# MME 4506 Biomaterials

Bioceramics

The major characteristics of ceramics are their brittleness, high hardness, thermal and electrical insulation, and corrosion resistance

Their hardness and resistance to abrasion makes them useful for bones and teeth replacement

The chemical inertness fits in the initial criterion for selection of suitable materials in the biological applications, as the human body is a hostile environment for any material

However the solubility of inert bioceramics are low in aqueous medium
An implant needs to be biodegradable to some extent so that it is removed by the body itself

In an ideal situation, a biodegradable implant material is slowly resorbed and replaced by natural tissue. However, to match the rate of resorption with that of the expected bone tissue regeneration for a biodegradable material is a great challenge.

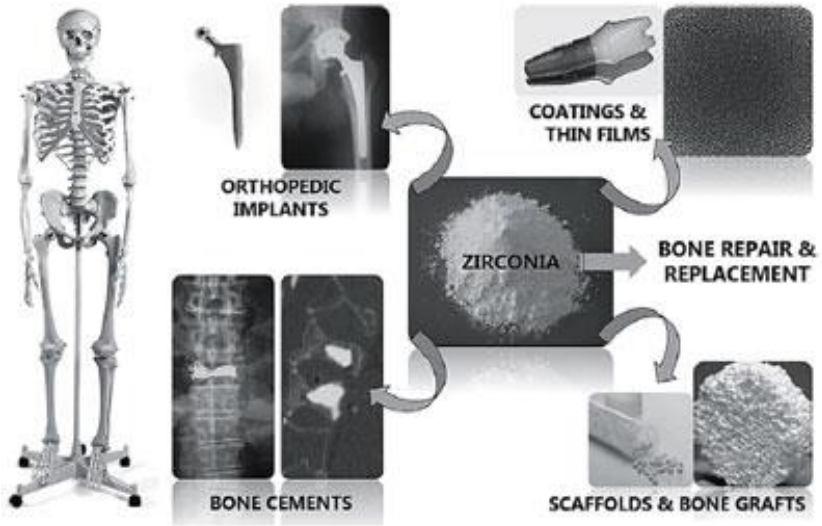
Clinical applications of bioceramics:

- Repair of the skeletal system comprising bone, joints and teeth
- Augmenting both hard and soft tissues

They are mostly used as orthopedic and dental implants
Also porous scaffolds for tissue engineering

Joint replacements are commonly coated with bioceramic materials to reduce wear and inflammatory response
Other examples of medical uses for bioceramics are in pacemakers, kidney dialysis machines, and respirators

The global demand on medical ceramics and ceramic components was about U.S. $9.8 billion in 2010. It was forecast to reach U.S. $18.5 billion by 2018.



Types of bioceramics according to host tissue interactions

- Bioinert
- Bioactive
  - Resorbable
  - Non-resorbable

All types may be used in porous, dense bulk form, granule or coating forms

The function of cells grown in contact with a material is affected by the physicochemical characteristics of the material, such as crystallinity and surface roughness

It was found that micromolar concentration of inorganic ions, such as Si could stimulate osteoblast proliferation, differentiation and gene expression on orthopedic implants

The distinction between non-toxic bioceramics are made based on tissue responses that are affected by surface properties like chemical composition, surface energy, crystallinity and roughness

Bioinert ceramics, such as alumina and zirconia, have excellent mechanical properties for load-bearing applications, while bioactive glasses and ceramics have the potential for osteoconduction.

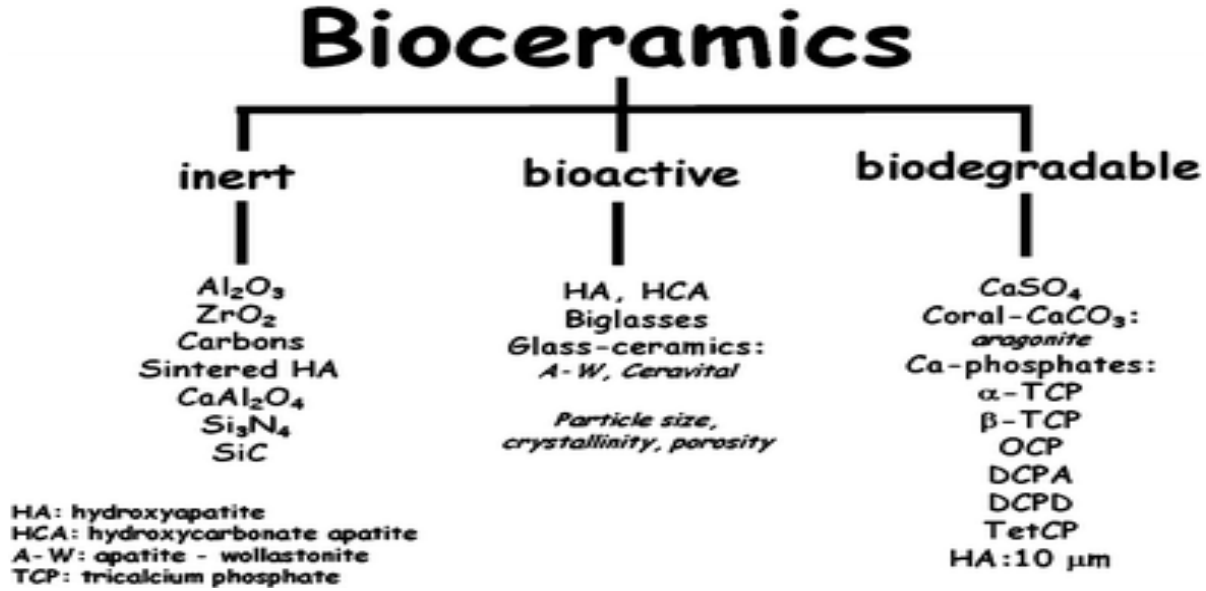



*Table 1.1* A summary of mechanical properties of various biomaterials (Hench and Andersson, 1993; Holand and Vogel, 1993; Hulbert, 1993; Hench and Best, 2004)

| Materials | Density ($g\,cm^{-3}$) | Hardness (Vickers, HV) | Young's modulus (GPa) | Bending strength (MPa) | Compressive strength (MPa) | Fracture toughness $K_{IC}$ ($MPa\,m^{1/2}$) |
|---|---|---|---|---|---|---|
| Bioglass® 45S5 | 2.66 | 458 | 35 | 40–60 | | 0.4–0.6 |
| A-W glass-ceramic | 3.07 | 680 | 118 | 215 | 1080 | 2.0 |
| Bioverit glass-ceramic | 2.8 | 5000 | 70–88 | 140–180 | 500 | 1.2–2.1 |
| Sintered HA | 3.156 | 500–800 | 70–120 | 20–80 | 100–900 | 0.9–1.3 |
| Alumina | 3.98 | 2400 | 380–420 | 595 | 4000–4500 | 4–6 |
| Zirconia (TZP) | 6.05 | 1200 | 150 | 1000 | 2000 | 7 |
| Zirconia (Mg-PSZ) | 5.72 | 1120 | 208 | 800 | 1850 | 8 |
| 316 stainless steel | 8 | | 200 | 540–1000* | | ~100 |

* = tensile strength.

# Clinical applications

| Devices | Function | Biomaterial |
|---|---|---|
| Artificial total hip, knee, shoulder, elbow, wrist | Reconstruct arthritic or fractured joints | High-density alumina, metal bioglass coatings |
| Bone plates, screws, wires | Repair fractures | Bioglass-metal fibre composite, Polysulphone-carbon fibre composite |
| Intramedullary nails | Align fractures | Bioglass-metal fibre composite, Polysulphone-carbon fibre composite |
| Harrington rods | Correct chronic spinal curvature | Bioglass-metal fibre composite, Polysulphone-carbon fibre composite |
| Permanently implanted artificial limbs | Replace missing extremities | Bioglass-metal fibre composite, Polysulphone-carbon fibre composite |
| Vertebrae Spacers and extensors | Correct congenital deformity | $Al_2O_3$ |
| Spinal fusion | Immobilise vertebrae to protect spinal cord | Bioglass |
| Alveolar bone replacements, mandibular reconstruction | Restore the alveolar ridge to improve denture fit | Polytetra fluro ethylene (PTFE) - carbon composite, Porous $Al_2O_3$, Bioglass, dense-apatite |
| End osseous tooth replacement implants | Replace diseased, damaged or loosened teeth | $Al_2O_3$, Bioglass, dense hydroxyapatite, vitreous carbon |
| Orthodontic anchors | Provide posts for stress application required to change deformities | Bioglass-coated $Al_2O_3$, Bioglass coated vitallium |

Bioinert ceramics

Alumina and zirconia have good biocompatibility, adequate mechanical strength, but are relatively biologically inactive (nearly inert) and lack direct bonding with host tissue

They have been used as an important alternative to surgical metal alloys in total hip prostheses and as tooth implants

The main advantages of using these ceramics over the traditional metal and polymer devices are lower wear rates at the articulating surfaces and the release of very low concentrations of inert wear particles

For example, using femoral heads of alumina ceramic bearing against alumina cup sockets significantly reduces wear debris when against ultra-high molecular weight polyethylene cups

There are two types of zirconia ceramics for surgical implants:

- yttria-stabilized tetragonal zirconia (Y-TZP)
- magnesium oxide partially stabilized zirconia (Mg-PSZ)

Zirconia ceramics have the advantages over alumina ceramics of higher fracture toughness and higher flexural strength, and relatively lower Young's modulus

However due to its lower wear resistance, the choice of zirconia components in hip procedures were significantly reduced after a number of implant failures

To improve the fracture toughness of alumina ceramics, nanophase alumina with grain size of 23 nm was synthesized

The modulus of elasticity of nano-phase alumina decreased by 70% but the biological responses of osteoblast cells were increased as a result

The fracture toughness of alumina can then be controlled through the use of nanophase formulations

