Bioglasses and Bioglass-ceramics

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Summer School

Ceramic & Glass Science & Technology

Application to Bioceramics & Bioglasses

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Overview

- Bioactive Glasses
- Structure
- Compositional Effects
- Bioactivity
- Clinical Applications
- Bioactive Glass-ceramics

Types of Ceramic / Glass - Bone Attachment

1. Dense, inert, non-porous ceramics attach by bone growth (or tissue growth) into surface contours:

   termed "morphological fixation"

2. Porous inert ceramics attach by bone in-growth (into pores) resulting in mechanical attachment of bone to material:

   termed "biological fixation"

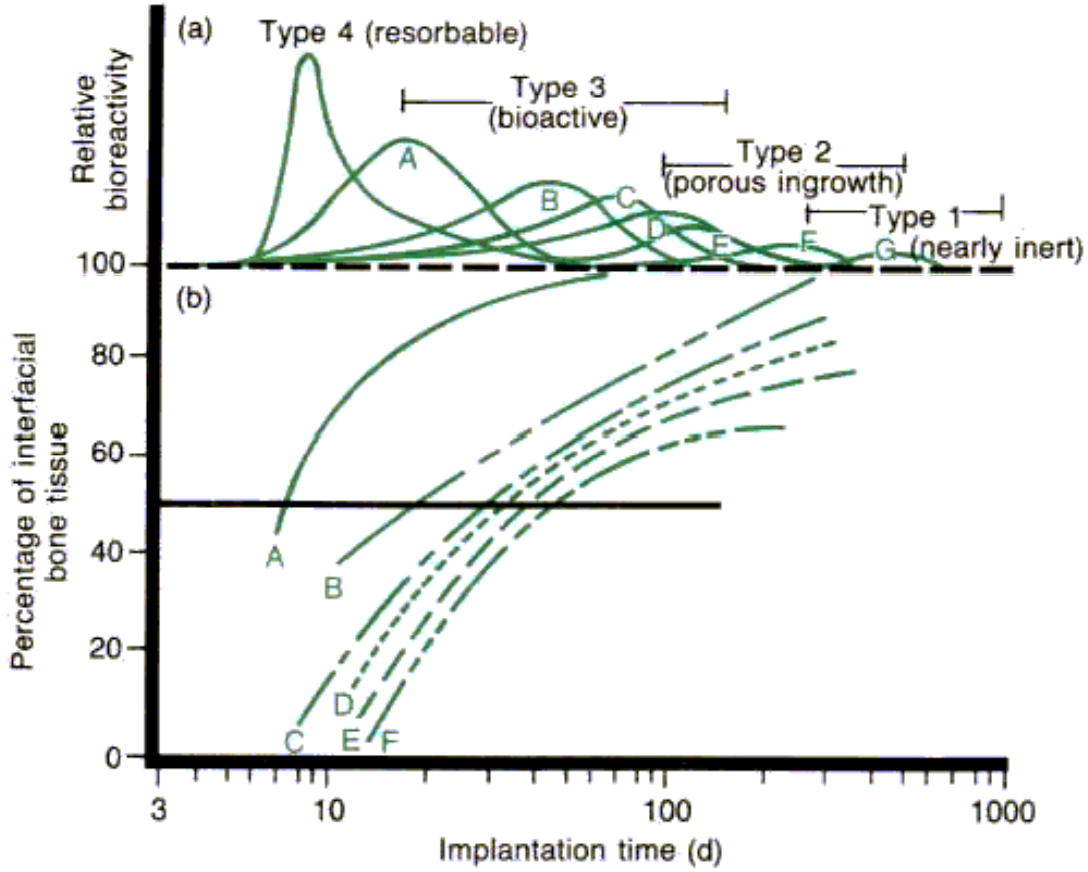
3. Dense, surface-reactive ceramics or glasses attach directly by chemical bonding with bone:

   termed "bioactive fixation"

   → **Bioactive glasses, ceramics and glass-ceramics**

4. Non-porous (or porous) *resorbable* ceramics or glasses are resorbed and replaced by new bone growth

Bioactivity spectrum for various types of ceramic / glass implants



(a) Relative rate of bioreactivity, (b) Time dependence of formation of bone bonding at an implant interface.

Requirements for Skeletal Repair

- biocompatible material
- implant must be incorporated into bone
- direct contact required
- osteointegration and osteogenesis

→ First bioactive material: Bioglass®

BIOGLASS 45S5

= Ca:P

Hench (1969)

Professor Larry Hench, holding Bioglass® samples

	wt. %	mol. %
SiO_2	45.0	46.1
CaO	24.5	26.9
Na_2O	24.5	24.3
P_2O_5	6.0	2.6

- first bioactive glass composition
- contains much less SiO_2 than normal soda-lime-silica glasses
- contains small amount of P_2O_5
- very high Ca:P ratio = 5

cf. hydroxyapatite = 1.67

$Ca_5(PO_4)_3(OH)$

REQUIREMENTS - BIOACTIVE GLASSES

- has composition such that it undergoes surface dissolution in physiological environments
- elicits a desirable response
- HA layer deposited on surface
- bonds directly to bone
- no interfacial scar tissue
- can alter rate of dissolution and level of bioactivity by varying composition
- most compositions contain SiO_2, CaO, Na_2O and P_2O_5 although others known to be bioactive

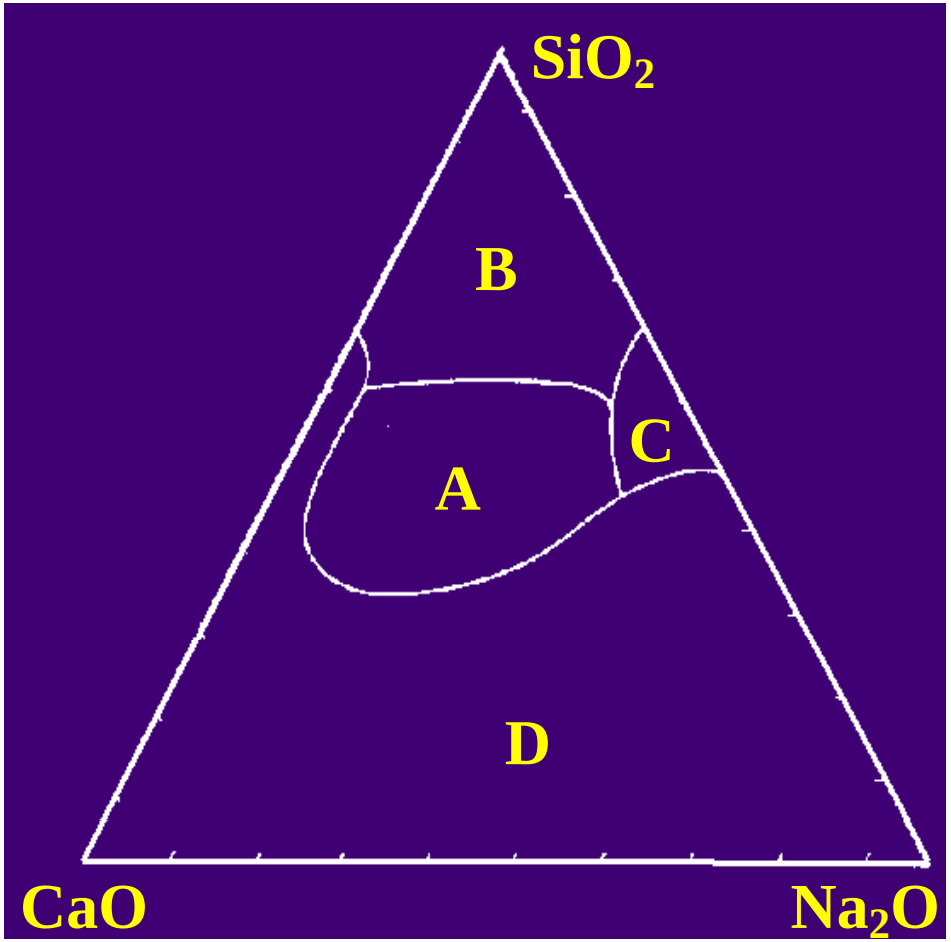
BIOACTIVE "BONE-BONDING" GLASSES

Region A – "bioactive bone-bonding boundary". A bioactive glass is one that elicits a specific biological response at the interface of the material which results in the formation of a bond between the tissue / bone and the glass.

Region B – high SiO_2 glasses [window or bottle glass] behave as Type 1 nearly inert materials and elicit a fibrous capsule at the implant-tissue interface.

Region C – glasses are resorbable and disappear within 10 to 30 days of implantation as new bone growth occurs.

Region D – glasses not technically practical and so have not been tested as implants.



+ 6 wt.% P_2O_5

BIOGLASSES AND BIOGLASS-CERAMICS

Bioglass 45S5 (1969)

When first discovered and implanted, the glasses

- did not form interfacial scar tissue isolating them from host femoral bone
- could not be removed from their implant site after a certain time.

• Now known that Bioglass 45S5 bonds with bone rapidly and also stimulates bone growth away from the bone–implant interface.

Mechanism for bone bonding is attributed to a hydroxycarbonate apatite (HCA) layer on the surface of the glass, following initial glass dissolution. HCA is similar to bone mineral hydroxyapatite and is thought to interact with collagen fibrils to integrate (bond) with the host bone.

The osteogenic properties (often termed osteoinduction) of the glass are thought to be due to the dissolution products of the glass, i.e. soluble silica and calcium ions, that stimulate osteogenic cells to produce bone matrix.

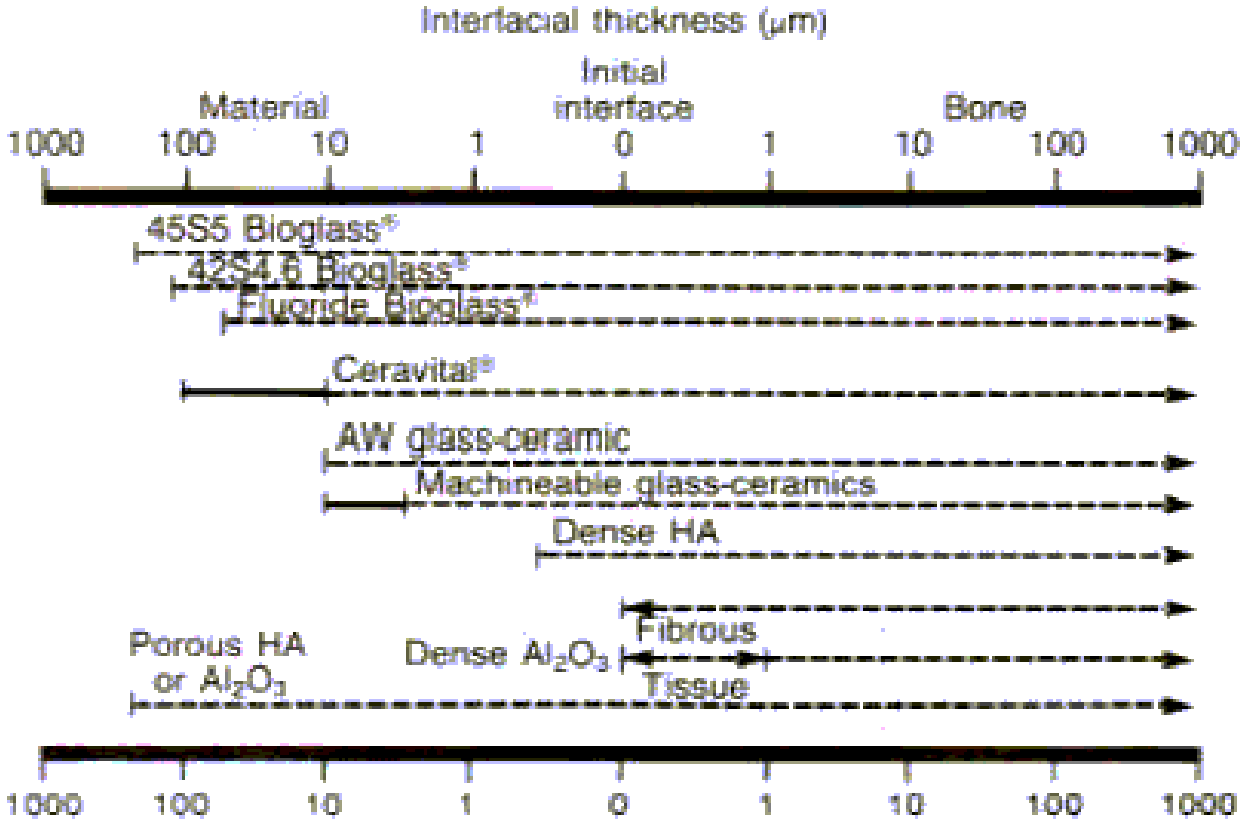
• No other bioactive glass composition has been found to have better biological properties than the original Bioglass 45S5 composition!

BIOGLASSES AND BIOGLASS-CERAMICS

Concept now expanded to include a large number of bioactive materials with a wide range of rates of bonding and thickness of interfacial bonding layers:

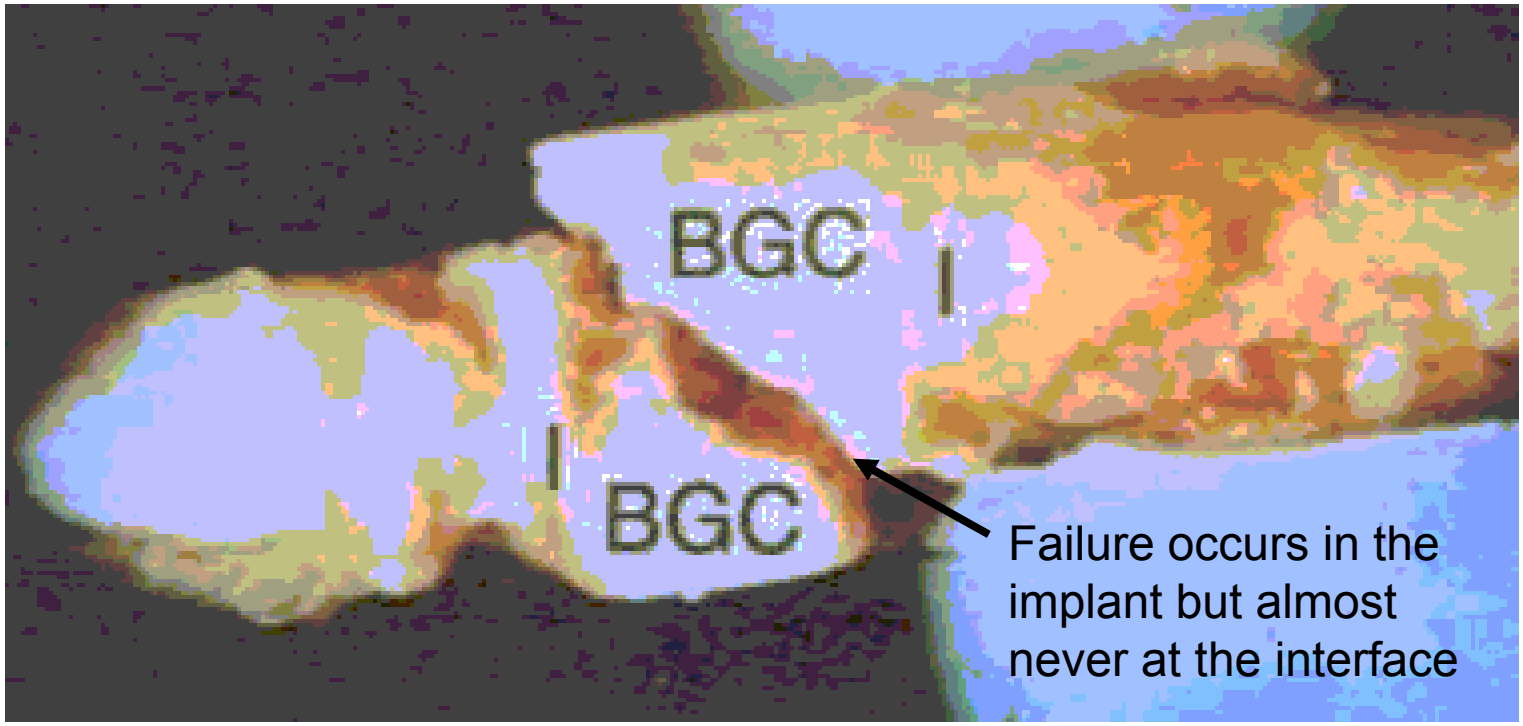
- bioactive glasses such as Bioglass® and related glasses; phosphate-based glasses; and borate-based glasses
- bioactive glass-ceramics such as Ceravital®
- Apatite/Wollastonite (A/W) glass ceramic, or machineable glass-ceramics
- dense hydroxylapatite such as Durapatite® or Calcitite®
- bioactive composites such as
  polyethylene-Bioglass®,
  polysulfone-Bioglass®
  polyethylene-hydroxylapatite (Hapex®) mixtures.

