave oven. The important thing is to reach 500°C. In going up to 500°C, water evaporated, $NaNO_3$ crystallized then rapidly melted and urea provided extra fuel (through an auto-ignition process) to increase the local temperature. The total thermal treatment time is less than 20 minutes. Pure HA or HA-TCP biphasic whiskers were formed during cooling back to RT. The material collected from the Pyrex

beakers were washed with an ample amount of deionized water (to remove the water-soluble mixed Na + K moiety from the product), followed by drying at 80°C in air.



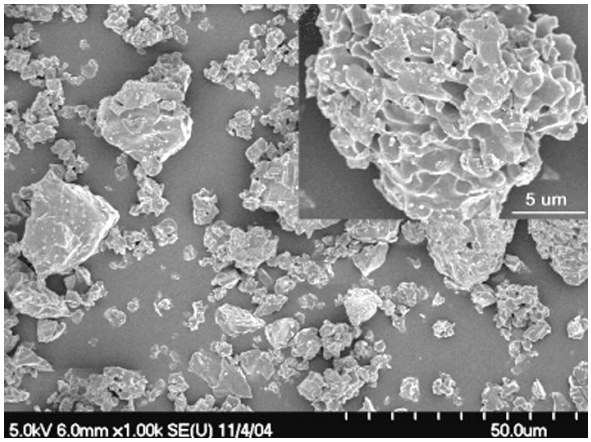
HA whiskers of publication-3

The above SEM photomicrograph shows the HA whiskers obtained from the MSS + CS hybrid process with a maximum synthesis temperature of 500°C. Although the temperature of MSS was now decreased from 1190/1150°C to 500°C in this MSS + CS approach, which presents a significant economical advantage, the whiskers were successfully formed but they were not monodisperse. Publication 3 has SEM images for pure β-TCP and biphasic HA - β-TCP samples produced by this MSS + CS hybrid process.

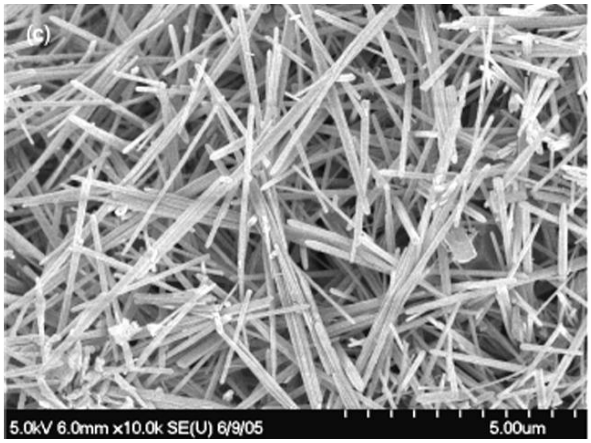


Osteoblast cell culture work on the products of the MSS + CS hybrid process (publication 4)

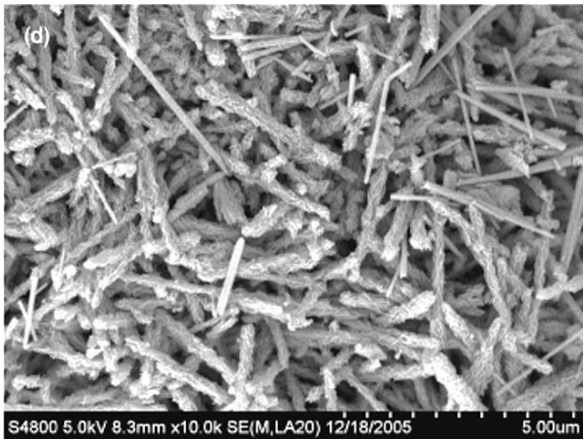
The fourth method (publication 5) lowers the apatitic calcium phosphate whisker synthesis temperature down to 90°C. One simply adds β-TCP powder to 30% H_2O_2 solution (of pH ~3) contained in a glass media bottle, followed by keeping the capped bottle in an oven at 90°C for 48 h (no stirring necessary) and filtering-washing w/water-drying the solids obtained. The images below are from publication 5.



Starting β-TCP powder



Apatitic calcium phosphate (Ap-CaP) whiskers formed in H2O2 at 90°C



Calcium phosphate whiskers upon keeping in synthetic body fluid (SBF) at 37°C for 6 days