Zirconia fabrication:

Obtained from the mineral zircon

Addition of MgO, CaO, CeO, or $Y_2O_3$ stabilize tetragonal crystal structure (e.g. 97 mol%$ZrO_2$ and 3 mol%$Y_2O_3$)

Usually hot-pressed or hot isostatically pressed

Applications:

Orthopaedics: femoral head, artificial knee, bone screws and plates, favored over UHMWPE due to superior wear resistance

Dental: crowns and bridges

Alumina fabrication:

Obtained from boehmite or corundum

Sol-gel processed, hot-pressed or hot isostatically pressed

Applications

Orthopedics: femoral head, knee prosthesis, bone screws and plates, porous coatings for femoral stems, porous spacers (specifically in revision surgery)

Dental: crowns and bridges

Zirconia ceramic has bioinertness and noncytotoxicity

Carbon is another alternative with similar mechanical properties to bone, and it also features blood compatibility, no tissue reaction, and non-toxicity to cells

None of the three bioinert ceramics exhibit bonding with the bone

However, bioactivity of bioinert ceramics can be achieved by forming composites with bioactive ceramics

Bioglass and glass ceramics are nontoxic and chemically bond to bone

Glass ceramics elicit osteoinductive properties, while calcium phosphate ceramics also exhibit non-toxicity to tissues and bioresorption

**TABLE 1.4. Mechanical Properties of Ceramic Biomaterials***

| | Young's Modulus, E (GPa) | Compressive Strength, $\sigma_{UCS}$ (MPa) | Tensile Strength, $\sigma_{UTS}$ (MPa) |
|---|---|---|---|
| Alumina | 380 | 4500 | 350 |
| Bioglass-ceramics | 22 | 500 | 56–83 |
| Calcium phosphates | 40–117 | 510–896 | 69–193 |
| Pyrolytic carbon | 18–28 | 517 | 280–560 |

*Compiled from L.L. Hench. Ceramics, Glasses, and Glass-Ceramics, pp. 73–84 in B.D. Ratner, A.S. Hoffman, F.J. Shoen, and J.E. Lemons (eds), *Biomaterials Science: An Introduction to Materials in Medicine*, Academic Press, San Diego (1996); J.B. Park and R.S. Lakes, *Biomaterials*, Plenum Press, New York (1992); and J. Black, *Biological Performance of Materials*, Marcel Dekker, New York (1992).

The nature and development of a stable interface between an implanted bioceramic and bone, which is crucial for the clinical success of the implant, are affected by many factors

In order to understand the mechanism of bonding of a bioactive material with host tissue, it is necessary to characterize the surface of a material in vitro (in physiological solution initially and then the cell and tissue responses)

The specific tissue compatibility of a material is highly dependent on the composition and structure of surface layers.

Such in vitro analysis is an aid to understanding the potential in vivo host tissue responses

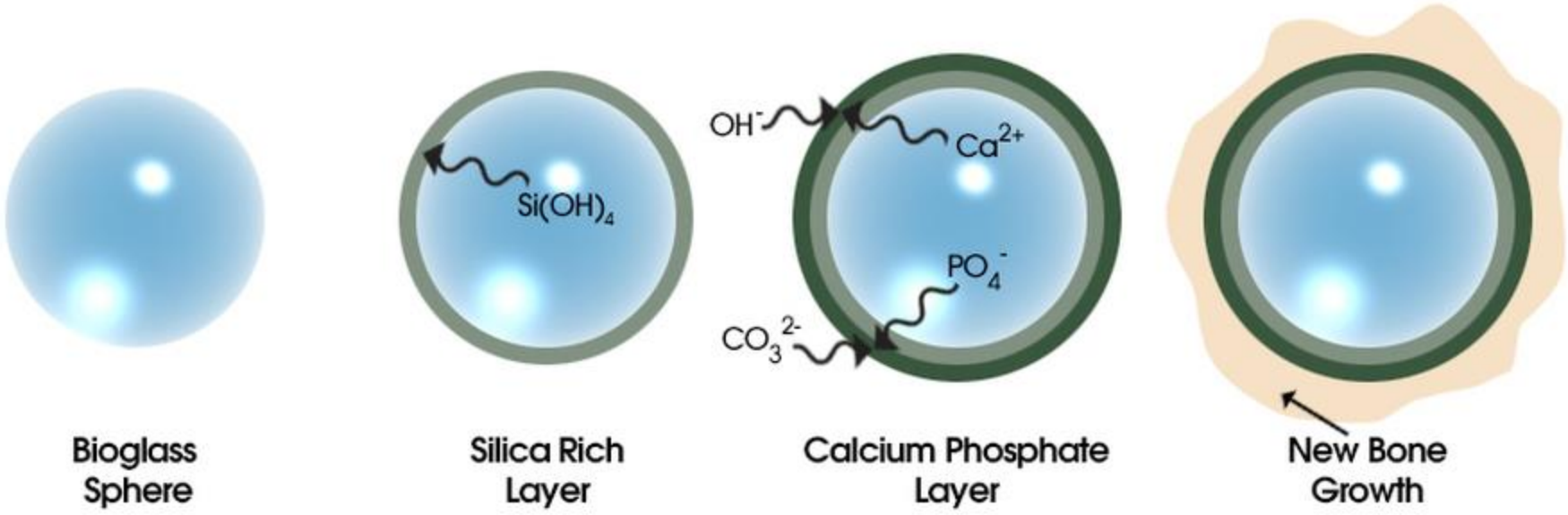
The quantification of the release products from bioactive glasses and ceramics by solution analysis is important for their application as scaffolds

For example, the dissolution products of bioactive glasses were found to have a positive effect on the expression of genes regulating osteogenesis

A series of surface reactions were found to occur when bioactive glasses were immersed in a physiological solution. Exchanges of $Na^+$ and $K^+$ with $H^+$ and $H_3O^+$ ions from solution at the glass surface lead to the loss of soluble silica and the formation of SiOH (silanols) at the glass solution interface

This stage is followed by the migration of calcium and phosphate ions through the silica-rich layer to the surface and the formation of an amorphous calcium phosphate layer, which can then crystallize by the incorporation of hydroxyl, carbonate and fluoride ions to create an apatite layer

In the presence of osteogenic precursors, bioactive glasses favor the formation and growth of osteoblasts



Bioactive ceramics

A series of bioactive ceramics, glasses and glass-ceramics are capable of promoting the formation of bone at their surface and of creating an interface, which contributes to the functional longevity of tissue

The most widely applied orthopaedic bioceramics, such as hydroxyapatite ceramics, Bioglass and apatite-wollastonite glass-ceramic are a few examples

Bioactive means that the material stimulates an advantageous biological response from the body on implantation. The termed was found by Larry Hench in 1971, when he and his colleagues, at the University of Florida, invented Bioglass, the first material that formed a strong bond to bone

Bioglass was designed as a glass that would contain large amounts of calcium and phosphorous, as they are found in bone

However, as bone mineral is carbonated hydroxyapatite, a more obvious choice of material for a bone-repairing implant was a synthetically produced apatite

Sintered hydroxyapatite has become a very popular bioactive implant material and has many more clinical products than Bioglass

Aside from glasses and ceramics, a third class of bioactive ceramics has been developed in Japan: glass-ceramics, particularly the apatite-wollastonite glass-ceramics that originated from Bioglass

A glass-ceramic is polycrystalline solid prepared by the controlled crystallisation or devitrification of a parent glass. It generally consists of fine grain (with crystal sizes ranging from 0.1 to 10 microns) and has a small volume of residual glass sited at the grain boundary

One advantage of glass-ceramics is that the crystallisation and the formation of the crystal phases can be controlled to develop materials with a combination of special properties, such as bioactivity, machineability and improved mechanical properties

Glass-ceramics are produced by the transformation of the glass into a ceramic. The glass is firstly heated at the temperature of 450-700 C to produce a large number of nuclei, then the temperature is increased to 600-900 C to promote crystal growth.

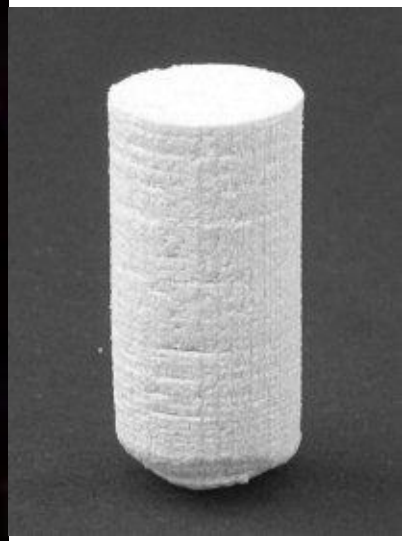
Apatite-wollastonite (A-W) glass-ceramic, with an assembly of small apatite particles effectively reinforced by wollastonite, exhibits not only bioactivity, but also a fairly high mechanical strength

A dense and homogeneous composite was obtained after heat treatment of parent glass, in which 38 wt% was oxyfluorapatite ($Ca_{10}(PO_4)6(O,F)_2$) and 34 wt% wollastonite ($CaOSiO_2$), both grain-like particles, 50-100 nm in size formin a MgO-CaO-SiO2 glassy matrix. It combines high bioactivity with desirable mechanical properties and has been successful in the load-bearing spinal area of the body.