All bioactive materials form an interfacial bond with bone. However, the time dependence of bonding, the strength of bond, the mechanism of bonding and the thickness of the bonding zone differ for the various materials.



Comparison of interfacial thickness of reaction layer of bioactive implants or fibrous tissue of inactive bioceramics in bone.

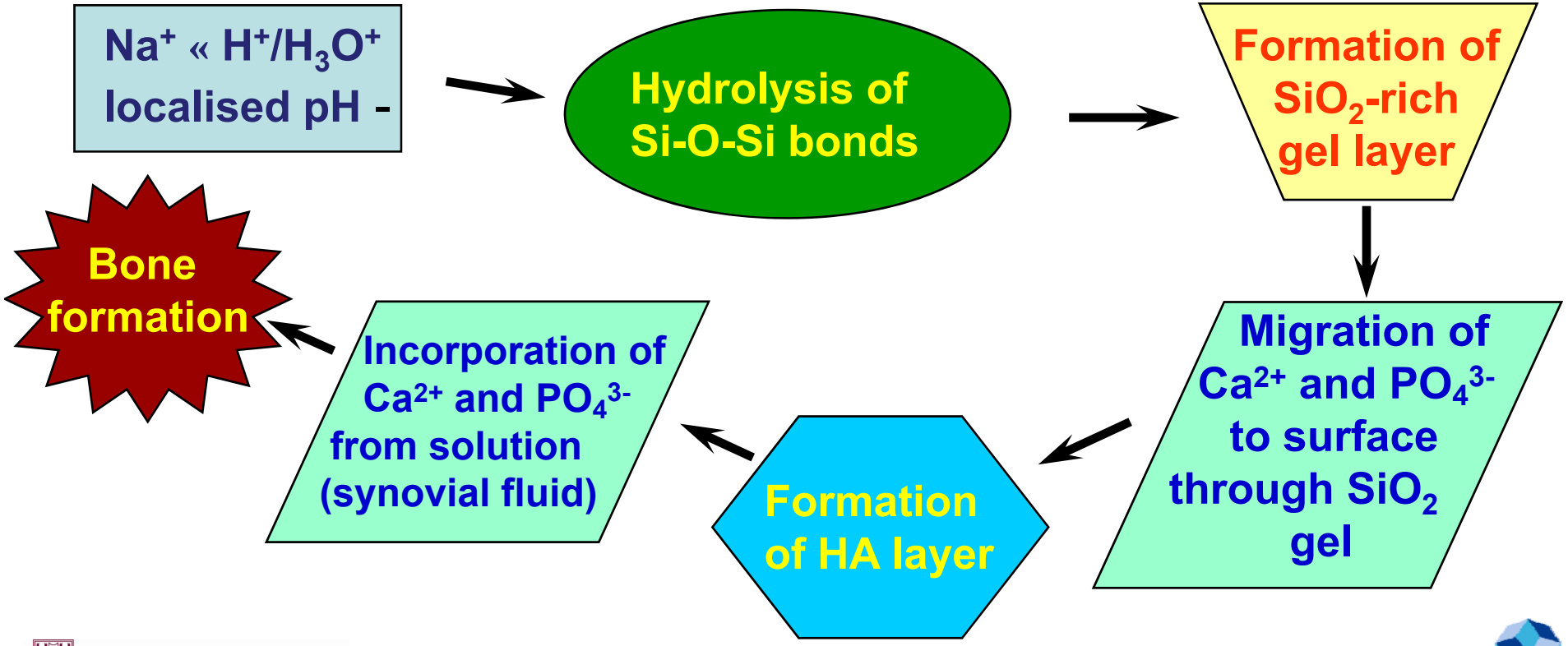
BIOGLASSES AND BIOGLASS-CERAMICS



Bioactive glasses and glass-ceramics develop an adherent interface with tissues that resists substantial mechanical forces. In many cases the interfacial strength of adhesion is equivalent or greater than the cohesive strength of the implant material or the tissue bonded to the bioactive implant. Figure shows fracture of 45S5 Bioglass-ceramic (BGC) segmental bone replacement in monkey due to impact torsional loading. Note bonded interface (I). (Photo: G. Piotrowski)

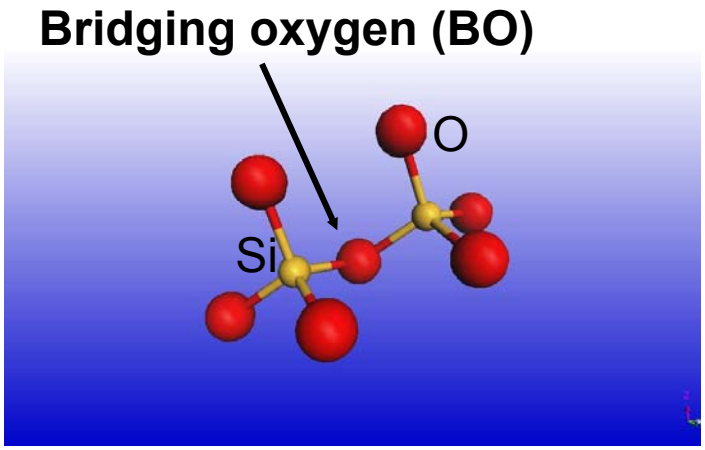
BIOACTIVITY

- Time dependent kinetic modification of the glass surface confers bioactivity (tissue / bone bonding)
- On implantation, surface of the glass is leached of cations resulting in the formation of a silica gel layer.

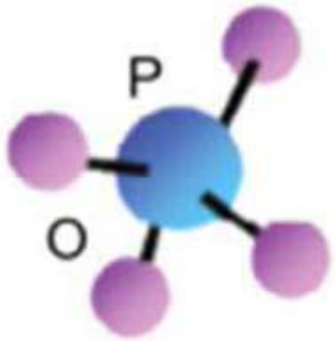


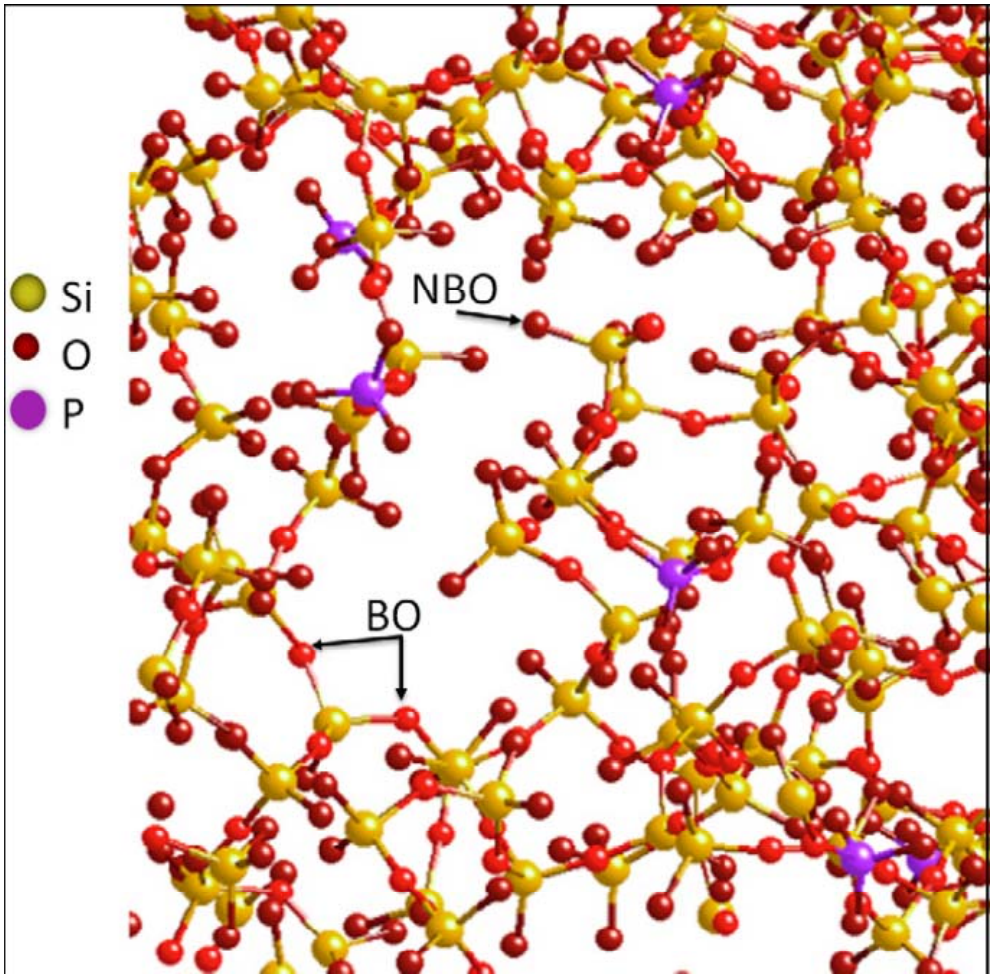
How does structure of Bioglass affect bioactivity?

$[SiO_4]$ units in silicates



$[PO_4]$ ortho-phosphate unit in glass with no BO





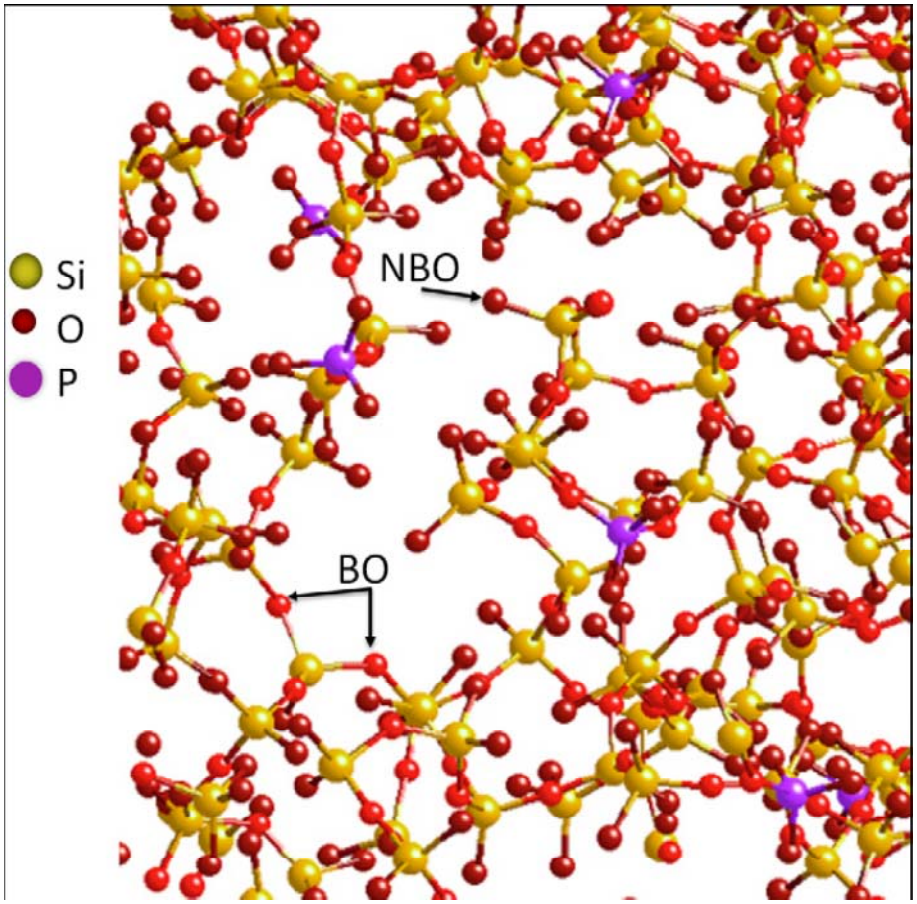
Structure of Bioglass

Bioglass consists of silica tetrahedra connected by

–Si–O–Si– bridging oxygen (BO) bonds described by Q^n notation

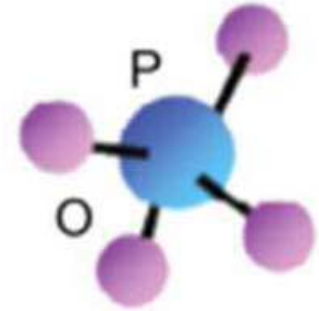
n is the number of bridging oxygen bonds

- NMR shows Bioglass 45S5 primarily consists of 69% chains and rings of Q^2, with 31% of Q^3 units providing some cross-linking of chains.
- Na and Ca are network modifiers that disrupt the network by forming non-bridging oxygens (NBOs).

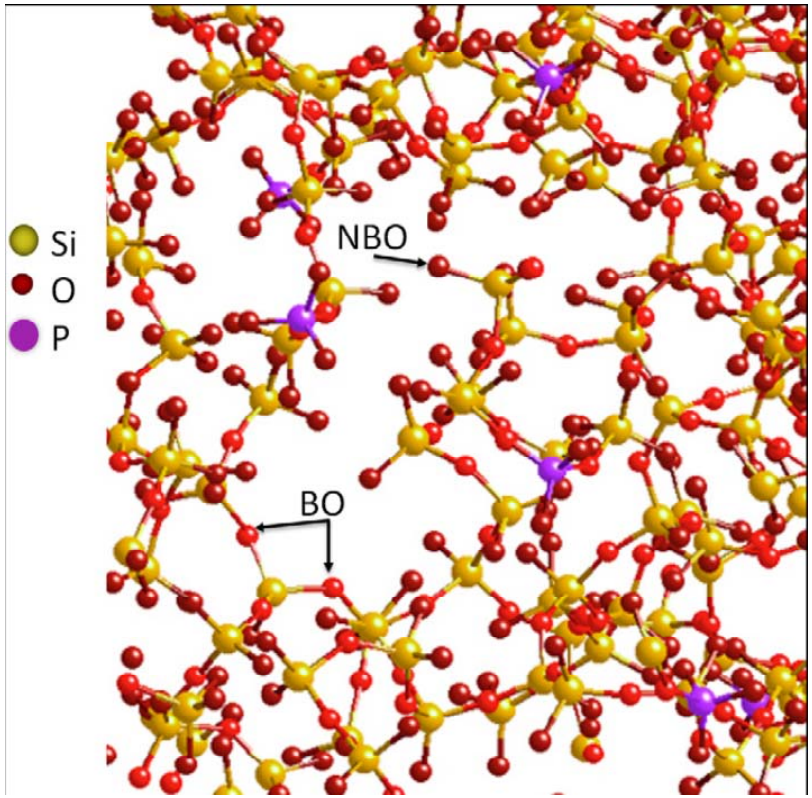


Structure of Bioglass

- NMR shows P is present as an orthophosphate unit (Q^0)



- Charge balance is by Na^+ and/or Ca^{2+} without any P–O–Si bonds.
- Phosphorus is therefore isolated from the silica network and removes Na^+ and Ca^{2+} cations from their network-modifying role.
- This explains why phosphate is rapidly lost from the glass on exposure to aqueous environments