All bioactive ceramics are used in dental applications, maxillofacial restoration and bone defect fillers in powder and moulded forms

HA and A-W glass-ceramics have been used in vertebral disc replacements and other bone defect replacements

The first suggestion of using sintered HA as a bone or tooth implant was in 1969. It was not used clinically until 1978 when dense sintered HA cylinders were used as immediate dental root implants after tooth extraction



Calcium phosphates

Calcium phosphates are the major constituents of bone mineral

The most extensively used synthetic calcium phosphate ceramic for bone replacement is hydroxyapatite (HA) because of its chemical similarities to the inorganic component of bone and teeth

*Table 1.2* Ca/P ratio of various calcium phosphates (Aoki, 1991)

| Name | Abbreviation | Formula | Ca/P ratio |
|---|---|---|---|
| Tetracalcium phosphate | TTCP | $Ca_4O(PO_4)_2$ | 2.0 |
| Hydroxyapatite | HA | $Ca_{10}(PO_4)_6(OH)_2$ | 1.67 |
| Tricalcium phosphate ($\alpha$,$\alpha'$,$\beta$,$\gamma$) | TCP | $Ca_3(PO_4)_2$ | 1.50 |
| Octacalcium phosphate | OCP | $Ca_8H_2(PO_4)_6{\cdot}5H_2O$ | 1.33 |
| Dicalcium phosphate dihydrate (brushite) | DCPD | $CaHPO_4{\cdot}2H_2O$ | 1.0 |
| Dicalcium phosphate (montite) | DCP | $CaHPO_4$ | 1.0 |
| Calcium pyrophosphate ($\alpha$,$\beta$,$\gamma$) | CPP | $Ca_2P_2O_7$ | 1.0 |
| Calcium pyrophosphate dihydrate | CPPD | $Ca_2P_2O_7{\cdot}2H_2O$ | 1.0 |
| Heptacalcium phosphate | HCP | $Ca_7(P_5O_{16})_2$ | 0.7 |
| Tetracalcium dihydrogen phosphate | TDHP | $Ca_4H_2P_6O_{20}$ | 0.67 |
| Calcium phosphate monohydrate | CPM | $Ca(H_2PO_4)_2H_2O$ | 0.5 |

CaP compounds with a Ca/P ratio less than 1 are not stable (soluble) at physiological conditions so they are not suitable for biological implantation

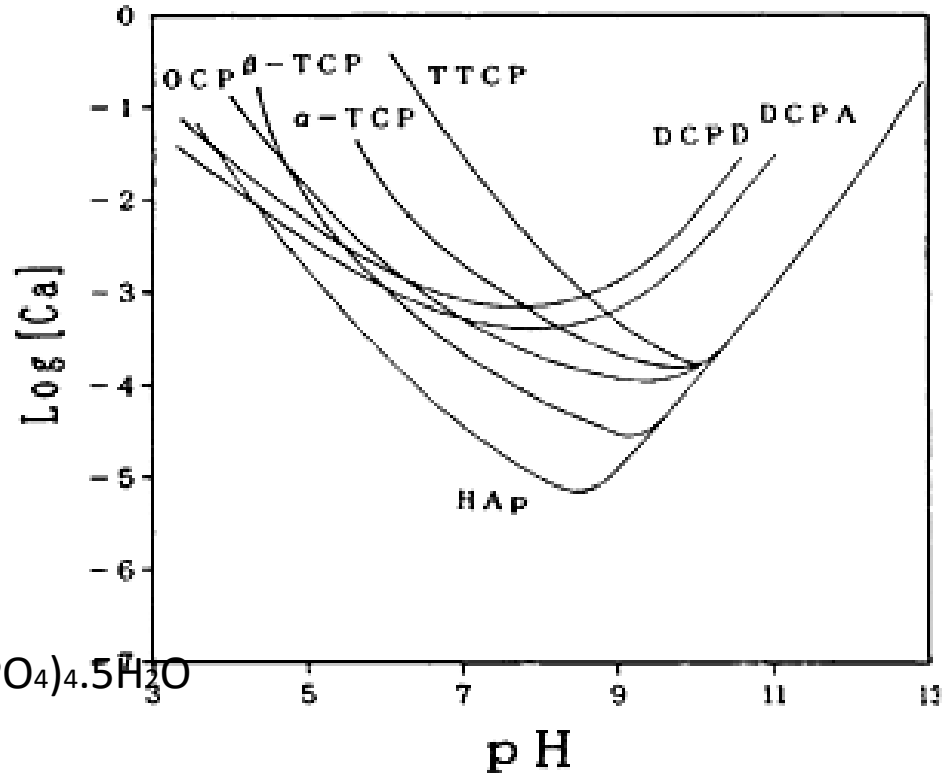
HA (Ca/P = 1.67) is much more stable than other calcium phosphate ceramics within a pH range of 4.2-8.0.

β-TCP or α-TCP are biodegradable bioceramics with the chemical formula of $Ca_3(PO_4)_2$. They dissolve in wet media and can be replaced by bone during implantation. They have higher bioresorbability than HA

The use of a mixture of HA and β-TCP, known as biphasic calcium phosphate (BCP), has been a common bone substitute. It has the advantage of tailor making its chemical properties, such as varying the ratio of HA/ β-TCP. The higher the TCP content in BCP, the higher the dissolution rate.

Basic CaPs

TTCP
$Ca_4P_2O_9$
β-TCP
$Ca_3(PO_4)_2$
α-TCP
$Ca_3(PO_4)_2$
OCP
$Ca_8(HPO_4)_2(PO_4)_4.5H_2O$




Acidic CaPs

DCPD
$CaHPO_4.2H_2O$
DCPA
$CaHPO_4$
MCPM
$Ca(H_2PO_4)_2.H_2O$

Figure 2. Solubility isotherms of calcium phosphates at ambient conditions

Synthesis of apatites has been grouped as follows:

- aqueous reactions
    - chemical precipitation (most commonly used method to produce a wide variety of particle sizes and morphologies)
    - hydrolysis
- solid state reactions
- hydrothermal reactions

The stoichiometry of HA is highly significant where thermal processing of the material is required

Slight imbalances in the ratio of Ca/P can lead to the appearance of other CaP phases

If the Ca/P is lower than 1.67, Beta-tricalcium phosphate (β-TCP) and other phases form

If the Ca/P is higher, CaO or tetracalcium phosphate may form with the HA phase

These other phases may adversely affect the biological response to the implants

Examples to chemical precipitation of HA

$10Ca(OH)_2 + 6H_3(PO_4) = Ca_{10}(PO_4)_6(OH)_2 + 18H_2O$ (pH>9)

$10Ca(NO_3)_2 + 6(NH_4)_2H(PO_4) + 2H_2O = Ca_{10}(PO_4)_6(OH)_2 + 12NH_4NO_3 + 8HNO_3$

Phosphate solution is added dropwise into a stirred calcium solution. Addition of ammonium hydroxide is needed to keep the pH of the reaction alkaline to ensure the formation of HA after sintering the precipitate

Processing at pH of less than 9 can result in the production of a calcium-deficient hydroxyapatite

The next step of ceramic processing is to break down the materials received from chemical synthesis, which is a solid aggregation of particles in a dried, filtered precipitate. The agglomerates have a deleterious effect on the microstructure of the ceramic, and therefore needs to be broken down by crushing and grinding

The HA powder obtained can then be made into dense or macroporous products using compaction (die pressing, isostatic pressing, slip casting, etc.) followed by solid state sintering

The concentrations of reagents need to keep the Ca/P molar ratio of 1.67 for the stoichiometric HA
The concentration of calcium or phosphate can be adjusted if substitution for calcium (e.g. strontium, magnesium) or phosphate (e.g. carbonate, silicate) is required

The mineral phase of bone, biological apatite, is not stoichiometric hydroxyapatite. The apatite is hospitable to a variety of cationic and anionic substitutions, and the type and amount of these ionic substitutions in the apatite phase vary from the wt% level (e.g. 3-8 wt% $CO_3$) to the ppm-ppb level (e.g. $Mg^{2+}$ or $Sr^{2+}$ )

Substitution in the apatite structure for (Ca), ($PO_4$) or (OH) groups result in changes in properties, such as lattice parameters, morphology, solubility without significantly changing the crystal symmetry

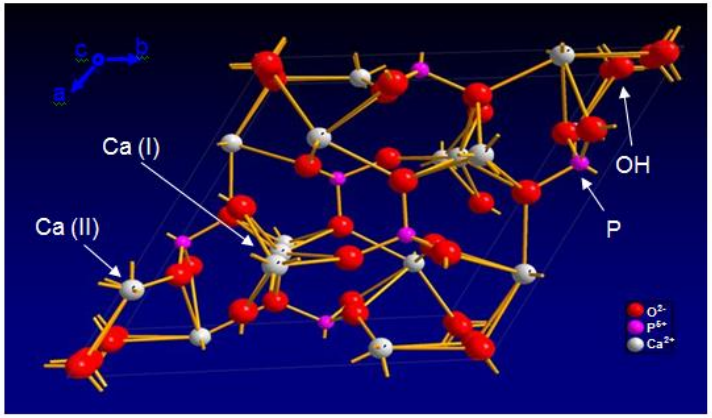
The fluoride substitution ($F^-$ for $OH^-$) has the consequence of increasing the crystallinity, crystal size and the stability of the apatite, which in turn reduces solubility
Fluoride substitution has been applied in caries prevention, where its presence in enamel crystals increases stability, which helps to resist dissolution in the acidic oral environment

Carbonate, $CO_3$, can substitute for either the hydroxyl (OH) groups or the phosphate groups An important effect of carbonate substitution in HA is on crystal size and morphology. An increase in carbonate content leads to changes in the size and shape of apatite crystal. As a result carbonate-substituted apatites are more soluble than carbonate-free synthetic apatites

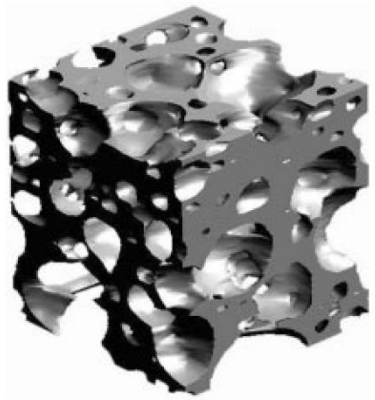
Silicon has been found in only trace quantities in bone mineral (up to a maximum level of ~0.5 wt%), but it has been shown to have a crucial role in bone mineralization, and is believed to be essential in skeletal development

In vitro and in vivo bioactivities are enhanced with the incorporation of silicon into HA lattice and Silicon-substituted HA has been used successfully as bone graft for spinal fusion

In addition strontium (Sr), magnesium (Mg), barium (Ba), lead (Pb), etc. are substituted for calcium, and vanadates, borates, manganates, etc. for phosphates in the hydroxyapatite molecule



In a macroporous form, HA ceramics can be colonized by bone tissue



*1.3* Three-dimensional structure of a hydroxyapatite scaffold ob
microtomography ($2 \times 2 \times 2 mm^3$). Courtesy of Dr X Fu
Cambridge.