Structure of Bioglass

- Network Connectivity (NC) of Glass is defined as number of bridging oxygens (BO) per tetrahedron (T)

$$NC = BO/T = 4 - NBO/T$$

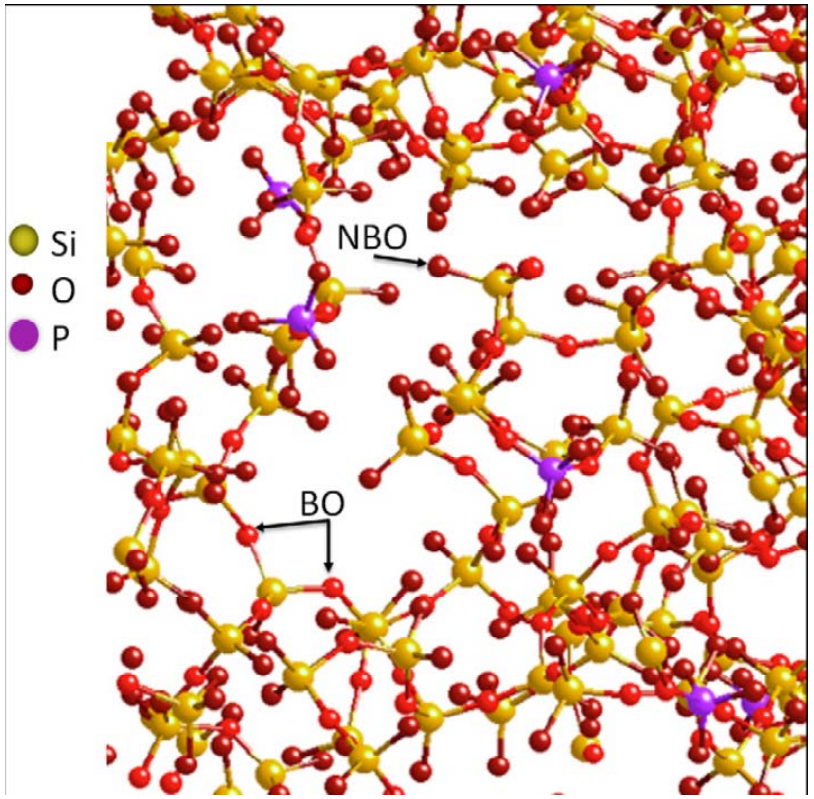
- For a silicate glass, each NBO must be associated with either 1 Na^+ ion or 2 NBOs must be associated with each Ca^{2+} ion

$NC = 4 - (v_{Na}(N_{Na}) + v_{Ca}(N_{Ca}))/(N_{Si}+N_P)$

N_X is the no. of ions of type X = Na, Ca, P or Si in the glass formulation and v_X is the valency of the cation X. Assuming P is a glass former, then:

NC = 4 – [(1 x 2 x 24.5 + 2 x 24.5) / 45 + 5.2] = 2.05; Therefore, theoretically:

>90% chains and rings of Q^2, <10% of Q^3 units



Bioactivty Assessment of Glasses in SBF

A simulated body fluid (SBF) was proposed as a useful solution for evaluating the bone-bonding ability of a material *in vitro,* and has been registered as an ISO 23317 standard (Kokubo and Takadama, 2006)

Glasses embedded in epoxy resin - surfaces polished

Immersed in Simulated Body Fluid (SBF) – Composition (g):

NaCl	$NaHCO_3$	KCl	$K_2HPO_4.3H_2O$	$MgCl_2.6H_2O$	$CaCl_2.2H_2O$	Na_2SO_4	+ H_2O
7.996	0.350	0.224	0.228	0.305	0.278	0.071	750mL

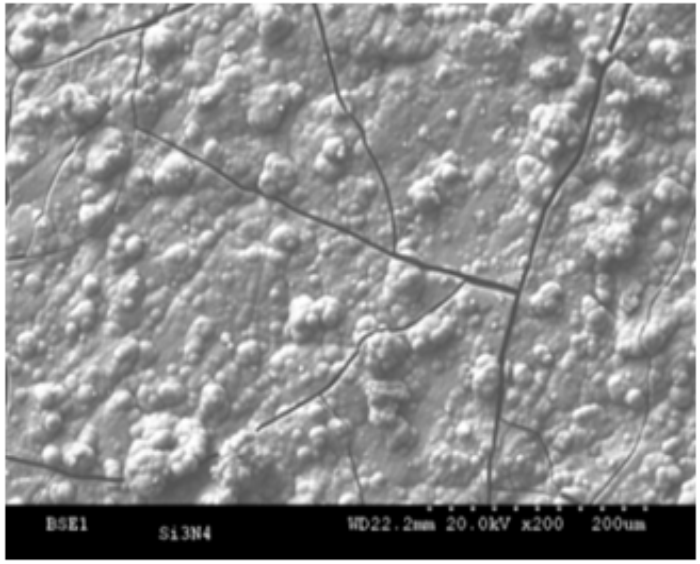
pH adjusted to 7.42 with 50mM tris(hydroxymethyl)aminomethane + 45 mM HCl

Held in a thermostatic bath at 37±0.5°C

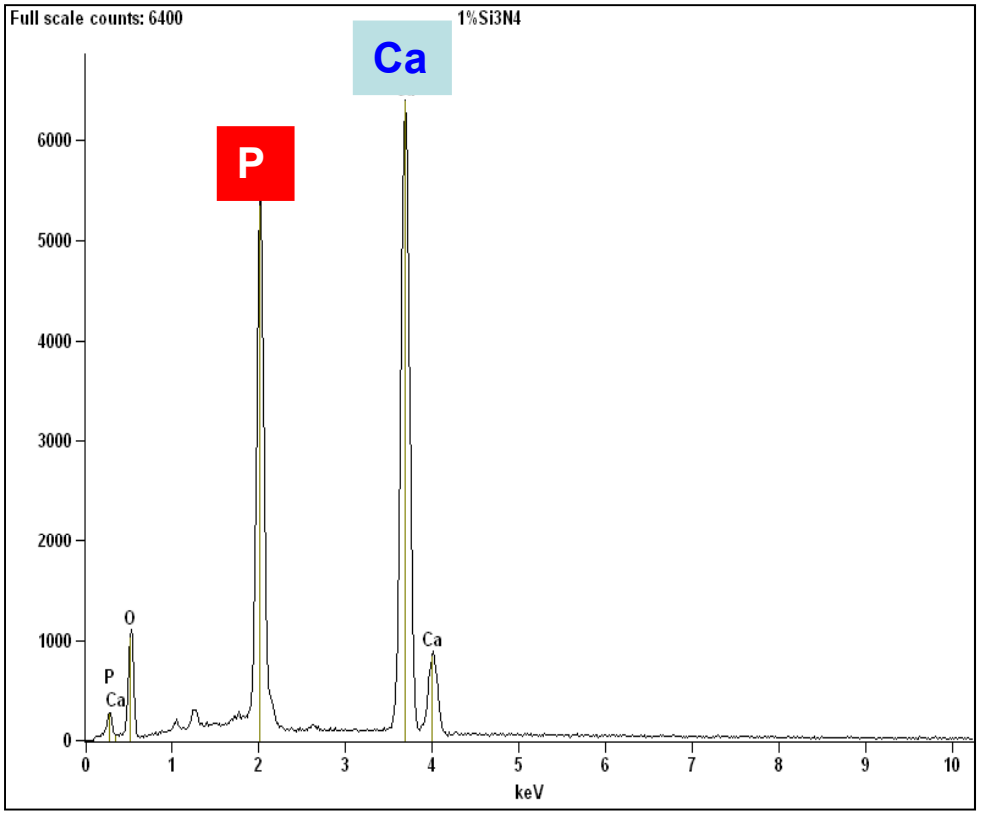
Glasses removed after X days, gently rinsed in ion exchanged water and stored in a vacuum dessicator

Analysed using grazing incidence X-ray powder diffraction and SEM combined with energy dispersive X-ray spectroscopy (EDS)

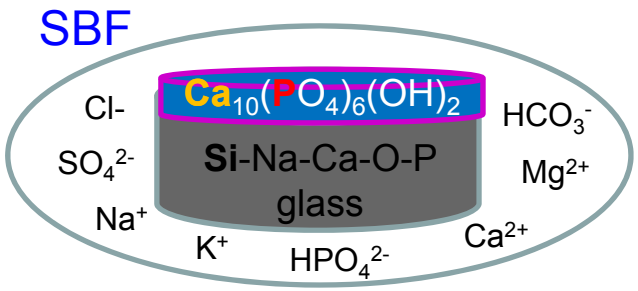
Bioactivty Assesment of Glasses in SBF



SEM : Surface of glass after immersion in SBF for 15 days



EDS spectrum



Apatite formation: $Ca_{10}(PO_4)_6(OH)_2$

MECHANISMS OF BIOACTIVITY

Depends on glass composition

The most widely supported mechanism is a five stage process:

- *Stage 1*

  Rapid exchange of cations with H^+ from solution occurs initially. The cations are leached out of the glass relatively easily as the cations are *network modifiers* and not part of the glass network. This process is diffusion dependent.

- $Si\text{-}O\text{-}Na^+ + H^+ + OH^- = Si\text{-}OH^+ + Na^+ + OH^-$ (aq.)

MECHANISMS OF BIOACTIVITY

The pH of the solution increases and a silica-rich (cation-depleted) region forms near the glass surface. Phosphate is also lost from the glass if present in the composition.

- ***Stage 2***

  Loss of soluble silica in the form of $Si(OH)_4$ to the solution resulting from breakage of Si-O-Si bonds by attack from $(OH)^-$ in high pH soln and formation of Si-OH (silanols) at the glass-solution interface. The dissolution of the network of the glass occurs in localised regions and releases silica into solution in the form of silicic acid. The rate of dissolution is very dependent on the concentration of non-bridging oxygens (NBOs) in the glass structure.

- $2(Si\text{-}O\text{-}Si) + (OH)^- + H^+ = Si\text{-}OH + OH\text{-}Si$

MECHANISMS OF BIOACTIVITY

- ***Stage 3***
- Condensation and repolymerisation then occurs of the hydrated silica on the surface depleted in alkalis and alkaline earth cations shown by NMR as an increase in the proportion of bridging oxygen bonds during leaching.
- $2(Si\text{-}OH) + 2(OH\text{-}Si) = Si\text{-}O\text{-}Si\text{-}O\text{-}Si\text{-}O\text{-}Si\text{-}O + 2H_2O$

- ***Stage 4***

  Migration of Ca^{2+} and PO_4^{3-} groups to the surface through the SiO_2 rich layer forming $CaO\text{-}P_2O_5$ rich film on top of the SiO_2 rich layer followed by growth of the amorphous $CaO\text{-}P_2O_5$ rich film by incorporation of soluble calcium and phosphate ions from solution.

MECHANISMS OF BIOACTIVITY

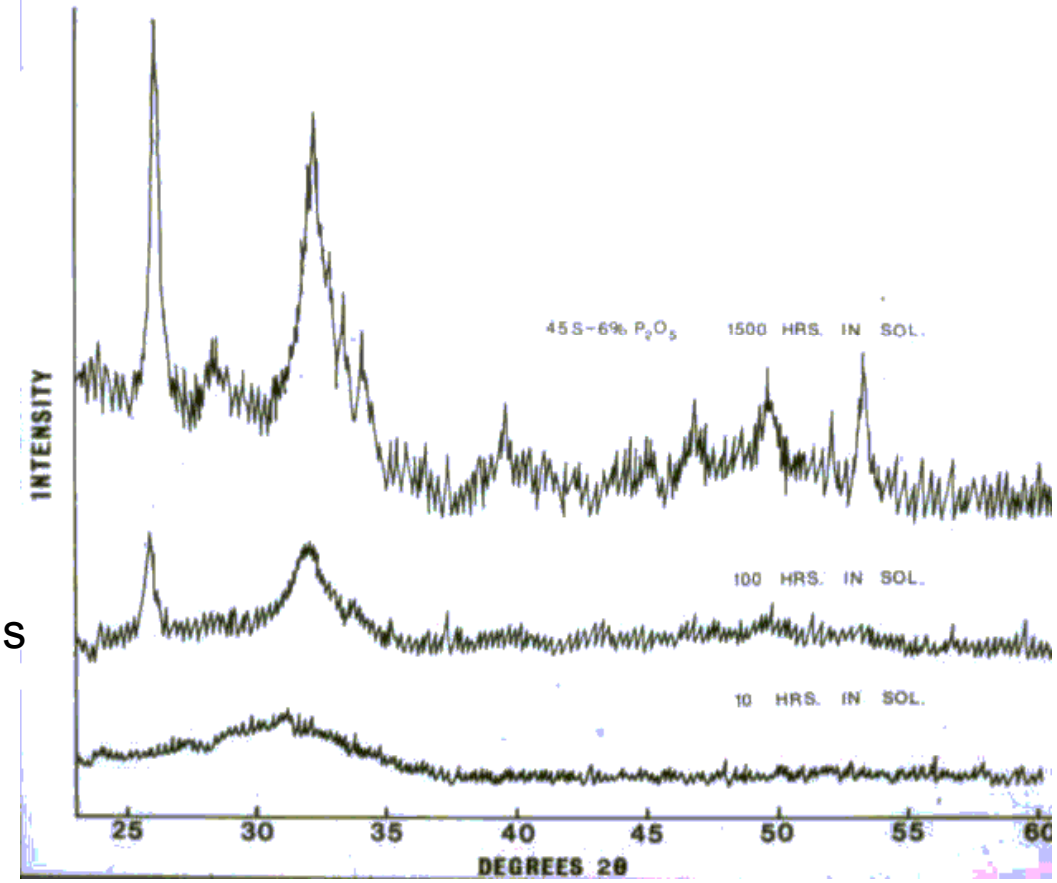
- ***Stage 5***
- Crystallization of the amorphous $CaO\text{-}P_2O_5$ film by incorporating OH^- and CO^{2-} or F^- ions from solution to form a mixed hydroxyl-carbonate apatite layer (HCA).
- Calcium phosphate was found to nucleate on the Si–OH groups, which have a negative charge in solution and the separation of the Si–OH groups is thought to dictate the orientation of the apatite crystals which grow with a preferred orientation in the 001 plane on Bioglass 45S5
- Further stages identified *in vivo*
- The bonding to tissue then occurs as biological moieties are adsorbed and biological action occurs.

MECHANISMS OF BIOACTIVITY

Fully crystallised HCA

Initial HCA crystals

amorphous



X-ray diffraction patterns of 45S5 Bioglass® after 10 hours, 100 hours and 1500 hours exposure to tris-buffer solution showing growth of XRD peaks associated with a biological hydroxycarbonate (HCA) layer on glass surface

MECHANISMS OF BIOACTIVITY

- Hench's mechanism may not always be useful for predicting reactivity of higher SiO_2 glasses
- Use network connectivity as a predictive measure of surface reactivity, solubility, bioactivity
- Lower network connectivity (< 2.5 – Hill, 1996)
  - high surface reactivity, high solubility
  - silicate structural units of low molecular mass
  - silicate structural units capable of dissolving and going into solution
  - depends also on proportion of Q^2 and Q^3 units in structure

GLASS AND GLASS-CERAMIC COMPOSITIONS

Component	45S5 Bioglass®	45S5.4F Bioglass®	45B15S5 Bioglass®	52S4.6 Bioglass®	55S4.3 Bioglass®	KGC Ceravital®	KGS Ceravital®	KGy213 Ceravital®	A/W glass-ceramic	MB glass-ceramic	S45P7
SiO_2	45	45	30	52	55	46.2	46	38	34.2	19–52	45
P_2O_5	6	6	6	6	6				16.3	4–24	7
CaO	24.5	14.7	24.5	21	19.5	20.2	33	31	44.9	9–3	22
$Ca(PO_3)_2$						25.5	16	13.5			
CaF_2		9.8							0.5		
MgO						2.9			4.6	5–15	
MgF_2											
Na_2O	24.5	24.5	24.5	21	19.5	4.8	5	4		3–5	24
K_2O						0.4				3–5	
Al_2O_3								7		12–33	
B_2O_3			15								2
Ta_2O_5/TiO_2								6.5			
Structure	Glass and glass-ceramic	Glass	Glass	Glass		Glass-ceramic	Glass-ceramic	Glass-ceramic	Glass-ceramic	Glass-ceramic	
Reference	14	14, 56	57, 58	44	44	5	5	5	36	32	54

- A/W glass-ceramic developed by Kokubo team at Kyoto University, Japan, has very high interfacial bond strength.
- MB glass-ceramic, containing phlogopite - $(Na,K)Mg_3[AlSi_3O_{10}]F_2$, a mica, and apatite crystals, bonds to bone even though Al_2O_3 is present in the composition.