The simplest way to generate porous scaffolds from ceramics such as HA is to sinter spherical HA particles
Porosity is often increased by adding sacrificial porogens, which are often particles that will be removed after compaction or during sintering
The sacrificial particles can either be soluble, (e.g. salt or sucrose) or combustible, (e.g. poly(methyl methacrylate) (PMMA) microbeads).
However, these methods give rise to a heterogeneous pore distribution and the interconnectivity of the pores is low.

To improve interconnectivity, open-celled polyurethane foams can be immersed in slurries of HA under vacuum to allow the slurry to penetrate into the pores of the foam. The foams are then heated at 250 C to burn out the organic components and sintered at 1350 C for 3 h, producing a scaffold with 300 micron interconnected pore diameters

One of the most successful method for creating interconnected HA is the gel-casting method, in which suspensions of HA particles and organic monomers are foamed with the aid of a surfactant. Once the foam is formed the monomers are polymerized and the porous network is set. The polymer gelling agent is burnt out (during sintering) before casting. The materials produced exhibited pores of maximum diameter of 100-200 microns

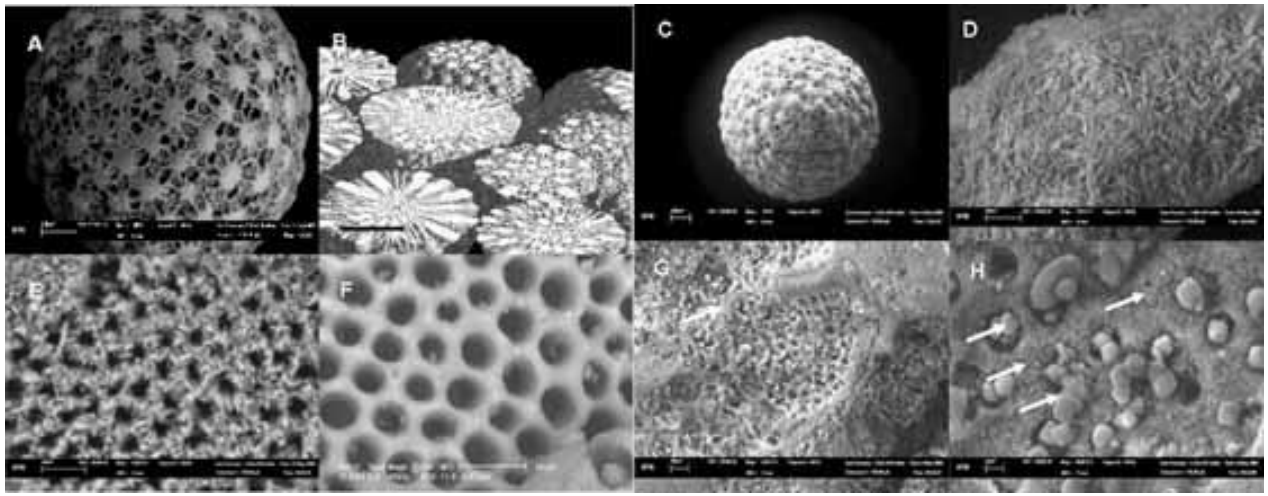
Hydroxyapatite has been derived from special species of corals (Porites) and from bovine bone

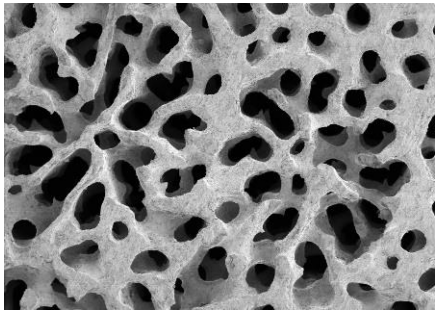
These HA are not pure but contain some of the minor and trace elements originally present in the coral or in the bone

Coralline HA contains traces of Mg, Sr, $CO_3$ and F

Bovine bone-derived apatite contains Mg, Na, $CO_3$ that were originally present

The great advantage of these materials is that they have an interconnected macroporous network that is conserved from the coral and bone.



Converting of coral, which is often $CaCO_3$ , to HA is often done hydrothermally, at 260 C and 15 000 psi in the presence of ammonium phosphate

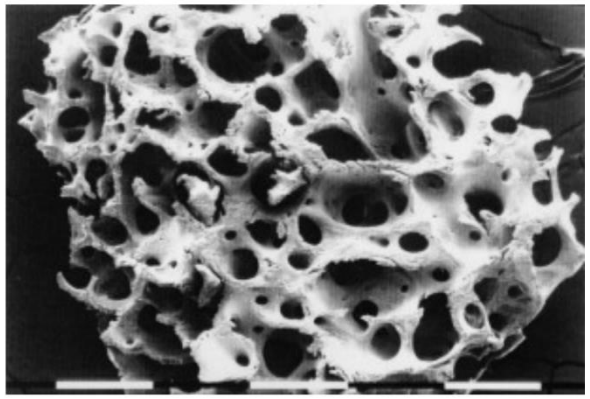
Ions such as F, Sr, and $CO_3$ present in the coral become incorporated in the resulting HA

A secondary phase of β-TCP also forms during the hydrothermal conversion

Bovine-derived apatites are produced by removal of the organic matrix. The resulting material is then either left unsintered or sintered above 1000 C. The unsintered bone mineral consists of small crystals of carbonated apatite, whereas the sintered bone mineral consists of much larger apatite crystals without $CO_3$

The small crystals in the unsintered HA have much higher surface area so that it will slowly resorb in the presence of body fluid, and therefore this material is more suitable for tissue engineering applications.

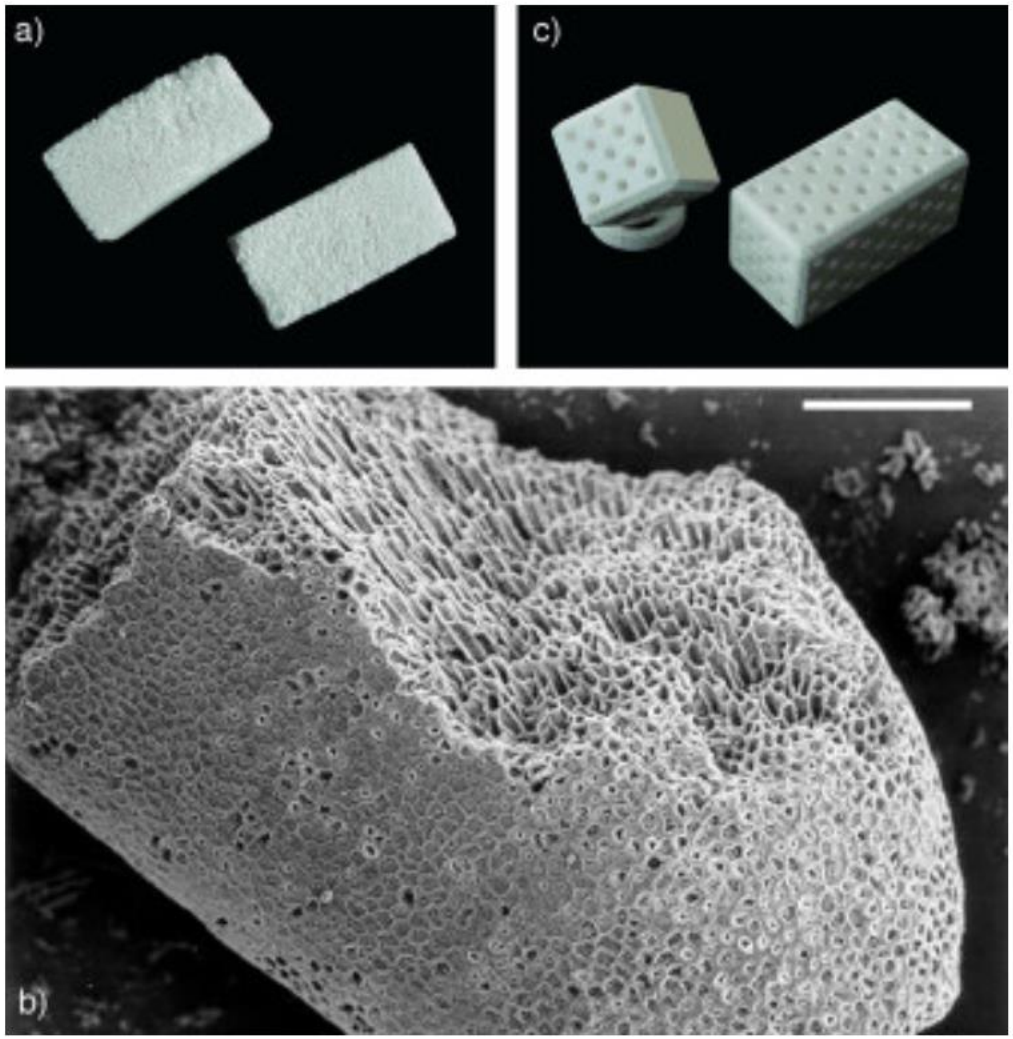
Figure 2: Calcined porous bone (spongiosa) showing the high porosity and the interconnecting network of pores (magnification: 20.4×).



A porous bovine bone-derived HA graft is marketed under the name Bio-Oss (Osteohealth, Shirley, New York), which is an unsintered material and therefore has some resorbability in vivo

Porous coralline HA is sold as Interpore and Pro-Osteon (Interpore International, Inc, Irvine, CA.)

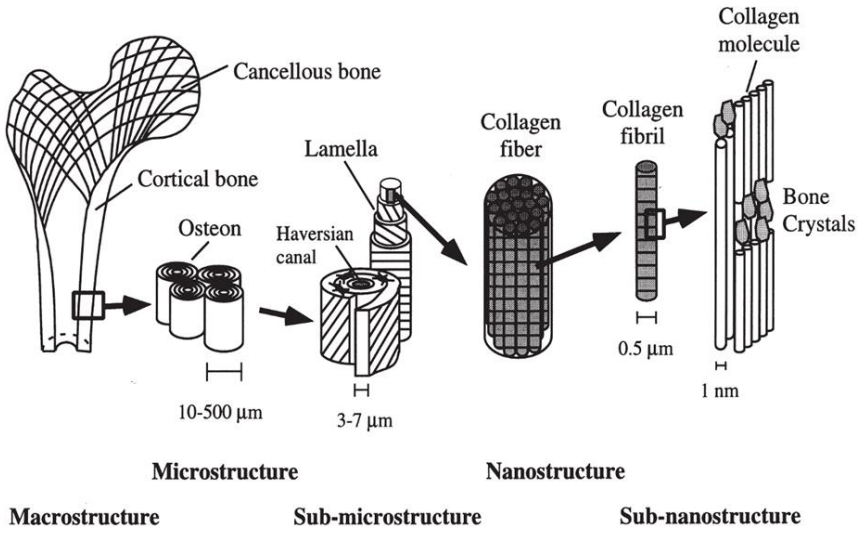
Figure 9: Examples of porous calcium phosphate-based bone-substitution materials: a) Cerabone (hydroxyapatite) from spongious calcined bovine bone (about 3×1×1 cm3); b) Algipore (hydroxyapatite) from hydrothermal processing of calcium carbonate-containing algae with ammonium phosphate. Scale bar: 100 µm; c) Cerasorb (synthetic phase-pure β-TCP) with CNC (computer numerical control)-drilled holes (about 1×1×2 cm3).



In general hydroxyapatite is not intended to be used in place of cortical strut allograft bone where high tensile, torsion and/or bending strength are required

Commercial HA is used as bone substitutes in several orthopaedic and dental applications but they generally differ from bone in mechanical strength and physicochemical properties

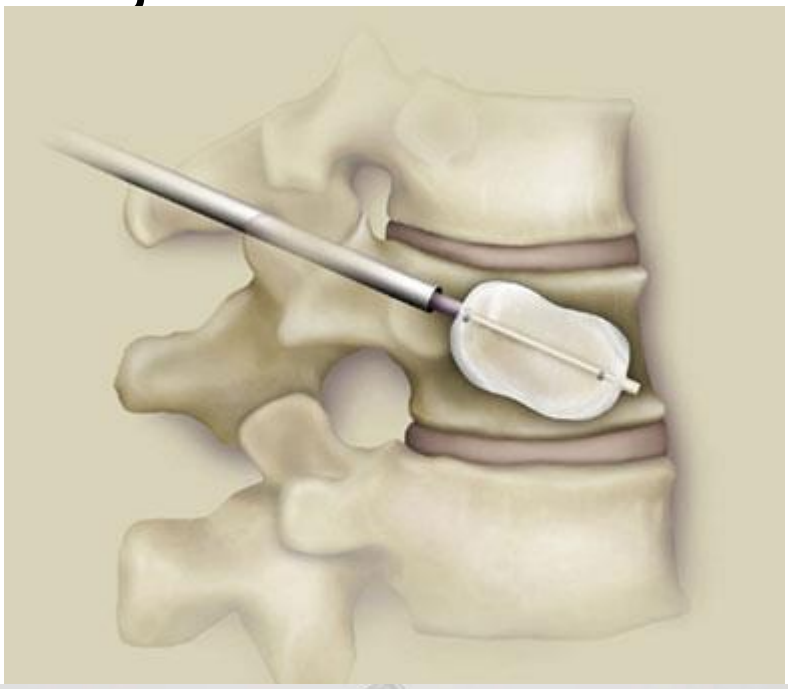
They cannot be used in load bearing applications because of their low fracture strength

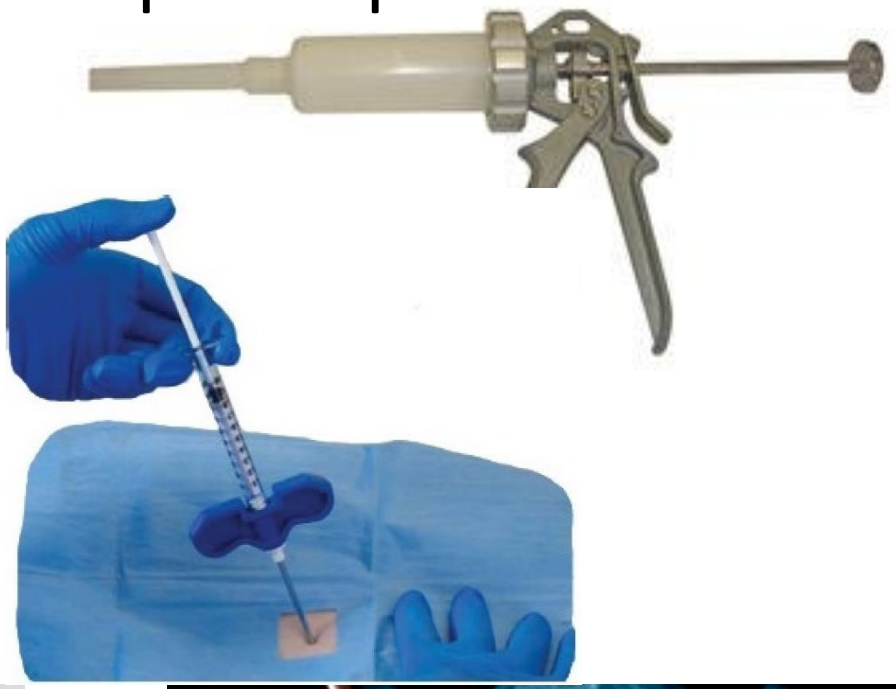


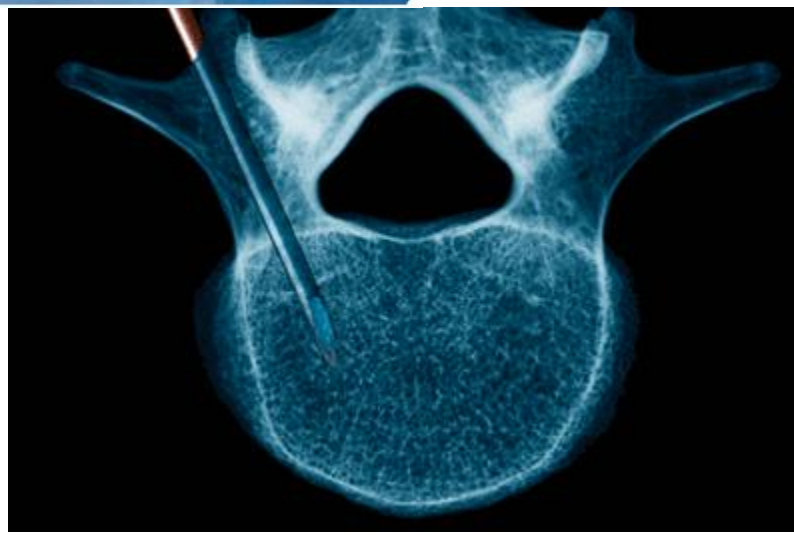

Although the relatively poor mechanical properties of calcium phosphate ceramics limit their clinical applications to non-major load-bearing parts of the skeleton, calcium phosphate-coated metallic implants are used in the load-bearing parts

The most popular commercial routes of calcium phosphate coatings are based on plasma spraying

# Injectable Calcium phosphates



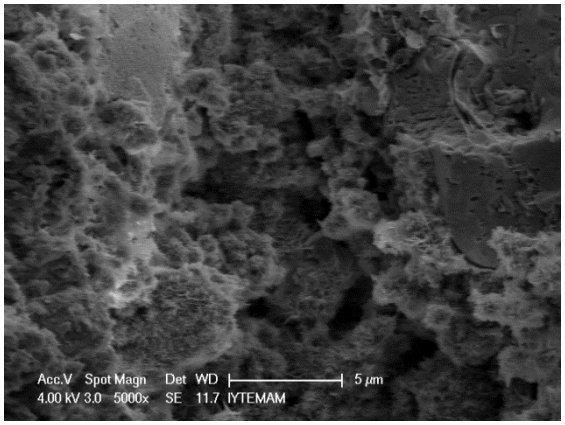


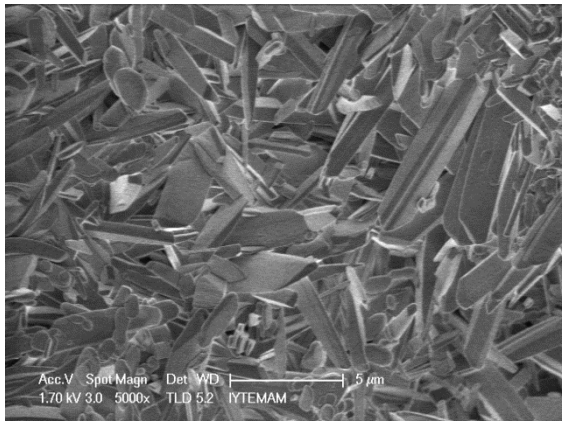


Calcium Phosphate Cements (CPC) are alternatives to heat treated calcium phosphate blocks where the material is needed to be delivered to the body by injection