However, the Al^{3+} ions are incorporated within the crystal phase and do not alter the surface reaction kinetics of the material. An advantage of these mica containing glass-ceramics, developed by the Friedrich Schiller University, Jena, Germany, is their easy machinability.

- Additional compositions of bioactive glasses with higher SiO_2 have been developed at Abo Akademi, Turku, Finland

SOL-GEL BASED GLASS COMPOSITIONS

Sol-gel based Bioglasses

Glasses can be made using the traditional melt-quenching route

and also:

a sol-gel chemistry-based synthesis route where a solution containing the compositional precursors undergoes polymer type reactions at room temperature to form a gel.

The gel is a wet inorganic network of covalently bonded silica, which can then be dried and heated to ~600^{o}C to form a glass.

Typical bioactive compositions are in the SiO_2-CaO-P_2O_5 ternary system:

- 58S (60 mol.% SiO_2, 36 mol.% CaO, 4 mol.% P_2O_5)
- 77S (80 mol.% SiO_2, 16 mol.% CaO, 4 mol.% P_2O_5)

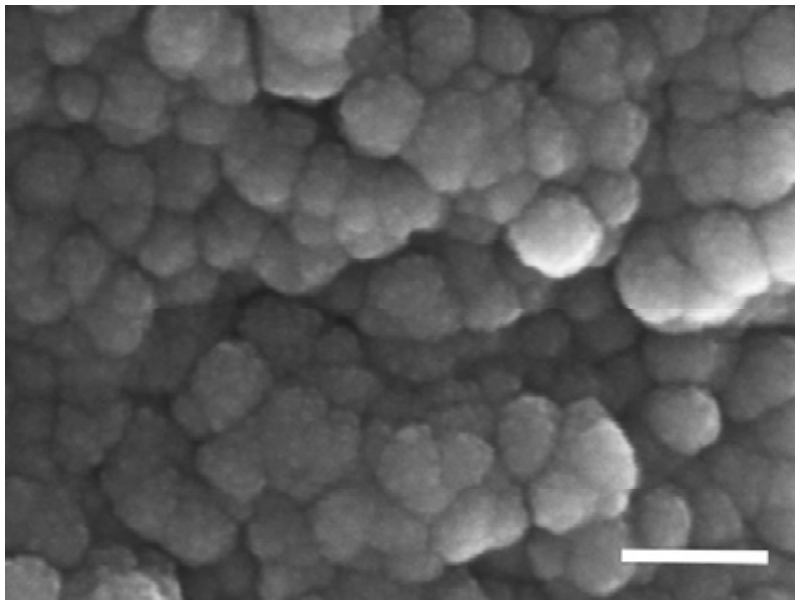
or the SiO_2-CaO binary system:

- 70S30C (70 mol.% SiO_2, 30 mol.% CaO)

SOL-GEL BASED GLASS COMPOSITIONS

The physical differences in melt- and sol-gel-derived glasses are that sol-gel glasses tend to have an inherent nano-porosity whereas melt-quenched glasses are dense.

The nanoporosity can result in improved cellular response due to the nanotopography and a specific surface area two orders of magnitude higher than for similar compositions of melt-derived glass.



100nm

Sol–gel compositions have fewer components than bioactive melt-quenched glasses. This is because the primary role of Na_2O in melt-quenched bioactive glass is to lower the melting point, improving processability. It also increases the solubility of the glass, which is important for bioactivity. The high surface area of sol-gel glasses results in high dissolution rates and, as there is no melting involved, Na is not required in the composition. Nonetheless, sol-gel glasses have been produced close to the 45S5 composition: 49.15 mol.% SiO_2, 25.80 mol.% CaO, 23.33 mol.% Na_2O, 1.72 mol.% P_2O_5, although the gels must not be heated above 600^{o}C if the glasses are to remain amorphous and avoid devitrification.

SOL-GEL BASED GLASS COMPOSITIONS

Regeneration and repair strategies currently use synthetic, temporary scaffolds to support and promote the healing of bone and dental tissue. Sol-gel based bioactive glasses are suitable candidates for this application.

Researchers from Imperial College London and the University of Manchester, UK and Nagoya Institute of Technology, Japan have designed inorganic sol-gel solutions that can be electrospun into a cotton-wool-like three-dimensional bioactive glass scaffold [G. Poologasundarampillai, *et al.,* *Acta Biomaterialia 2014; 10: 3733-3746.*

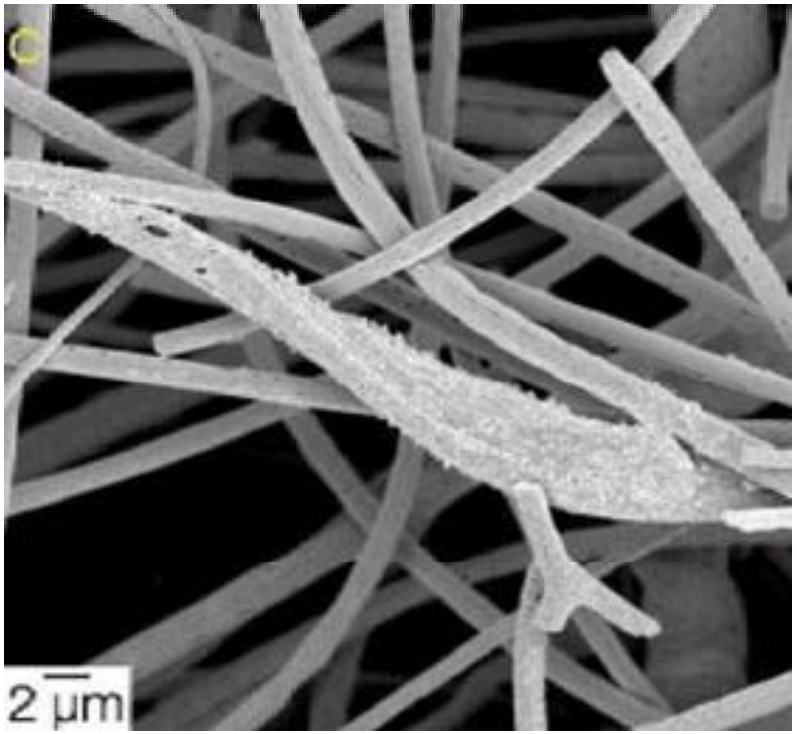


Figure shows SEM micrograph of MC3T3-E1 preosteoblasts cultured on 70S30C (70 mol.% SiO_2, 30 mol.% CaO) cotton-wool-like fibrous scaffolds

GLASS COMPOSITIONAL EFFECTS

- SiO_2
  - increases network connectivity
  - reduces bioactivity
  - rate of network dissolution decreases
- P_2O_5
  - increases surface reactivity
  - increases bioactivity
  - increases degradation rate
  - high conc's result in adverse effects
- CaO, Na_2O
  - reduce network connectivity

GLASS COMPOSITIONAL EFFECTS

- F
  - increase bone formation at low conc's
  - toxic at high conc's
- Mg, K, B
  - little effect on bioactivity
- Al
  - increases network connectivity
  - can inhibit bone bonding
  - increases resistance to ion exchange surface reactions
  - interferes with osteoblast and fibroblast metabolism
- Ta, Ti, Sb, Zr
  - increase network connectivity

BIOACTIVITY

Bioactivity index

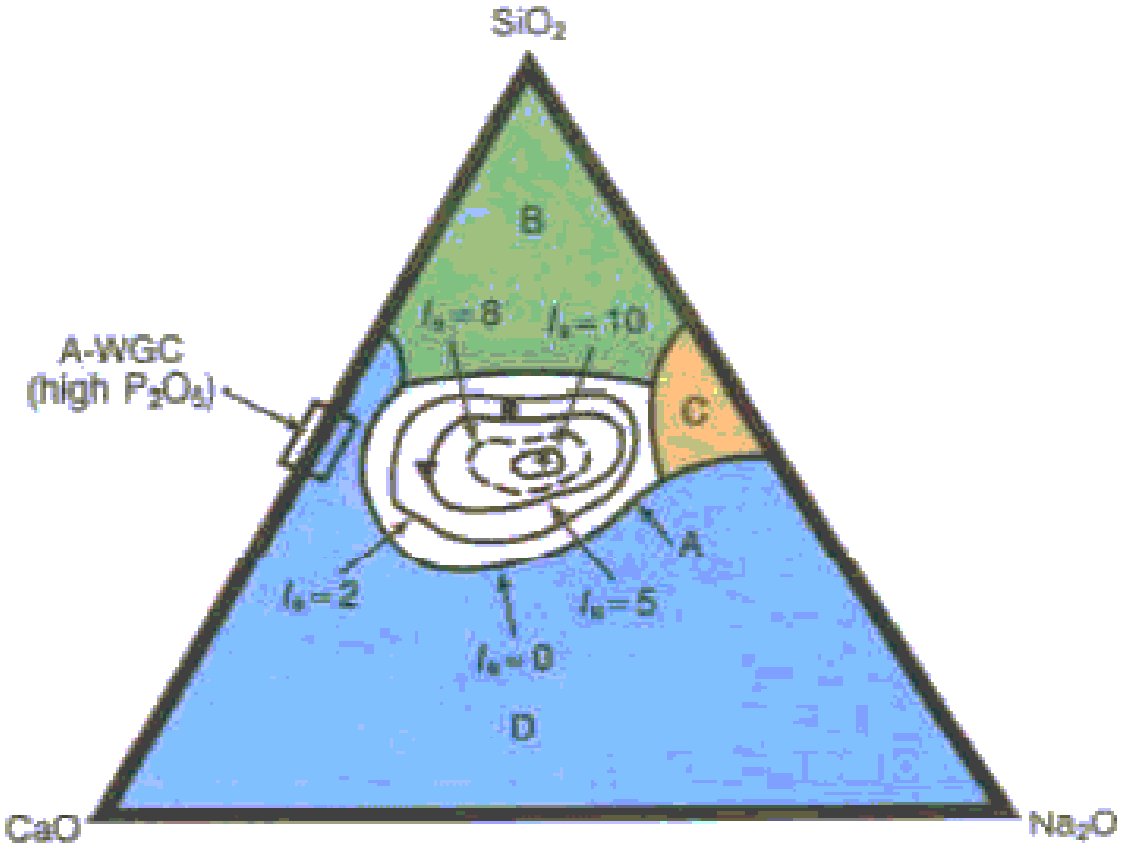
$$I_B = [100/t_{0.5}] \text{ (days}^{-1})$$

$t_{0.5}$ = time needed for 50% of an implant surface to attach to bone

I_B = 0 at bone bonding boundary

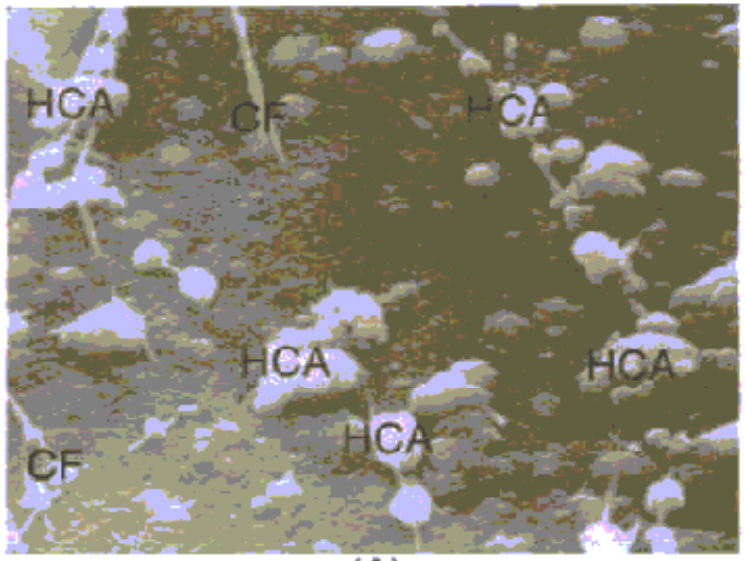
Region E (soft tissue bonding) is inside the dashed line where $I_B > 8$

The collagenous constituent of soft tissues can strongly adhere to the bioactive glasses within the Region E compositional range.



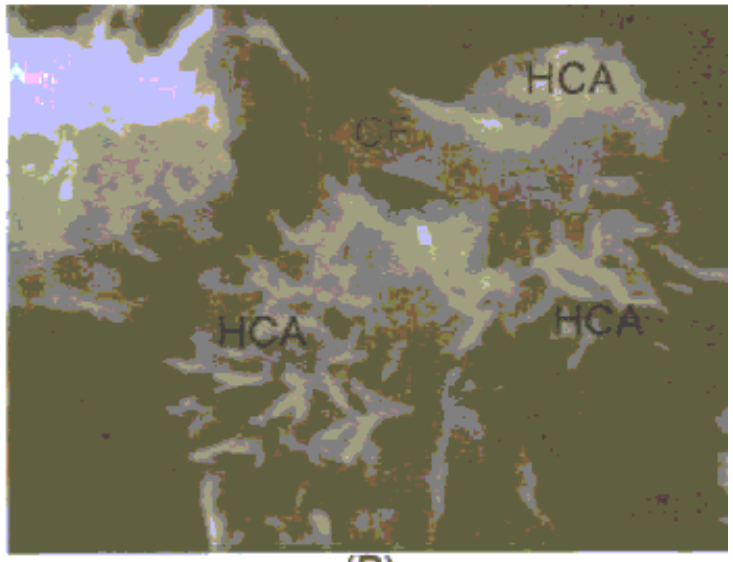
BIOACTIVITY

Scanning electron micrograph of collagen from a 10 days *in vitro* test bonded to a 45S5 Bioglass® surface by agglomerates of HCA crystallites growing on the surface.



(A)

The collagen fibrils (CF) are woven into the interface by growth of the HCA layer.

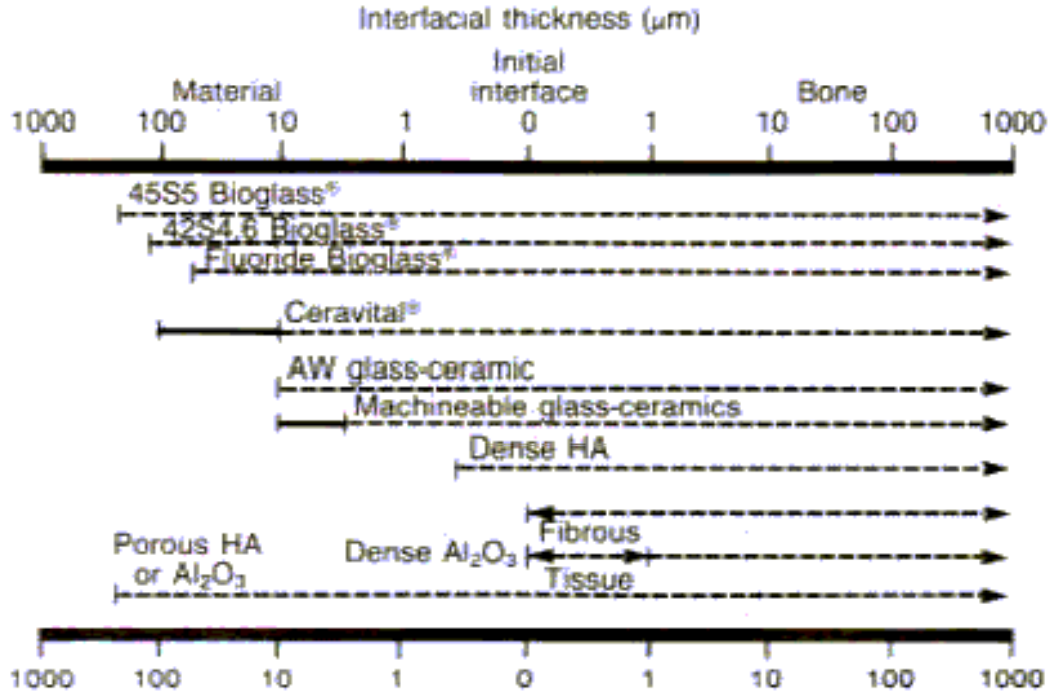


(B)

The dense HCA-collagen agglomerates mimic the nature of bonding between tendons and ligaments, composed entirely of collagen fibrils and bone which is a composite of HCA crystals and collagen.