Formation mechanism: Acid-Base reaction involving dissolution of highly soluble calcium phosphates, precipitation and intergrowth of relatively stable calcium phosphate crystals

Advantages: High surface area and roughness enabling rapid osteoconduction





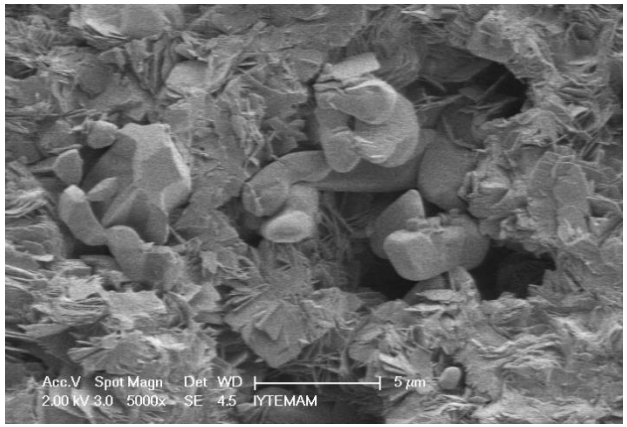



Figure 1. SEM images of hydroxyapatite, brushite and monetite cements respectively

Formulation of Brown & Chow forming Hydroxyapatite intergrowing crystals

$$Ca_4P_2O_9 + CaHPO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2$$

Formulation of Mirtchi & Lemaitre forming Brushite or Monetite intergrowing crystals

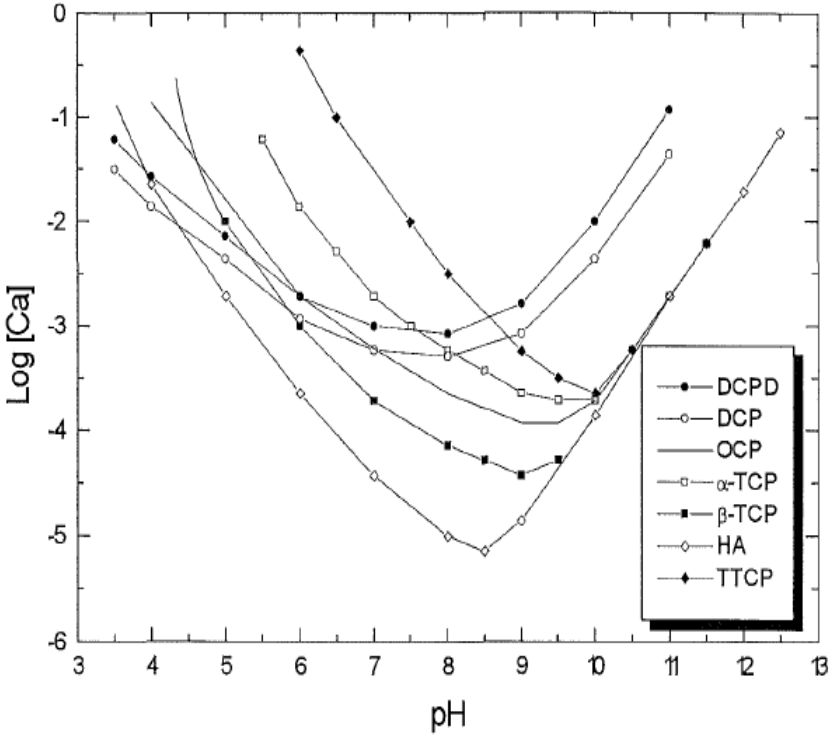
$$\beta\text{-}Ca_3(PO_4)_2 + Ca(H_2PO_4)_2 \cdot H_2O + 7H_2O \rightarrow 4CaHPO_4 \cdot 2H_2O$$

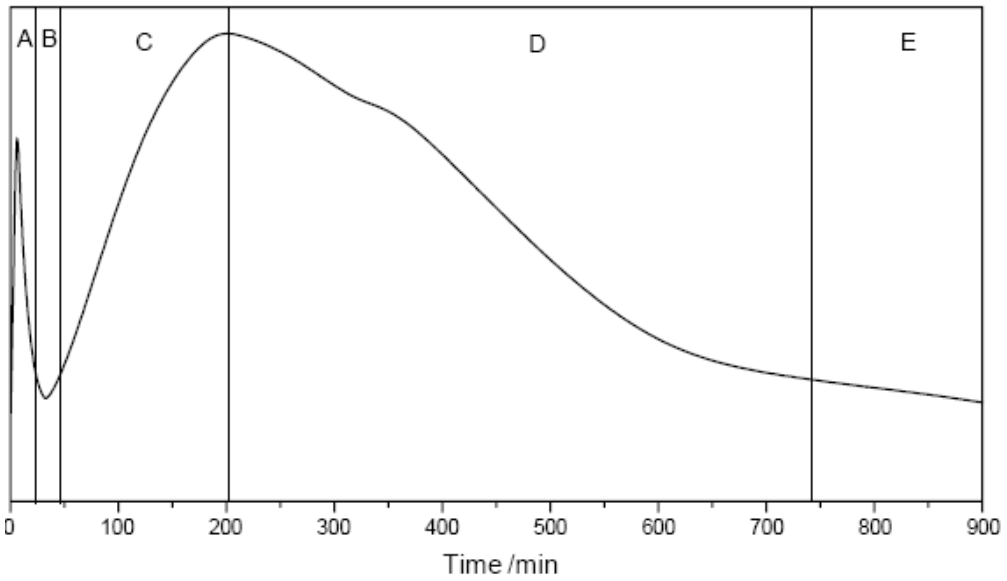
$$4CaHPO_4 \cdot 2H_2O \rightarrow 4CaHPO_4 + 8H_2O$$

Bioresorbability - Brushite > Monetite > Hydroxyapatite

Strength - Hydroxyapatite > Monetite > Brushite

# Thermodynamics of CPC's




Heat evolution during CPC setting:

A) Dissolution period
B) Induction period
C) Accelerating period
D) Decelerating period
E) Termination period

*From Liu et al. 2003*

$$S = \frac{[a_A(A^{y+})]^x\ [a_B(B^{x-})]^y}{K_{sp}}$$

$A^{z+} + Bz^- \rightarrow AB$

$$-\log a_A = Cy^2\ [I^{1/2}/(1+I^{1/2}) - 0.3I]$$

$$\Delta G = -\frac{R_g T}{\upsilon} \ln\frac{IP}{K_s^0} = -\frac{R_g T}{\upsilon} \ln S$$

$$-\log a_B = Cx^2\ [I^{1/2}/(1+I^{1/2}) - 0.3I]$$

$$I = 0.5\sum_i m_i z_i$$

Thermodynamics determine the direction of the reaction
Kinetics determine the rate and order of the reaction

# Kinetics of CPC's

The setting reaction of CPC's consists of three stages:

- Dissolution of reactants to saturate the mixing liquid with calcium and phosphate ions
- Nucleation of crystals
- Growth of crystals


SEM images of cement at various periods of reaction: (a) after 15 min; (b) after 1 hr; (c) after 64 hrs; (d) after 360 hrs. From Fernandez et al. 1997

# Bioactive glass

The composition of Bioglass is a series of special designed glasses, consisting of a $Na_2O$-CaO-$SiO_2$ glass with the addition of $P_2O_5$, $B_2O_3$ and $CaF_2$

*Table 1.3* Composition of bioactive glasses and glass-ceramics (wt%) (Gross *et al.*, 1993; Hench and Andersson, 1993; Holand and Vogel, 1993)

| | 45S5 Bioglass | 52S4.6 Bioglass | 55S4.3 Bioglass | 58S Sol–gel glass | A-W GC | KG Cera GC | Kgy 213 GC | Bioverit GC |
|---|---|---|---|---|---|---|---|---|
| $SiO_2$ | 45 | 52 | 55 | 60 | 34.2 | 46.2 | 38 | 29.5–50 |
| $P_2O_5$ | 6 | 6 | 6 | 4 | 16.3 | | | 8–18 |
| CaO | 24.5 | 21 | 19.5 | 36 | 44.9 | 20.2 | 31 | 13–28 |
| $CaF_2$ | | | | | 0.5 | | | 2.5–7 |
| $Ca(PO_3)_2$ | | | | | | 25.5 | 13.5 | |
| MgO | | | | | 4.6 | 2.9 | | 6–28 |
| $Na_2O$ | 24.5 | 21 | 19.5 | | | 4.8 | 4 | 3–5 |
| $K_2O$ | | | | | | 0.4 | | 3–5 |
| $Al_2O_3$ | | | | | | | 7 | 0–19.5 |
| $Ta_2O_5$ | | | | | | | 5.5 | |
| $TiO_2$ | | | | | | | 1 | |

Three key compositional features distinguish them from traditional soda-lime-silica glasses:

(a) less than 60% of $SiO_2$,

(b) high $Na_2O$ and CaO content,

(c) high CaO:$P_2O_5$ ratio

These compositional features make the surface highly reactive when exposed to an aqueous medium and therefore lead to in vitro and in vivo bioactivity

The structure of Bioglass is regarded as a three-dimensional $SiO_2$ network, modified by incorporation of other oxides

A number of bioactive glasses have been developed and investigated for tissue engineering and probably the best known of these is Bioglass

The first bioactive glass (45S5 Bioglass, 46.1% SiO2, 24.4% NaO, 26.9% CaO and 2.6% P2O5, in mol%) was the first material seen to form an interfacial bond with host tissue after implantation
The strength of the interfacial bond between Bioglass and cortical bone was equal to or greater than the strength of the host bone. It can bond to soft tissue as well as bone

The advantages of bioactive glasses are the speed of their surface reactivity and the ability to alter the chemical composition, thus enabling bonding with a variety of tissues. A disadvantage is their mechanical properties, as these materials have relatively low bending strength and Young's modulus.