BIOACTIVITY

The composite interface composed of HCA collagen on the bioactive glass is approximately 30-60 μm of the 100-200 μm total interfacial thickness. This junction thickness is equivalent to that at naturally occurring interfaces where a transition occurs between tissue with a low Young's modulus (tendons and ligaments) and bone with a moderately high Young's modulus.



The thickness of the hard tissue-bioactive ceramic interface is indicated in figure for several bioglasses and g-cs vs. bioceramics. The interfacial thickness decreases as the bone bonding boundary is approached.

BIOACTIVITY

- Compositions such as 45S5 Bioglass with high rates of bioactivity produce rapid regeneration of trabecular bone with an amount, architecture and biomechanical quality of bone that matches that originally present in the site.
- The rapid regeneration of bone is due to a combination of processes called osteostimulation and osteoconduction.
- Large differences in rates of *in vivo* bone regeneration and extent of bone repair indicate that there are two classes of bioactive materials, A & B

BIOACTIVITY

Bioactive materials, A & B used for medical and dental applications

Composition (wt%)	45S5 Bioglass (NovaBone)	S53P4 (AbminDent1) (BonAlive)	A-W Glass-ceramic (Cerabone)
Na_2O	24.5	23	0
CaO	24.5	20	44.7
CaF2	0	0	0.5
MgO	0	0	4.6
P2O5	6	4	16.2
SiO2	45	53	34
Phases	Glass	Glass	Apatite, beta-wollastonite, Glass
Class of bioactivity	A	B	B

Rates of osteoproduction of various bioactive particulates have been quantified by Oonishi *et al. (2000)* that provide the fundamental *in vivo* comparisons of Class A vs. Class B bioactive materials

BIOACTIVITY

Two classes of bioactive materials, A & B

- Class A bioactivity leads to both osteoconduction and osteostimulation as a consequence of rapid reactions on the bioactive glass surface.
- The surface reactions involve dissolution of critical concentrations of soluble Si and Ca ions that give rise to both intracellular and extracellular responses at the interface of the glass with its physiological environment.
- The intracellular and extracellular response of osteoprogenitor cells results in rapid formation of osteoid bridges between particles, followed by mineralization to produce mature bone structures.

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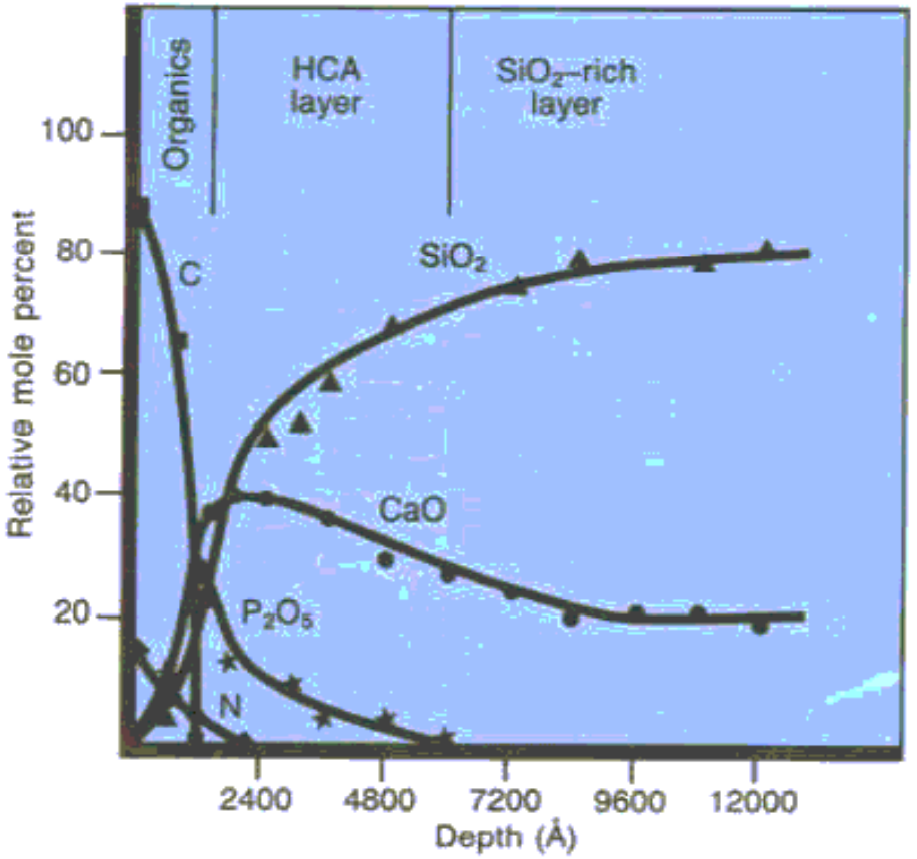
- For a Class A bio-active glass with highest levels of bioactivity, e.g. 45S5, the first five stages of surface reactions occur very rapidly and go to completion within 24 hours
- The effect of the surface reactions is rapid release of soluble ionic species from the glass into the interfacial solution.
- A high surface area composed of hydrated silica and a polycrystalline hydroxyl-carbonate apatite (HCA) bi-layer is formed on the glass surface within 10 hours of implantation, growing to ~4μm in thickness (Stages 1-5).



Bi-layer formed in 1 hr after implantation in rats

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- Incorporation of osteocytes onto mixed apatite layer occurs. Within a week of implantation a bonded interface between glass and tissue is formed.
- Further **stages (6-11)** identified as biological action occurs.

Stage 6

- Reaction layers enhance adsorption and desorption of biological moeties, growth factors, proteins, etc.

Stage 7

- macrophages prepare the implant site for tissue repair
- Reaction layers greatly decrease the length of time required

Stage 8: Attachment of stem cells

Stage 9: synchronized proliferation and differentiation of cells rapidly occurs on the surface of Class A bioactive glasses.

- Several weeks are required for similar cellular events to occur on the surface of bio-inert and Class B bioactive materials.

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Stage 10

- Attachment of osteoprogenitor cells
- Cells colonize the surface of Class A bioactive materials within 24-48 hours and begin production of various growth factors which stimulate cell division, mitosis, and production of extracellular matrix proteins.
- Differentiation of progenitor cells into a mature osteoblast phenotype does not occur on bio-inert materials and is rare on Class B bioactive materials because of the lack of ionic stimuli.

Stage 11

- Mineralization of the matrix follows soon thereafter and mature osteocytes, encased in a collagen-HCA matrix, are the final product after 6-12 days *in vitro* and *in vivo* (Stage 11).

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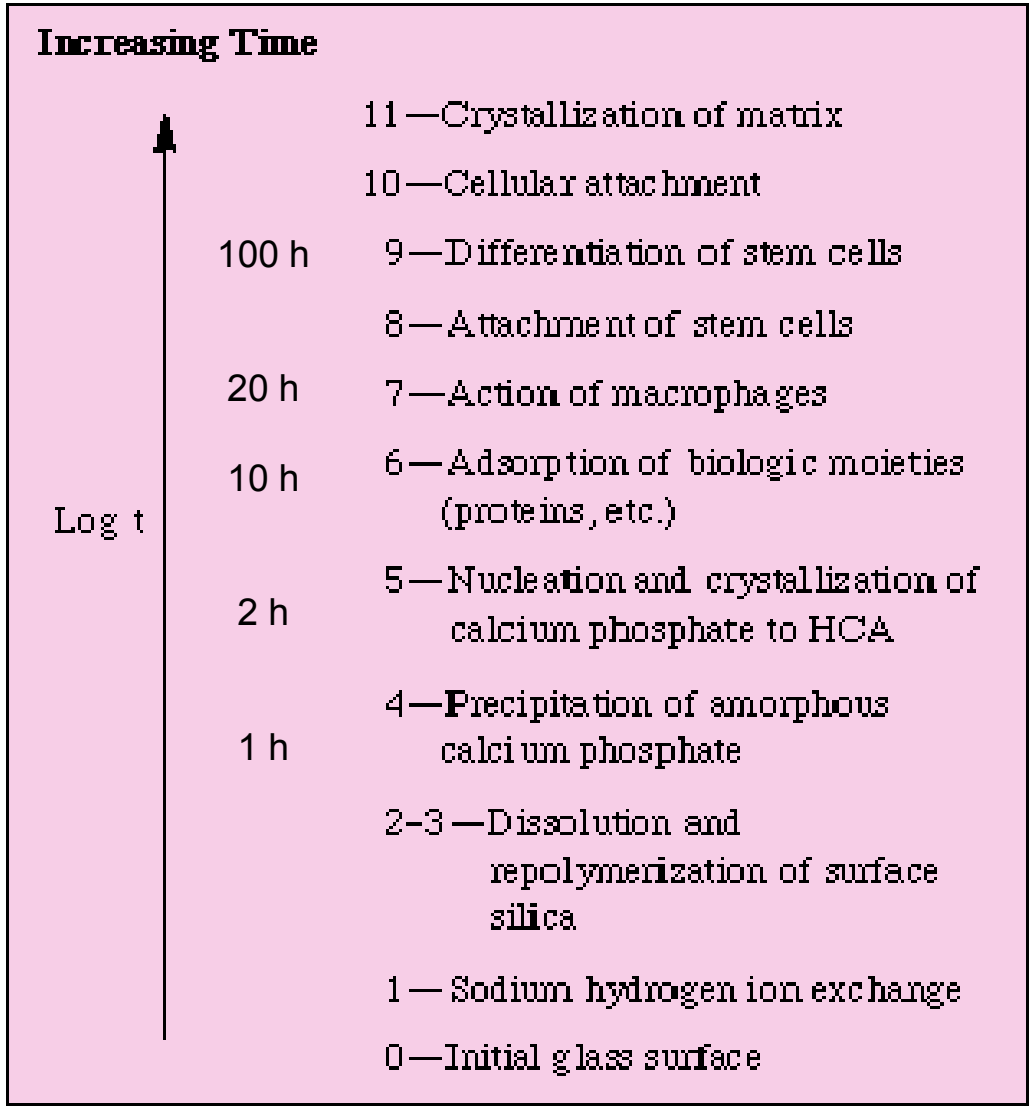
Stages 1-11 and their time dependence correspond to implants with high I_B values.

As I_B values decrease, times for various stages increase



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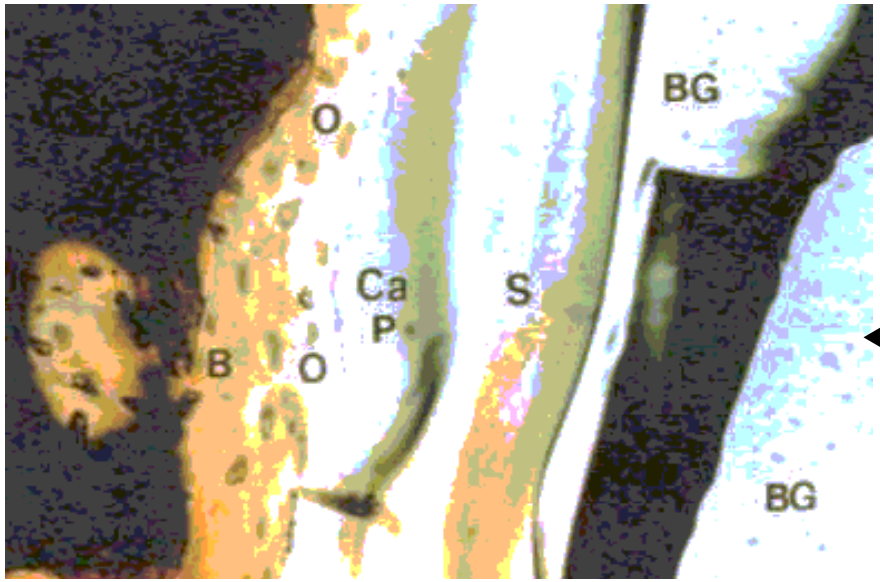
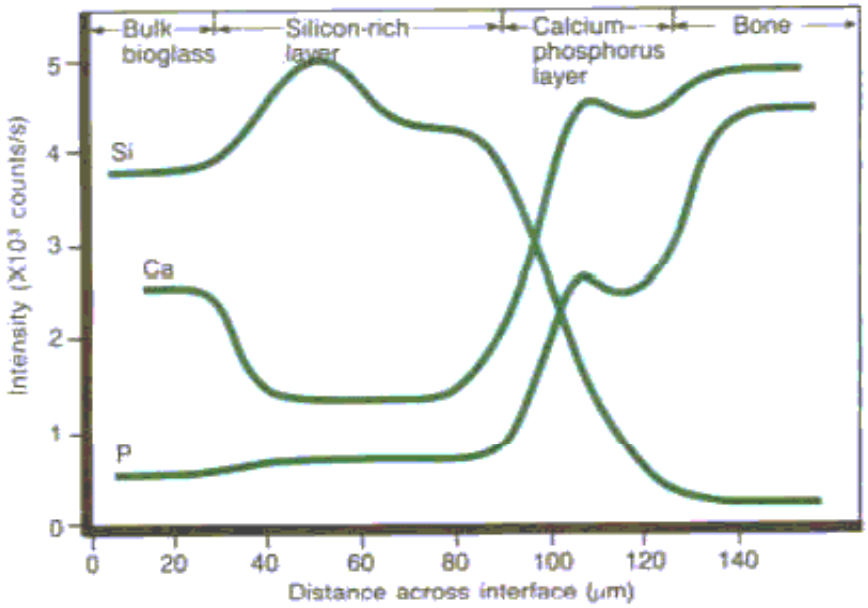


The thickness of the bonding zone between a bioactive implant and bone is proportional to its bioactivity index (I_B)

Micrograph of 45S5 Bioglass (BG) bonded to rat bone (B) after 1 year

Shows osteocytes (O) or bone cells in conjunction with the HCA layer (Ca-P) formed on top of the Silica-rich layer (S)



No seam of interfacial fibrous tissue observed. Even using electron microscopy, no unmineralized tissue seen at the bonding interface

Electron micro-probe analysis across the implant–bone interface

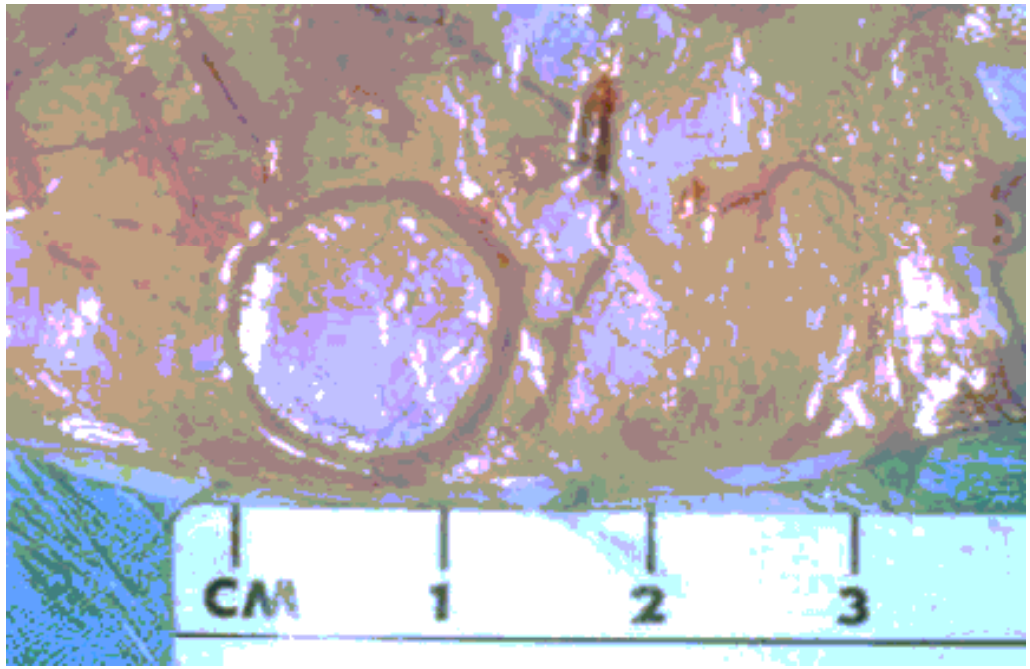
MSSI

BIOACTIVITY

Wilson was first to recognize that an adherant interface can develop between a bioactive glass and ***soft*** connective tissue if the implant interface is immobile during the early days of healing.