Sol-gel-derived bioactive glasses have a porous texture in the nanometer range, giving them a surface area of 150-600$m^2$/g, which is two orders of magnitude higher than that of melt-derived glasses. Dissolution is therefore more rapid for sol-gel glasses of similar composition, and more silanol groups are on the sol-gel glass surfaces to act as nucleation sites for the formation of the apatite layer

Bioactive glasses have been found to bond more rapidly to bone than HA, and to be osteoinductive, i.e. they stimulate new bone growth on the implant away from the bone/implant interface.

HA is classified as osteoconductive, i.e. it encourages bone to grow along the implant from the bone/implant interface

The reasons for bioactive glasses being a Class A bioactive and osteoinductive material and HA being a Class B osteoconductive material have been linked to the rate of formation of the HCA surface layer, allowing bone bonding to occur more rapidly.

The rate of bone bonding to implant and the strength and stability of the bond vary with the composition and microstructure of the bioactive materials:
Bioactive glasses with 42-53% $SiO_2$ form a bond to bone very rapidly, within days, and also form an adherent bond with soft tissues
Bioactive glasses with 54-60% of $SiO_2$ require 2-4 weeks to bond with bone, but do not bond with soft tissues
Bioactive glasses with more than 60% of $SiO_2$ do not have the ability to bond to any living tissue
However, using the sol-gel process, the compositional range of bioactivity was extended to 100% $SiO_2$

The mechanism for osteoinduction is more complicated than the mechanism of osteoconduction

It is vital to understand the biological response to bioactive materials, i.e. what signals do the osteogenic cells such as osteoblasts receive from the material?

As Bioglass degrades it releases silica, calcium, sodium and phosphate species into solution. It is thought that the combination of some of these ions triggers the cells to produce new bone, especially critical concentrations of soluble silicon and calcium ions

Molecular biology studies have shown that seven families of genes involved in osteogenesis have been stimulated by bioactive glass dissolution products, The effect has been seen to be concentration dependent, with approximately 17-20 ppm of soluble Si and 88-100 ppm of soluble Ca ions required. Sodium ions are not thought to be beneficial to cells, and the phosphate content of the glass is not thought to affect gene expression, although it may be needed in the body fluid for the extracellular matrix to mineralize

Enhanced differentiation of osteoblastic cell lines were reported when exposed to soluble silica (orthosilicic acid) and the collagen extracellular matrix production increased in all cells treated with orthosilicic acid

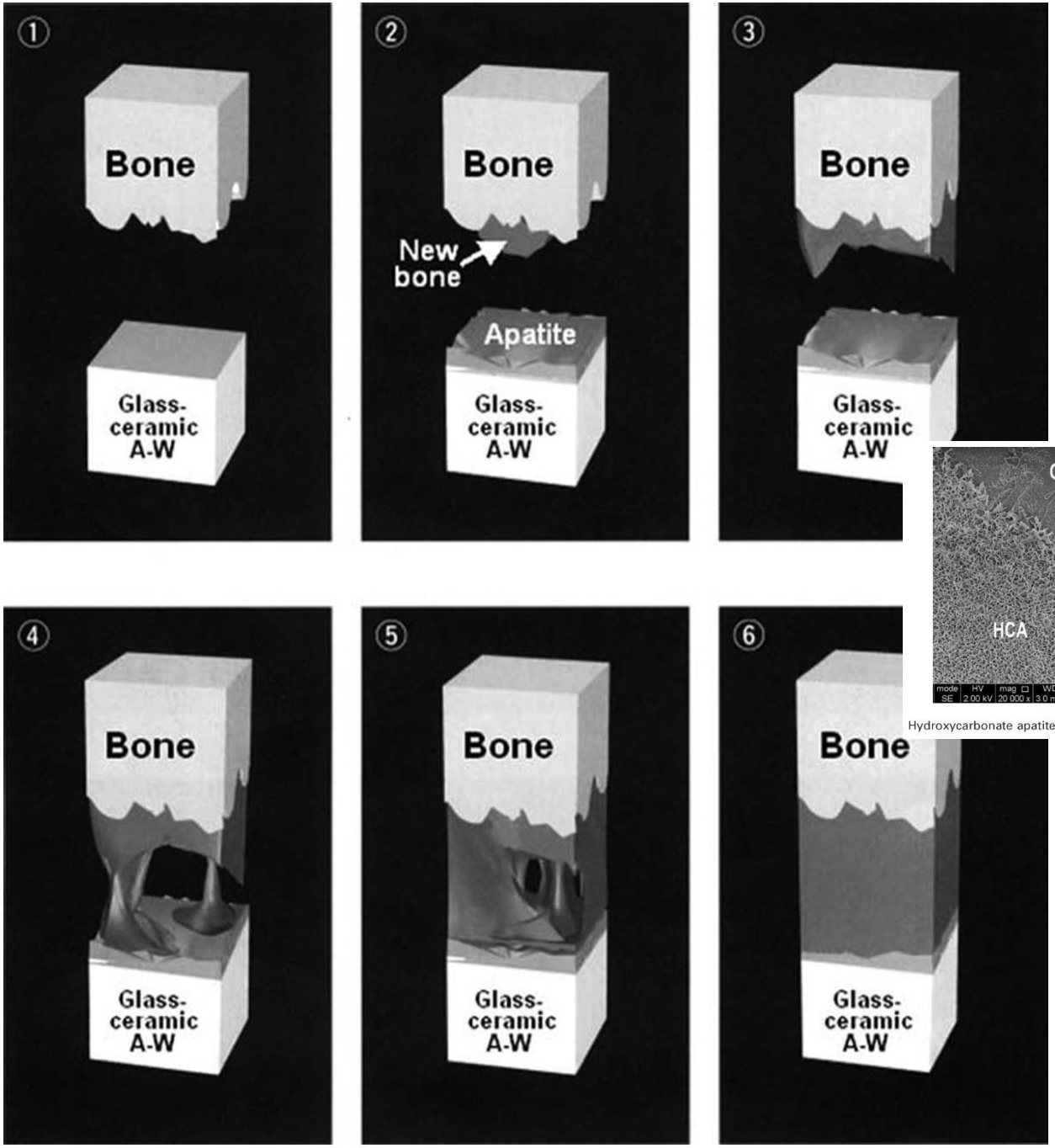
The invention of Bioglass encouraged the design of new glass and glass-ceramic compositions, of which Ceravital-type glass-(ceramic) was one. One of the advantages of Ceravital glass is that the solubility of the material can be adjusted by the addition of metal oxides, but with negative influence on the cellular function and the development and maturation of the extracellular matrix

A-W development was the most important modification of bioactive glasses
Composition modification and higher processing temperatures lead to a very fine-grained glass-ceramic composed of very small apatite (A) and wollastonite ($CaSiO_3$) crystals bonded by a bioactive glass interface

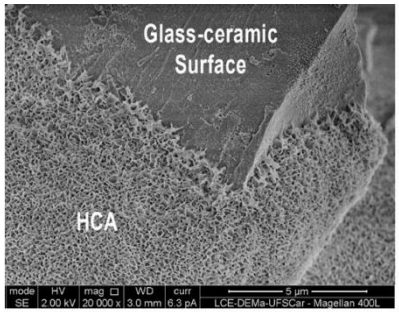
The bending strength, fracture toughness and Young's modulus of A-W glass-ceramic are the highest among bioactive glasses and glass-ceramics, enabling it to be used in some compression load-bearing applications, such as vertebral prostheses and iliac crest replacement

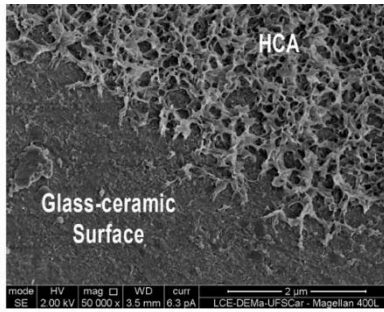
**TABLE I. Crystalline phases, bending strength and fracture toughness of parent glass, apatite GC, apatite-wollastonite GC and human cortical bone.[5]**

| Samples | Phases (wt %) | Bending strength (MPa) | Fracture toughness ($MPa \cdot m^{1/2}$) |
|---|---|---|---|
| Parent glass | 100% glass | 70 | 0.8 |
| Apatite GC | 38% apatite + 62% glass | 90 | 1.2 |
| Apatite-wollastonite GC | 38% apatite + 34% wollastonite + 28% glass | 220 | 2.0 |
| Human bone | Mainly apatite and collagen | 160 | 2–12 |




Bone bonded to A/W-GC implants with high interfacial bond strengths. The bioactivity of this glass-ceramic was attributed to apatite formation on its surface in the body, brought about by the dissolution of calcium and silicate ions from the glass-ceramic




Hydroxycarbonate apatite (HCA) formation on the GC surface after 24 h exposure to simulated body fluid (SBF).[11]

The AW-GC material was approved for orthopaedic applications in Japan with particular success in vertebral replacement and spinal repair It showed bioactivity and a high compressive strength (80 MPa).