Figure shows a disc of 45S5 Bioglass® implanted subcutaneoulsy in a rabbit.

No inflammation is present, the implant is stabilized by an adherant bond to the collagen fibers of the connective tissue.



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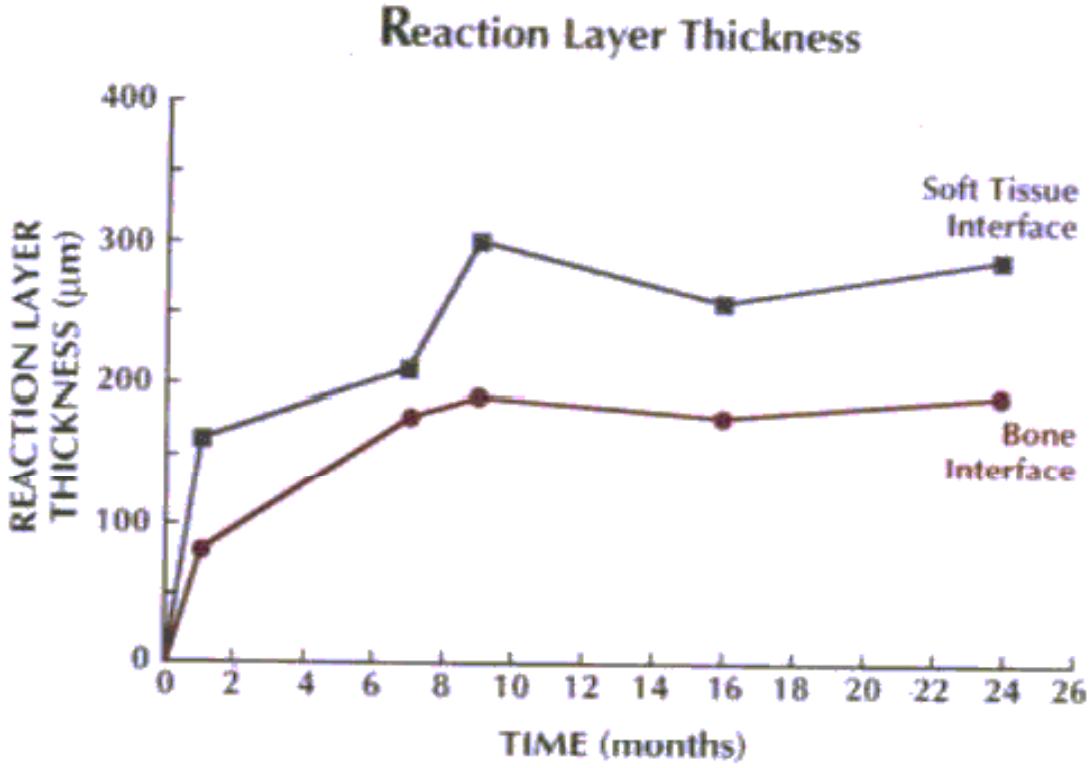
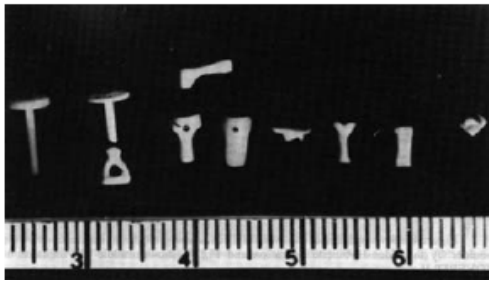


The reaction stages involved in forming a soft tissue bond are equivalent to those required to form a bone-bond. However, the time dependent change of the thickness of a soft tissue bonding interface is greater than for the bone-bonding interface with 45S5 Bioglass® endosseous ridge dental implants in dogs.

Applications (current clinical & commercial)



- ***Solid*** Bioglass® first used as cochlear implant (1984)

The patient was deaf from an infection that caused degradation of two of the three bones of her middle ear. The implant was designed to replace the bones and to transmit sound from the eardrum to the cochlea, restoring hearing.

- Previous materials used for this indication were metals and plastics, selected because they were inert in the body. However, they failed because fibrous tissue formed around them after implantation.
- The Bioglass 45S5 middle ear prosthesis (MEP) was cast into shape from the melt. Early prototypes were cast to shape to fit each patient's indication. After 10-year follow-up studies, four out of 21 had failed due to fracture, but the others retained function, improving on polymeric, metallic and ceramic implants. The four that failed were all the same shape.
- Custom design of each implant was not commercially viable, so the device was remodelled to cone shapes of three sizes (Douek-MED™) for optimal mechanical properties.

Applications (current clinical & commercial)

2nd use of Bioglass® - Endosseous Ridge Maintenance Implant (ERMI) (1988) - simple cone of Bioglass 45S5.

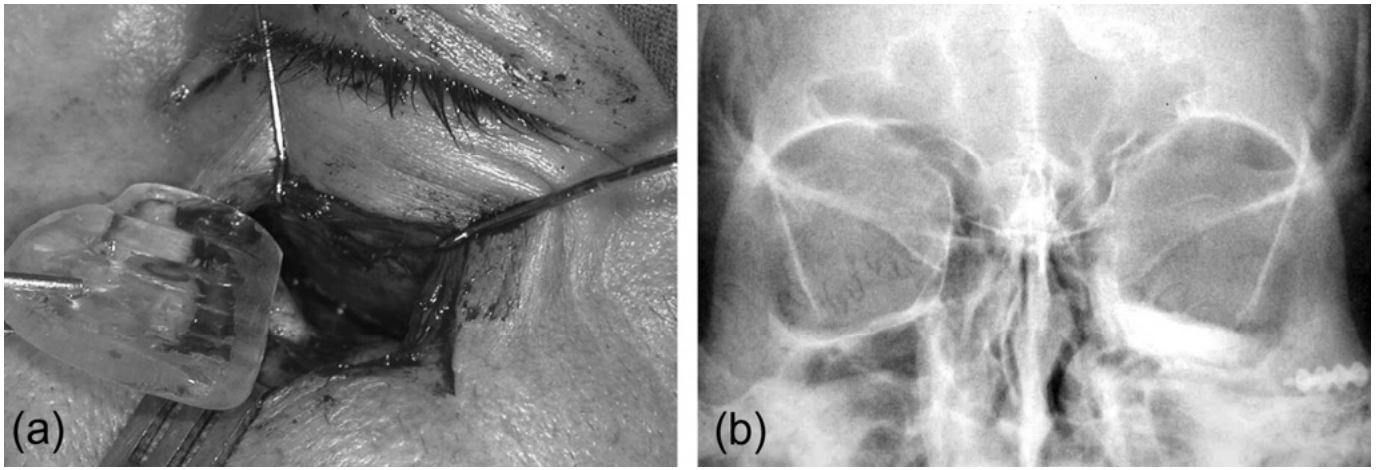
The devices were inserted into fresh tooth extraction sites to repair tooth roots and to provide a stable ridge for dentures. Proved to be extremely stable. 5-year study quantified improvements over HA tooth root implants.

None of these products is in widespread clinical use, as surgeons needed to be able to cut the implant to shape rather than be limited to cones of fixed size, which prevented commercial success.

Monolithic Bioglass 45S5 is more suited to implants that are custom made for the patient's need.

Applications (current clinical & commercial)

Thompson et al. performed clinical trials on 30 trauma patients with orbital floors that were so badly damaged that their vision was blurred. Traditional methods of repair (e.g. autograft) failed and patients were likely to become blind due to kinking of the optical nerve. Using computed axial tomography (CAT) scans of the defect site, a rapid prototyping (or ‘‘additive manufacturing’’) machine was used to produce moulds for casting the Bioglass 45S5 implants, which were then sutured into place.



(a) Inserting the glass implant beneath the eye. (b) Post-operative X-ray, showing that the bioactive glass implant has repaired the orbital floor and the eyes are now the same height.

At 5-year follow-up, patients regained full movement of their eyes; their vision was no longer blurred and the cosmetic appearance of the face was much improved.

Applications (current clinical & commercial)

Bioactive glasses of composition S53P4 (53.8 mol.% SiO_2, 21.8 mol.% CaO, 22.7 mol.% Na_2O, 1.7 mol.% P_2O_5) developed at Abo Akademi, Turku, Finland used in similar trials.

See Kinnunen I, Aitasalo K, Pollonen M, Varpula M. Reconstruction of orbital floor fractures using bioactive glass. J Craniofac-Maxillofac Surg 2000;28: 229–34.

Implants were supplied as 1 mm thick, round, heart- or kidney-shaped plates.

The glass implants were successful, and performed as well as the more traditional procedure of cartilage harvested from the patient's ear.

Despite these successes, products that are in commercial use internationally are those based on particles rather than monolithic shapes.

Applications (current clinical & commercial)

The first particulate Bioglass 45S5 product was PerioGlas (now sold by NovaBone in over 35 countries)

- released in 1993 as a synthetic bone graft for repair of defects in the jaw that result from periodontal disease.
- PerioGlas has a particle size range of 90–710 μm
- can be used to regenerate bone around the root of a healthy tooth to save the tooth
- can also be used to repair bone in the jaw so that the quality of bone becomes sufficient for anchoring titanium implants.

Early success was supported by in vivo and clinical studies which showed:

- defects treated with PerioGlas were 70% filled with new bone compared to 35% for controls.
- For infra-bony defects, which are between the roots of molars, its regenerative properties were further enhanced with low-level laser therapy post-operatively.

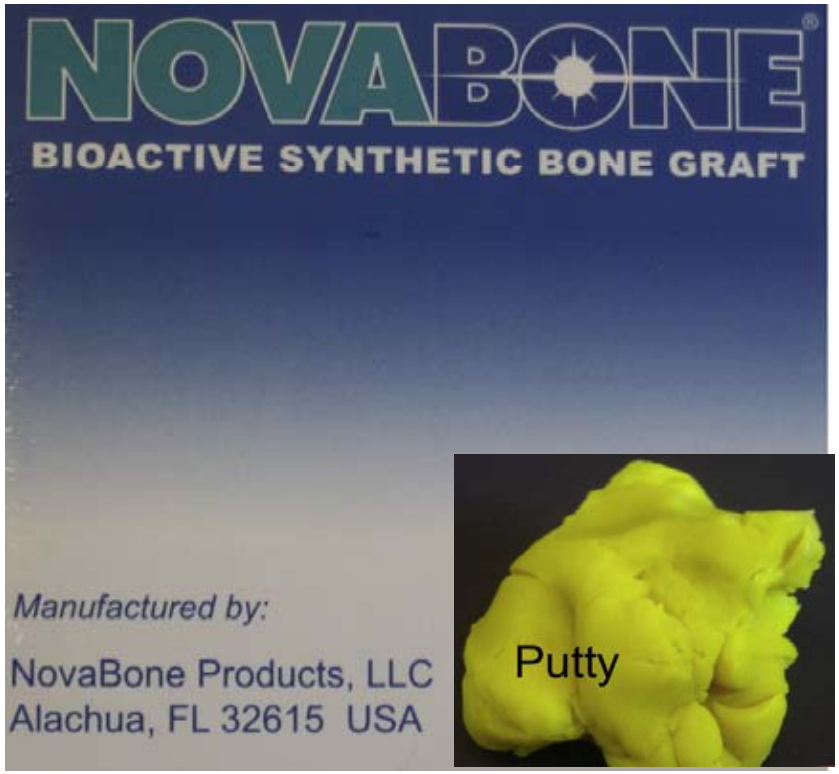
The product has also been used with polymeric membranes, termed ‘‘guided tissue regeneration’’.

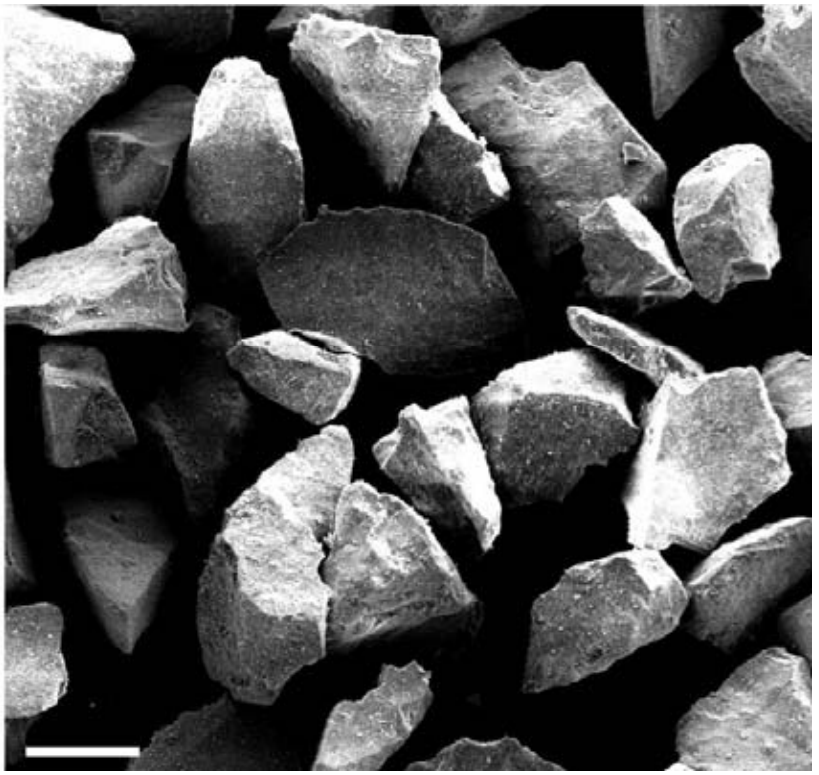
Bioactive glass slurry can also be used as a root canal sterilization tool, prior to insertion of implants. Conventionally, calcium hydroxide is used to raise pH to bactericidal levels, but a Bioglass 45S5 slurry is a possible alternative, as fine particles in high concentration can trigger high pH in addition to its bioactive properties.

Applications (current clinical & commercial)

Owing to the success of bioactive glass particles in dental bone regeneration, a particulate for orthopaedic bone grafting of non-load-bearing sites was released in 1999: NovaBone

Surgeons usually mix it with blood from the defect site and work it into a ***putty-like*** consistency as the blood starts to clot, before pushing it into the defect. The particles have a similar size distribution to PerioGlas (90–710 μm), so packing of the particles in the defect is random. Gaps between the particles are thought to increase the rate of bone ingrowth.





200 μm

Applications (current clinical & commercial)

NovaBone was compared to autograft in posterior spinal fusion operations for treatment of adolescent idiopathic scoliosis (curvature of the spine).

In a group of 88 patients, 40 received iliac crest autograft and 48 received NovaBone.

The NovaBone (15 cm^3) was mixed with the patient's blood and secured in place by compressing the neighbouring vertebrae with metal screws and hooks.

The NovaBone performed as well as autograft over the follow-up period of 4 years but with fewer infections (2% vs. 5%) and fewer mechanical failures (2% vs. 7.5%) and with the main benefit that a donor site (from the patient's own skeleton) was not needed with NovaBone.

Other particulate glasses:

- Biogran (BIOMET 3i, Palm Beach Gardens, FL) with the Bioglass 45S5 composition, but with a narrower particle size range (300–360 μm) – a synthetic bone graft used in jaw bone defect regeneration.
- BonAlive (BonAlive Biomaterials, Turku, Finland) with the S53P4 composition received European approval for orthopaedic use as a bone graft substitute in 2006.
- 13-93 glass (54.6 mol.% SiO_2, 22.1 mol.% CaO, 6.0 mol.% Na_2O, 1.7 mol.% P_2O_5, 7.9 mol.% K_2O, 7.7 mol.% MgO) with particle size range 0.5-1 mm showed improved bone repair in terms of quantity and quality, compared to synthetic HA.
- Bone growth is faster for BonAlive than for 13–93 which is likely to be due to the Mg content of the glass which would reduce the bioactivity of 13–93.

Applications (current clinical & commercial)

Biogran with the Bioglass 45S5 composition, but with a narrower particle size range (300–360 μm) is a synthetic bone graft used in jaw bone defect regeneration.

Small bioglass particles develop microcracks, due to the shrinkage associated with the formation of the apatite layer. Phagocytes (cells that protect the body by ingesting (phagocytosing) harmful foreign particles, etc) penetrate these microcracks and initiate the excavation and resorption of the inner silica gel core.

Lab research has shown that osteoprogenitor cells penetrate these microcracks and differentiate into osteoblasts, thus promoting new bone formation.

Histology sections of sites grafted with Biogran show bone formation in the core of the granules. This leads to an *"inside- out"* growth of bone within the glass particles. At the same time osteoconductive bone growth is seen on the periphery of the particles. This leads to a dual mode of bone formation.

Particles which are in close proximity to existing bone exhibit greater bone formation on the periphery, while particles which are further away from pre-existing bone show greater bone formation in the core. It is also important to note that the bone being formed in the central core is not connected initially to the bone forming on the periphery of the particles.

Bone trabaculae form along the periphery of the particles ultimately leading to and connecting with the bone forming in the cores of the particles.

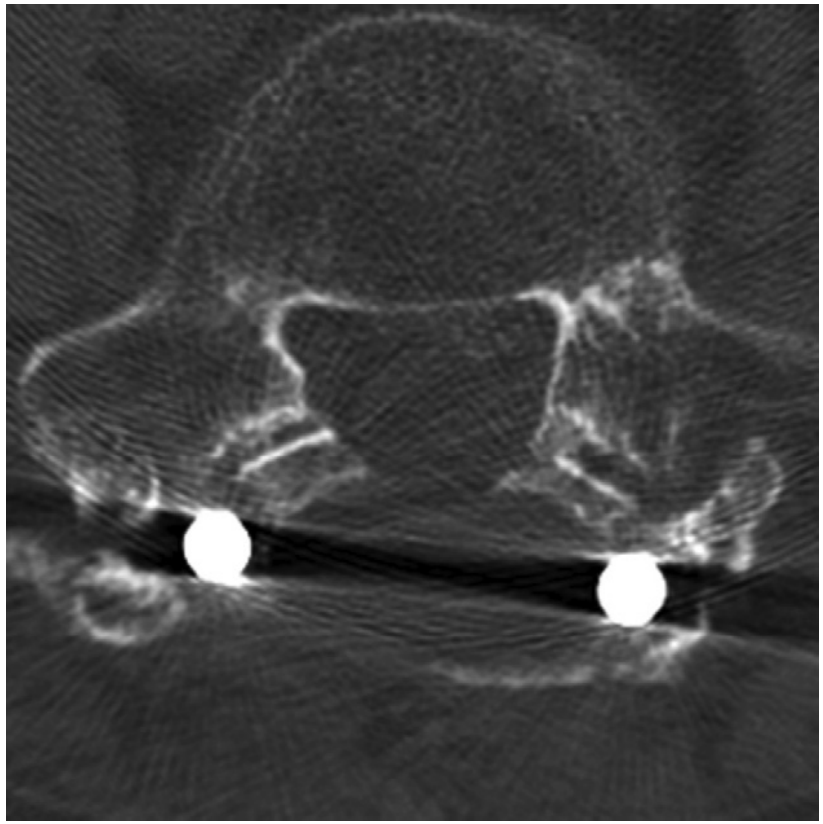
By 6 months most of the particles are totally engulfed by the new bone and by about 12 months the particles are almost totally replaced by newly formed bone tissue.

Applications (current clinical & commercial)

Clinical trials for cases of severe spondylolisthesis (displacement of the vertebral column) used BonAlive granules of 1–2 mm. The S53P4 glass (20–40 g, depending on the amount needed) and autograft were implanted in the same site in each patient. The implants were held in position between vertebrae by compression of the vertebrae assisted by a metal screw system.

X-ray image showing the position of S53P4 glass rods compressed between vertebrae in 11-year follow-up clinical trials.

Courtesy Dr. Janek Frantzén, Turku University Hospital.



After 11 years, the fusion rate for the glass was 88% compared to 100% for autograft.

Similar results were seen for treatment of osteomyelitis, where the bone quality of the vertebrae is reduced due to bacterial infection.

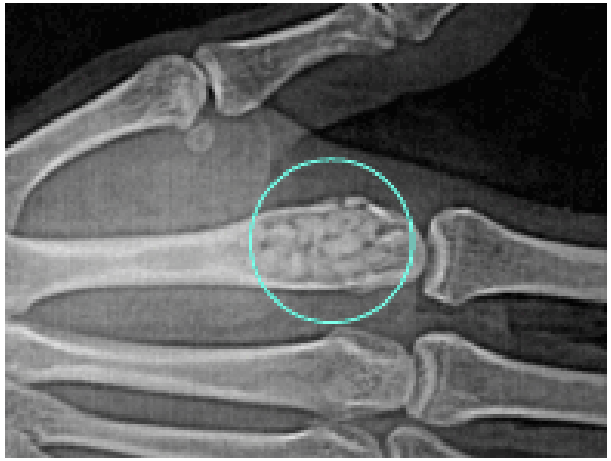
BonAlive was also compared to autograft in the same patient in spondylodesis procedures for treatment of spine burst fractures.

At 10 years follow-up, five out of 10 implants had full fusion compared to all 10 autografts.

Applications (current clinical & commercial)

Glass granules (1–4 mm) were also observed after 14 years when BonAlive was used in trials for repairing bone defects (1–30 cm^3) left by benign bone-tumour surgery in hands, tibia and humerus.

The cortical bone was twice as thick as it was when autograft was used. In shorter-term studies, the glass was observed to begin to decrease in size (degrade) between 12 and 36 months, and this stimulated remodelling of the bone.



However, remodelling was slower than it was for autograft (12 months) and the glass particles were still present at 3-year follow-up.

BonAlive has also been used successfully in trials for filling cavities in the middle ear created by surgeons removing mastoid air cells and mucous membranes that were damaged by chronic infection.

Applications (current clinical & commercial)

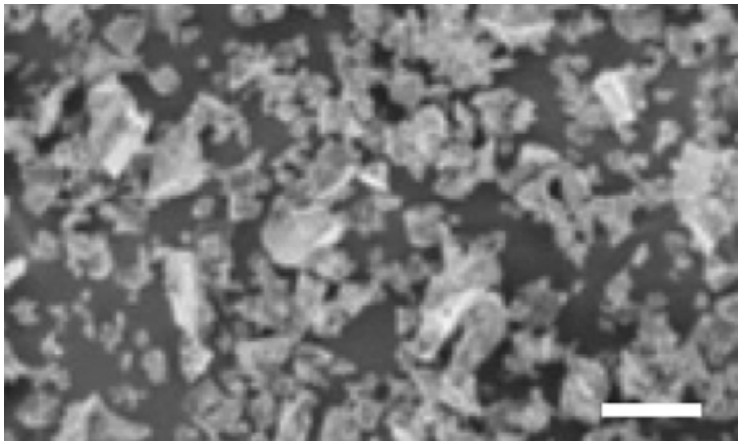
A very fine Bioglass 45S5 particulate - NovaMin (acquired by GlaxoSmithKline, UK - 2010) with a particle size (D_{50} value) of ~18 μm is used in toothpaste for treating tooth hypersensitivity, which affects up to 35% of people.

NovaMin was first available in the USA in fluoride-free toothpastes. Now a NovaMin- and fluoride-containing toothpaste is available in more than 20 countries (Sensodyne® Repair and Protect®).

The common abrasive additive in toothpaste is alumina particles, which can be replaced by Bioglass 45S5.

Tooth hypersensitivity occurs when dentine becomes exposed around the gum line. The dentine contains tubules that link to the pulp chamber, which contains nerve endings. Change in fluid flow (hydraulic conductance) through the tubules, ion concentration or temperature can cause pain.

Clinical studies show that Bioglass 45S5 particles adhere to dentine and form an HCA layer that is similar in composition to tooth enamel and blocks the tubules, which are 1 μm diameter, relieving the pain for longer.



NovaMin particles

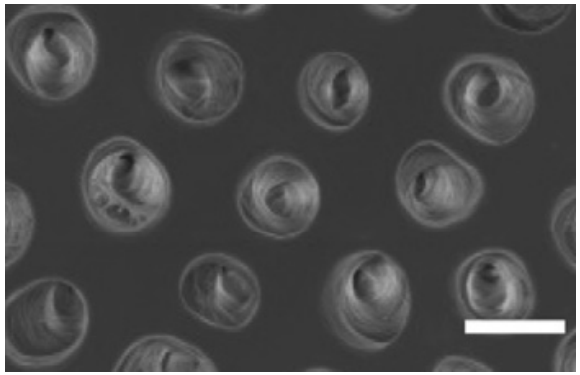
Applications (current clinical & commercial)

In vitro trials showed that the Bioglass 45S5 particles seem to attach to dentine. This may explain how the particles stimulate long-term repair even though brushing may only be for a few minutes a day.

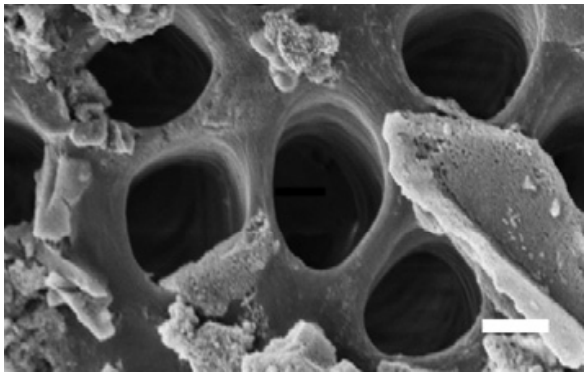
Immediately after the NovaMin was brushed onto the dentine, the particles attach and within 24 h the surface is almost completely covered by an HCA layer.

This indicates that NovaMin seems to work by stimulating mineralization (calcium phosphate deposition over the dentine tubules). The glass dissolution products probably stimulate the mineralization. HCA deposition is promoted by a rise in pH, resulting from dissolution of Ca and PO_4 from the glass in saliva in the mouth

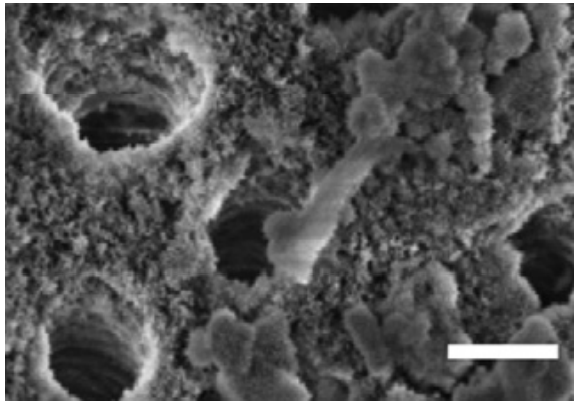
SEM micrographs of human dentine (bar = 1 μm) from Earl et al.



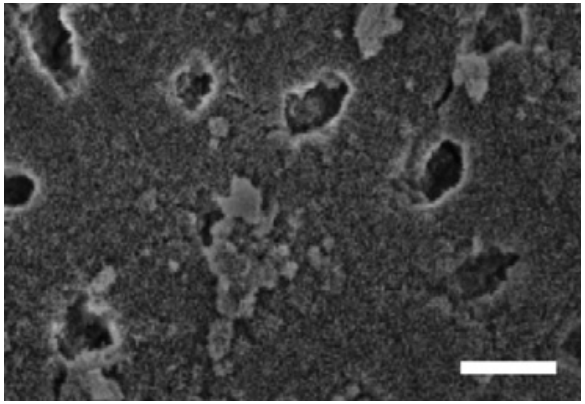
untreated (lightly etched surface to reveal the tubules)



immediately after application of NovaMin in artificial saliva (AS)



24h after application of NovaMin in artificial saliva (AS)



5 days after application of NovaMin in artificial saliva (AS)

Applications (current clinical & commercial)

Glass granules

Applications (current clinical & commercial)

StronBone®

- Strontium Releasing Bioactive Glass.
- Produced by RepRegen
- CE Marked
- Medical Device Approval in EU

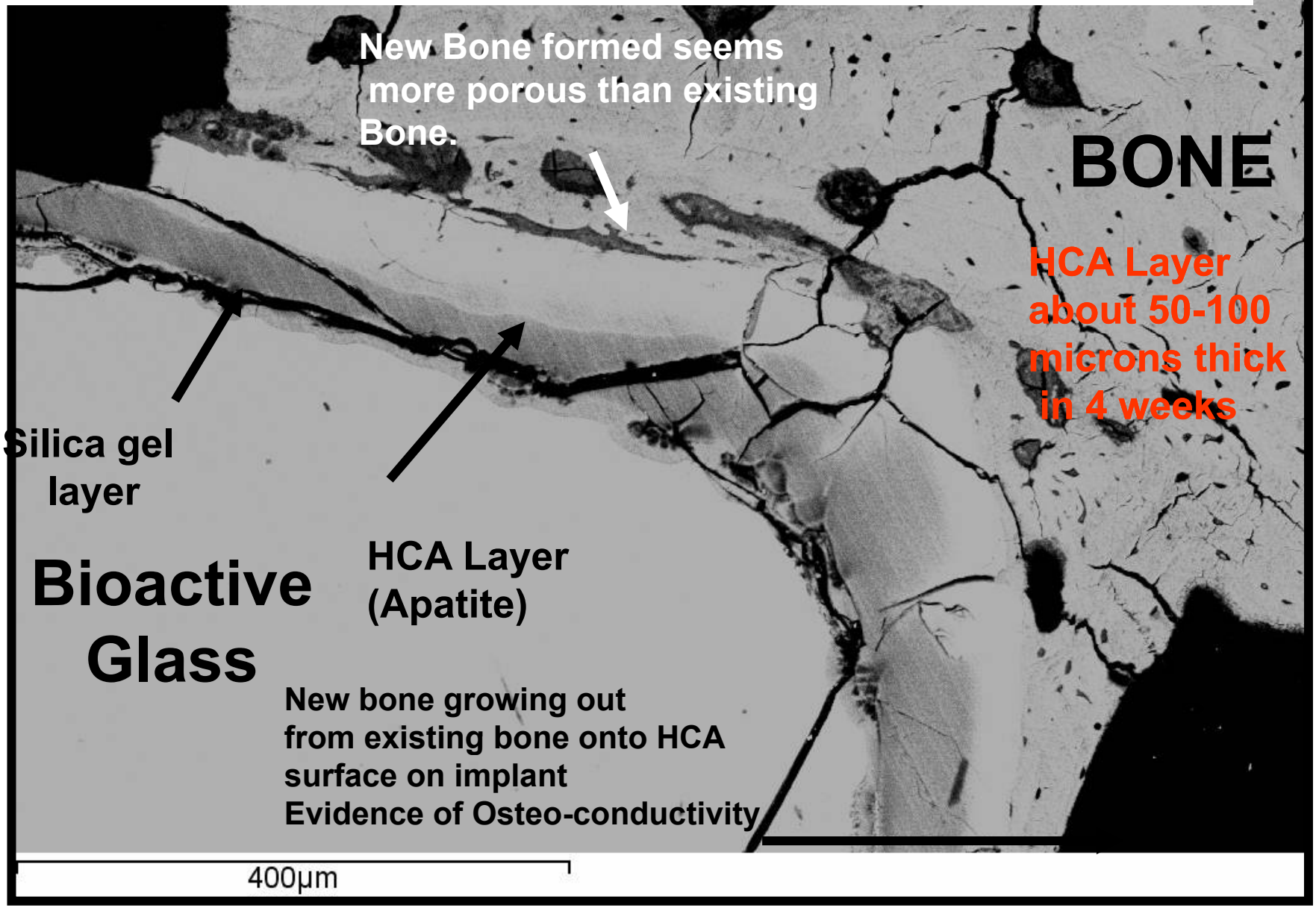
RepRegen™
The Smart Biomaterials Company

Applications (current clinical & commercial)

Stronbone - Why Strontium?

- The strontium ion is about 8% larger than the calcium ion.
- Strontium substitutes for calcium in the Apatite Lattice and in Bioactive Glasses.
- Strontium stimulates osteoblasts (bone forming cells) and inhibits osteoclasts (bone resorbing cells).
- Used as a treatment for Osteoporosis in the form of Strontium Ranelate–Protelos in Europe.
- Strontium substitution for calcium, expands the glass network and accelerates bioactive glass dissolution and apatite formation.
- Local delivery of strontium.
- Strontium incorporation results in radio-opacity.
- Strontium has a bacteriocidal action.