: 5. Bone-bonding mechanism for A-W GC: (1) just after implantation; (2) formation of bonelike apatite; (3) growth of new bone; (4) bond-
ıew bone with apatite layer; (5) and (6) increase in density of new bone.[5]

The machinable bioactive Bioverit glass-ceramics have been successfully applied in the middle ear, nose and jaw and in the general region of the head and neck or as thoracic vertebra substitutes

The presence of the mica phase in the glass ceramic enables it to be machined, with standard metal working tools by the surgeon, if necessary during an operation

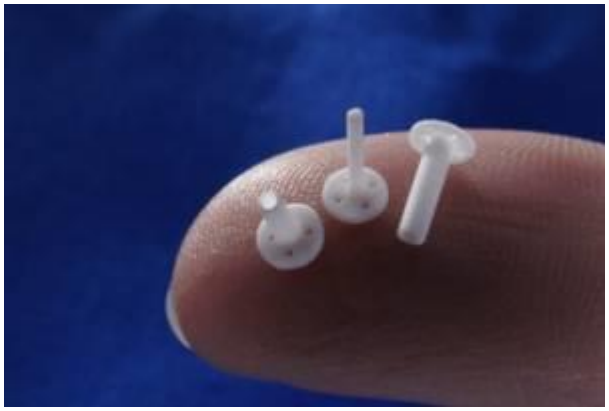
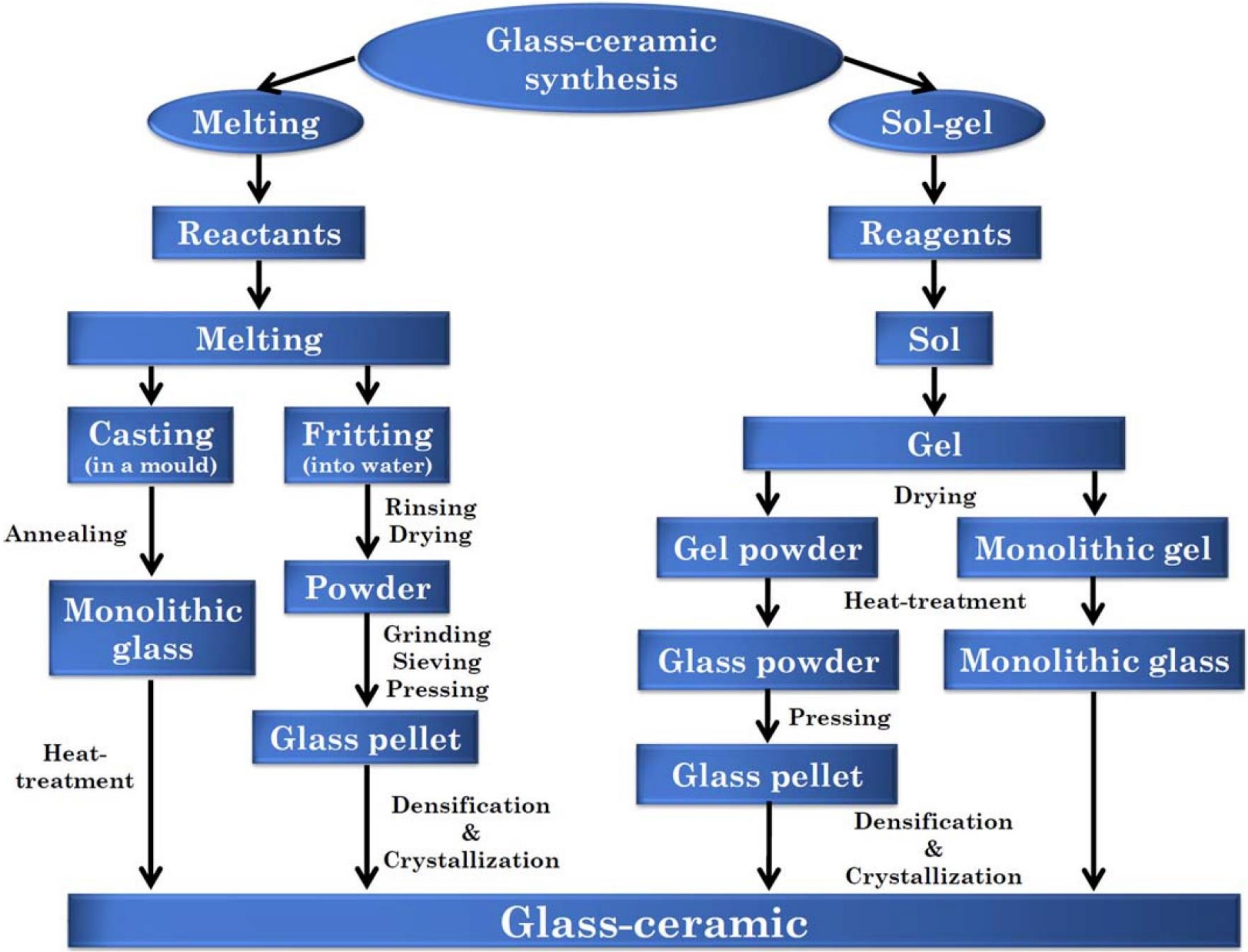


**TABLE II. Bioverit® I and II (mica and mica-apatite GCs) compositions.[3]**

| | Bioverit® I | Bioverit® II |
|---|---|---|
| $SiO_2$ | 29.5–50 | 43–50 |
| MgO | 6–28 | 11–15 |
| CaO | 13–28 | 0.1–3 |
| $Na_2O/K_2O$ | 5.5–9.5 | 7–10.5 |
| $Al_2O_3$ | 0–19.5 | 26–30 |
| F | 2.5–7 | 3.3–4.8 |
| $P_2O_5$ | 8–18 | 0.1–5 |
| $TiO_2$ | some | – |

**TABLE III. Mechanical properties of Bioverit® I and II.[3]**

| Properties | Bioverit® I | Bioverit® II |
|---|---|---|
| Density ($g/cm^3$) | 2.8 | 2.5 |
| Bending strength (MPa) | 140–180 | 90–140 |
| Compressive strength (MPa) | 500 | 450 |
| Young's modulus (GPa) | 70–88 | 70 |
| Hardness Vickers (GPa) | 5 | ~8 |
| Fracture toughness ($MPa \cdot m^{1/2}$) | 1.2–2.1 | 1.2–1.8 |


Glass-ceramic synthesis
Melting
Reactants
Melting
Casting (in a mould)
Fritting (into water)
Annealing
Rinsing Drying
Monolithic glass
Powder
Grinding Sieving Pressing
Heat-treatment
Glass pellet
Densification & Crystallization
Sol-gel
Reagents
Sol
Gel
Drying
Gel powder
Monolithic gel
Heat-treatment
Glass powder
Monolithic glass
Pressing
Glass pellet
Densification & Crystallization
Glass-ceramic

Many attempts have been made to improve the poor fracture toughness of bioactive glasses and ceramics, such as stainless steel fibre or titanium fibre-reinforced Bioglass composites and hydroxyapatite particles reinforced polymer composites

Despite all these developments, bioactive glass clinical products in use remain few, especially when compared with the less bioactive synthetic HA.

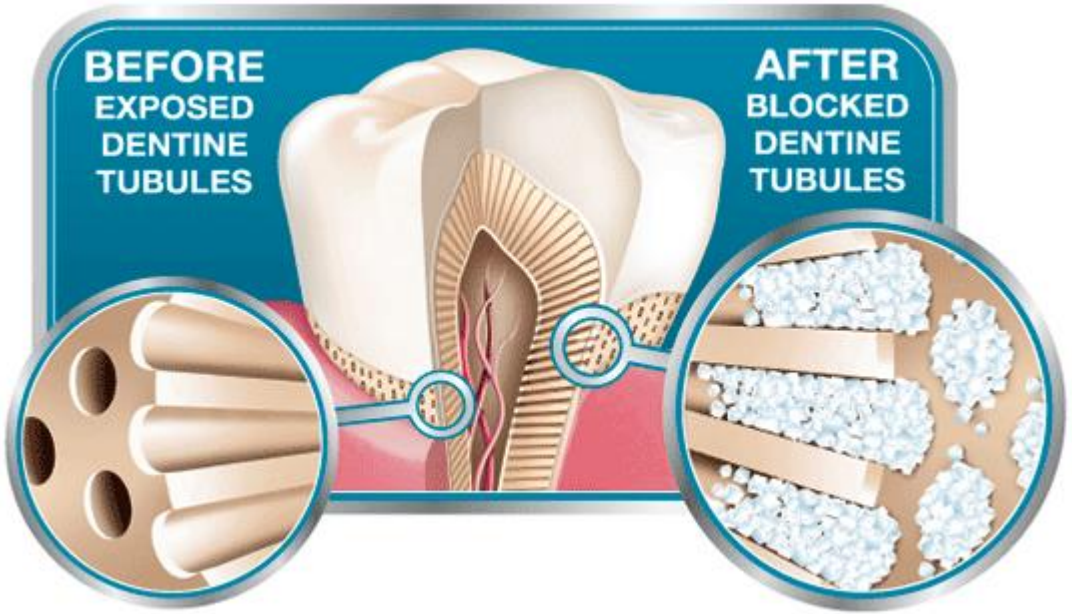
The first Bioglass device was approved in the USA in 1985 and was used to treat conductive hearing loss by replacing the bones of the middle ear. Its advantage over other devices in use at the time was its ability to bond with soft tissue (tympanic membrane) as well as bone tissue.

The first particulate material cleared for sale in the USA was PerioGlas, which was approved by FDA in December, 1993 and produced by USBiomaterials, Alachua, Florida.

PerioGlas has demonstrated excellent clinical results with virtually no adverse reactions to the product and is sold in over 35 countries. Bioactive glass particles have also been shown to undergo continual dissolution after the formation of the HCA layer to such an extent that a hollow shell of HCA remained, in which new bone formed

A Bioglass particulate for orthopaedic bone grafting was introduced into the European market in 1999, under the trade name NovaBone

Bioglass particulate is also used for the treatment of dentinal hyper-sensitivity
The Bioglass material used in this application is a very fine particulate that is incorporated into toothpaste, or used with an aqueous vehicle and applied to the tooth surface around exposed root dentin. When Bioglass particles are put in contact with dentin, they adhere to the surface, rapidly form an HCA layer and occlude exposed tubules, thereby relieving pain.


Novathera Ltd, Cambridge, UK, have developed a wound healing gel that incorporates particles of the 70S30C gel-glass composition, which is modified by 2 mol% of silver ions, termed Theraglass. Low concentrations of silver ions have been found to be bactericidal without killing useful cells