Back Scattered SEM ICIE1Sr10 Bioactive Glass



Properties of Bioactive Glass-ceramics

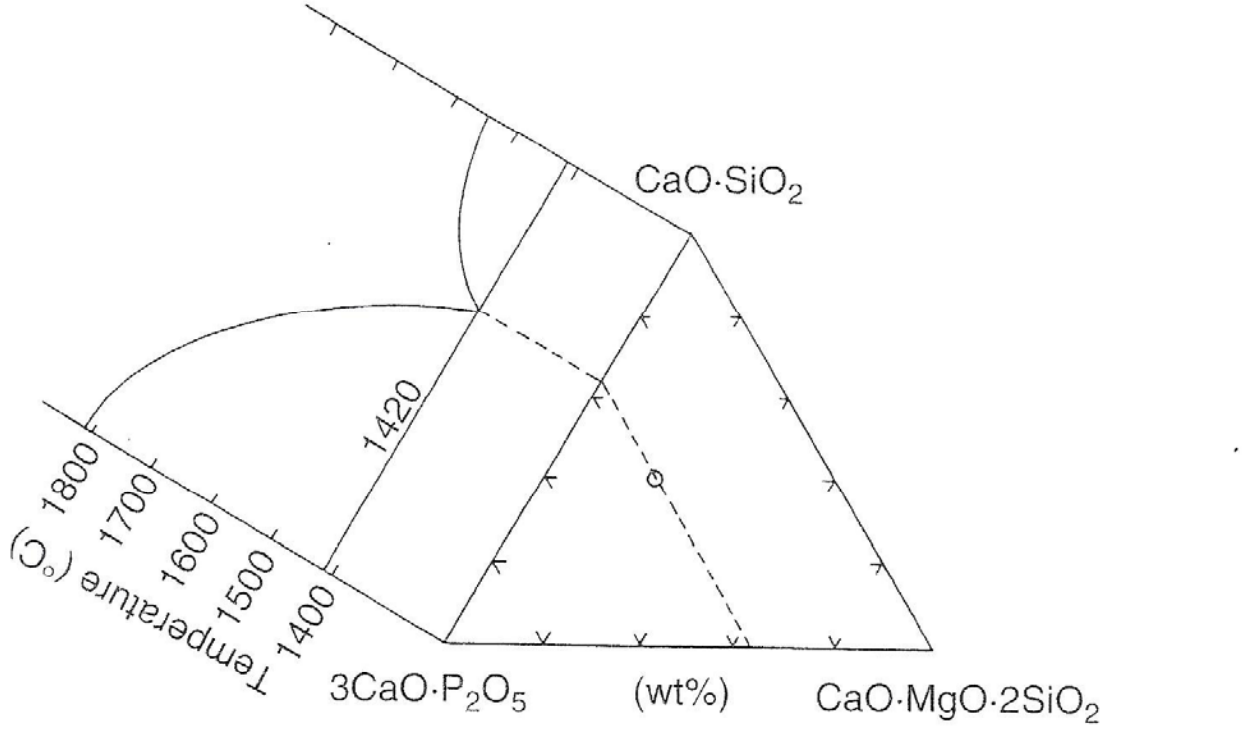
Property	Cerabone	Bioverit I	Highly bioactive glass ceramic
Bioactivity class	B†	B†	A‡
Machinability	Low	Good	Fair
Density (g/cm^3)	3.1	2.8	2.6
Three-point flexural strength (MPa)	215	140–180	210
Young's modulus (GPa)	120	70–90	70
Vickers hardness (HV)	680	500	600
Toughness ($MPa.m^{1/2}$)	2.0	1.2–2.1	0.95
Slow crack growth index n	33		

†Biomaterial class B bonds only to bone.

‡Biomaterial class A bonds to hard (bone) and soft (cartilage) tissues.

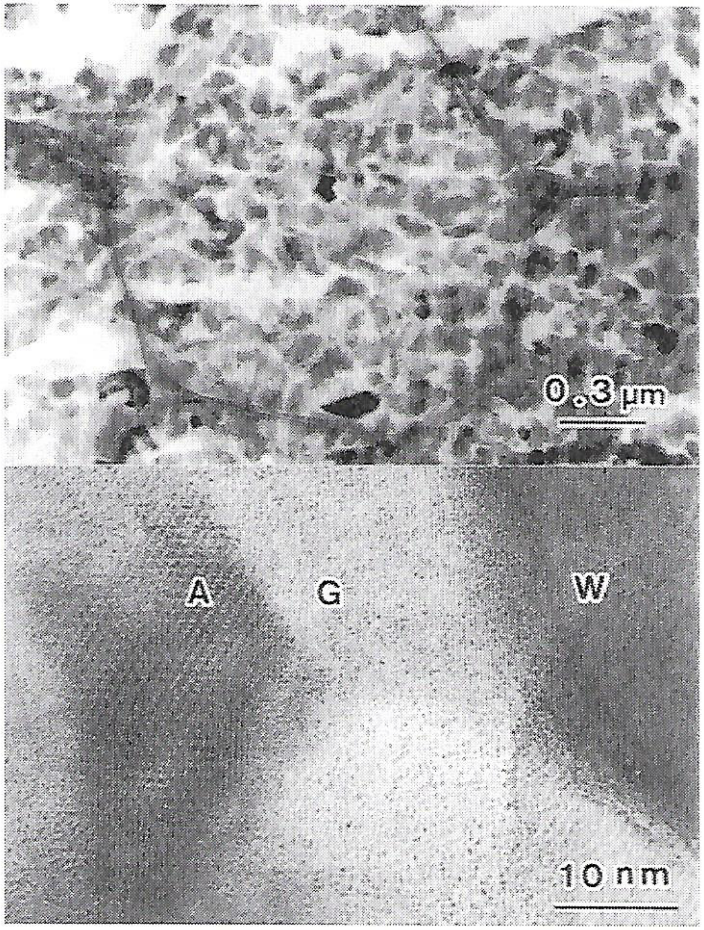
A-W Bioactive Glass-ceramic

Apatite-Wollastonite (A-W) Glass-ceramic
Composition: 46 MgO, 44.9 CaO, 34.2 SiO_2 16.3 P_2O_5 (in wt.%)



Pseudo-ternary system of $CaO \cdot SiO_2$–$CaO \cdot MgO \cdot 2SiO_2$–$3CaO \cdot P_2O_5$. A small open circle in the triangle denotes the base composition of glass-ceramic A-W.

A-W Bioactive Glass-ceramic



Transmission electron micrograph of glass-ceramic A-W. A: apatite, W: wollastonite, G: glassy phase (Ohtsuki *et al.*, 1995).

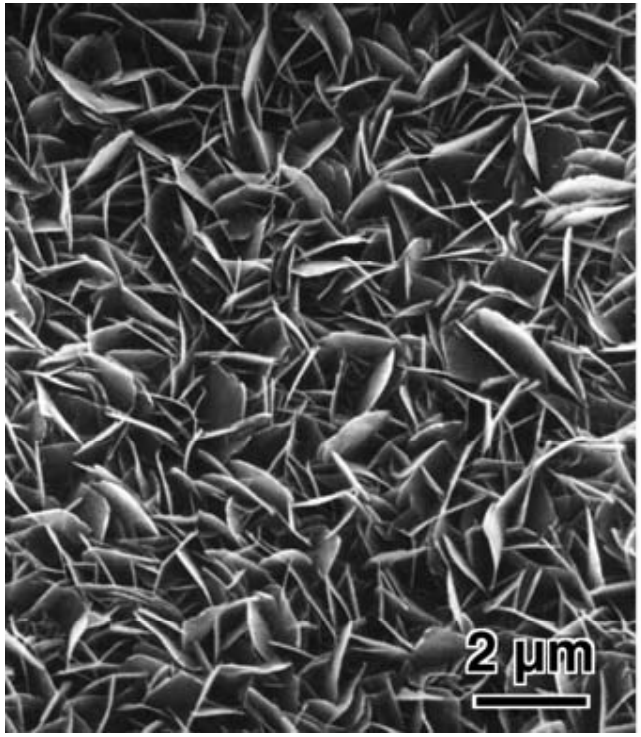
Microstructure

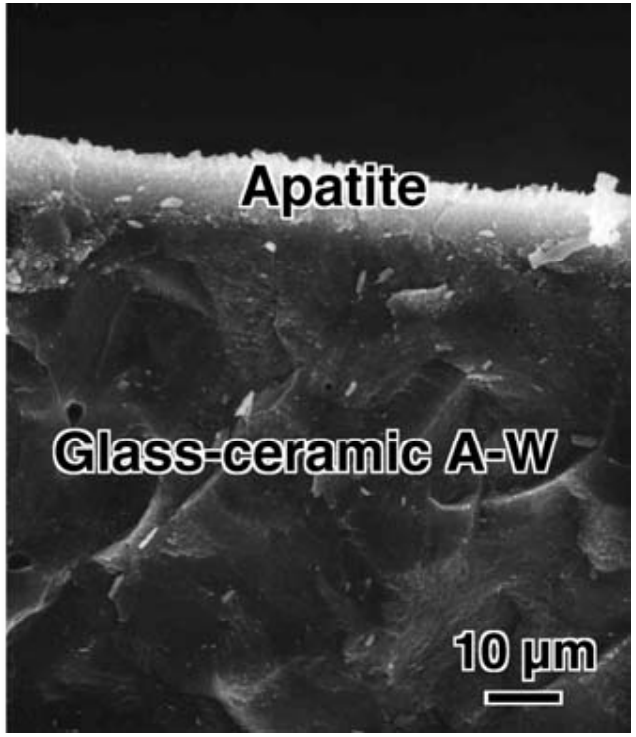
Specimen	Phase	Bending strength (σ)	Fracture toughness (K_{1C})
G	g(100)	70 MPa	0.8 MPa $m^{1/2}$
A	a(38) g(62)	90	1.2
AW	a(38) W(34) g(28)	220	2.0
HAp		115	1.0
Human bone		160	2~6

a: Oxyfluoroapatite, w: β-wollastonite, g: glassy phase
HAp: sinterd dense hydroxyapatite

Phase, bending strength and fracture toughness of glass G, glass-ceramic A, glass-ceramic A-W, sintered hydroxyapatite (HAp) and human cortical bone.

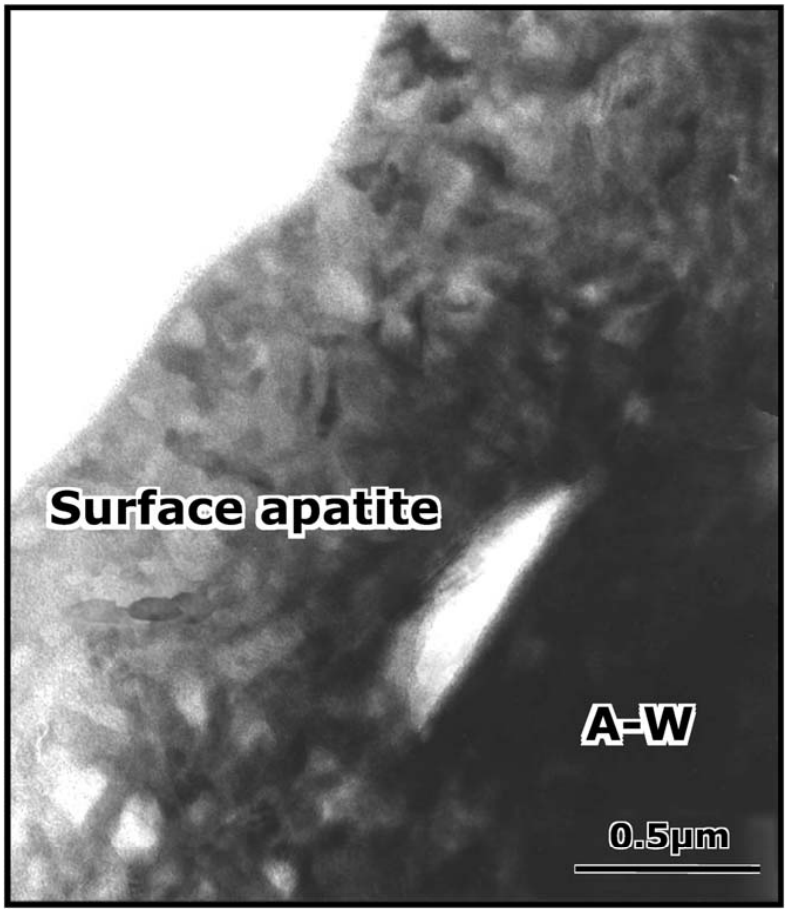
A-W Bioactive Glass-ceramic



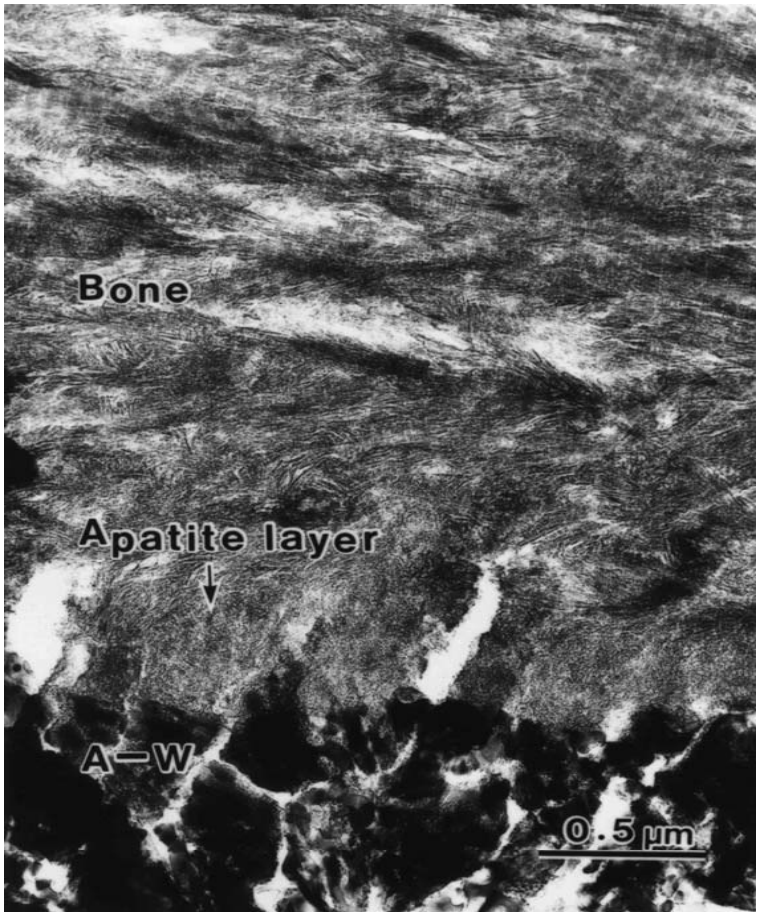


Scanning electron micrograph of surface (left) and cross section (right) of apatite layer formed on glass-ceramic A–W in SBF

A-W Bioactive Glass-ceramic



Transmission electron micrograph of cross section of apatite layer formed on glass-ceramic A–W in SBF



Transmission electron micrograph of interface between glass-ceramic A–W and rat tibia

Summary

- Bioactive glasses are formed in the SiO_2-CaO-Na_2O-P_2O_5 system by melting to form dense monoliths or particles and also by sol-gel processing.
- They are able to bond to both soft and hard tissue and promote bone growth.
- The bioactivity behaviour of these glasses is related to the formation of a biologically active hydroxycarbonate-apatite layer on the surface of the glasses.
- The mechanism of bonding of bioactive glasses to tissues includes a series of surface reactions that occur when the glass is exposed to an aqueous environment.
- Bioactivity varies with composition and with network connectivity
- Applications include bone grafts, cochlear implants, dental restoratives, particles used in toothpaste, etc.
- Bioactive glass-ceramics can be formed by crystallisation of parent glasses.
- Apatite-Wollastonite glass-ceramics have high bending strength and fracture toughness.
- Now a large range of materials compositions and types available as bone substitutes including as scaffolds

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