

Bioactive Glasses and their Applications in Dentistry



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ABSTRACT:

Biomaterials have always been used for the replacement, repair and regeneration of dental hard tissues. As the research continues, there is a significant development in the field of dental materials in terms of either developing new materials or improving the performance of the existing materials. Contrary to the development of bioinert materials, the recent hard tissue research has witnessed the development and subsequent applications of bioactive materials, a hallmark of which is the development of bioactive glass. Originally discovered in 1969, bioactive glasses have provided a reliable alternative to inert implant materials by virtue of their ability to form a stable bond with host tissues and induce subsequent remineralization especially of the dental hard tissues. This article comprehensively reviews the early development, chronological applications and mechanism of action of bioactive glasses in general and briefly encompasses their applications in clinical dentistry.

KEYWORDS: Bio-active, Bioinert, Biocompatible, Glass, Dental regeneration, Bone bonding.

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INTRODUCTION

Biomaterials have been used to repair or replace the lost tissues that perform within the biological environment. In dentistry, many factors must be considered to determine which properties are relevant to the optimal performance of a biomaterial. The term “biocompatibility” implies that the material exhibits in-vivo

harmony^{1,2}. Biomaterials such as natural or synthetic polymers, metals, composites, ceramics and bioactive glasses have been developed for dental applications ranging from restorations and artificial teeth to endodontic and periodontal regeneration^{3,4}. Recent research has focused on the development of materials that, in addition to being biocompatible, have the ability to stimulate repair and regeneration of oral tissues^{5,6}. The development and use of bioactive glasses is of considerable interest due to the incorporation of mechanically biocompatible and biologically active components such as inorganic hydroxyapatite due to their potential to interact with calcified tissues¹. For instance, common applications of bioactive materials in dentistry include implant coatings^{7,8}, bone grafts^{9,10}, restorative materials^{11,12} and tissue engineering scaffolds^{5,13}. The aim of this article is to review the historical background, development of bioactive glass (BG), structure and degradation in the body fluids. In addition, current and potential applications of bioactive materials for clinical dentistry have been highlighted.

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Table 1. Key developments during the development of bioactive (Bioglass)¹⁴

Year	Development
1969	Bioactivity bone bonding of Bioglass(45S5) was discovered
1972	Bonding of Bioglass to bone in monkeys
1975	Bioglass used for hip implants in sheep
1977	Use of Bioglass implant in the middle ear of guinea pig
1977	Bioglass coated alumina ceramics and metals were patented
1981	Discovery that Bioglass can bond to soft tissues
1981	Several in-vivo and in-vitro studies concerning the biocompatibility and toxicity of Bioglass; applied safety clearance to FDA
1985	FDA clearance of MEP (an ear prosthesis consisting of Bioglass)
1987	Discovery of the osteopductive effect of Bioglass particles for the repair of periodontal defects
1988	FDA clearance of Bioglass implant for alveolar ridge maintenance
1991	Development of sol-gel processes for synthesis of Bioactive gel glasses
1993	Use of Bioglass particles to treat periodontal bone loss via bone grafting
1996	Use of Bioglass for bone grafting following removal of teeth as well as for augmentation of alveolar ridge
2000	Bioglass (NovaBone) cleared by FDA for orthopedic use
2001	The speculation that the ionic dissolution products of Bioglass could control osteoblast cell cycles and regulate gene expression was analyzed
2005	Development of dentifrices containing Bioglass for the non-invasive treatment of dentine exposure and sensitivity
2011	Global Marketing of Bioglass containing toothpaste by GlaxoSmithKline

HISTORY OF BIOACTIVE GLASS (BG)

Early materials that were used for biological applications were designed to be biologically inert, and the purpose was to reduce the development of scar tissue at the material-host tissue interface². These biomaterials were mainly metals that resisted corrosion or polymers that were insoluble and non-toxic¹⁴. A chronological overview of the developments in Bioactive glass (BG) research and products is summarized in Table 1. The magnificent breakthrough came in 1969, a novel and bioactive material called Bioactive glass (BG) was reported for its ability to bond with host tissues^{2,14-16}. A glass ceramic consisting of calcium and phosphate in a silicon oxide-sodium oxide matrix (45S5 Bioglass^R) was introduced in rats as a bone implant². A series of in-vitro tests and the results obtained from in-vivo experiments further confirmed the hypothesis by summarizing, that the Bioactive glass used as a bone implant in rats, bonded to bone by the formation of hydroxyapatite (HA) and its subsequent chemical bonding with the collagen fibrils produced by osteoblasts at the bone-implant interface, demonstrated by transmission electron microscopy (TEM)². Later studies involving both in-vitro and in-vivo observations also concluded that the Bioactive glass (BG)

with a specific composition formed a stable bond to bone in other higher vertebrates as well².

The concept of bone bonding using the bioactive glass was further expanded and later studies led to the development of a large number of Bioactive materials that exhibited a range of bonding characteristics, such as rate of bond formation, bond strength and the thickness of bonding interface between BG and the living tissues¹⁶. These newer materials included Bioactive glass ceramics (Ceravital^R) and the stronger apatite-wollastonite (A/W) Bioactive glass ceramic which was developed by Kokubo and colleagues in Tokyo, Japan¹⁵. Other developments included synthetic hydroxyapatite (HA) and polyethylene-hydroxyapatite (PE-HA) bioactive composites for orthopedic applications^{16,17}.

STRUCTURE OF BIOACTIVE GLASS AND RELATED BIOACTIVITY

Bioactive glasses mainly consist of four fundamental components namely, silicon oxide, sodium oxide, calcium oxide and phosphorus pentoxide (Fig. 1). The original Bioglass^R used by Hench was called the 45S5 Bioglass^R which consisted of about silicon oxide (46.2 mol%), sodium

oxide (24.3 mol%), calcium oxide (26.9 mol%) and phosphorus pentoxide (2.6 mol%)^{4,18,19}. The network of BG is primarily formed by silica^{19,20}. The molecular structure of BG appears to be highly disrupted and consists of Q^2 chains of silica having two free oxygen atoms per silicon tetrahedron²¹.

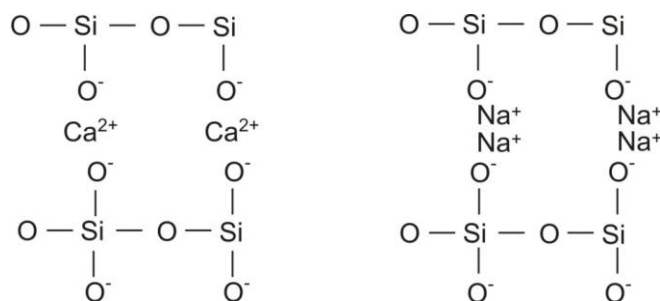


Fig. (1). Schematic presentation of silica chains in the glass structure²².

The structure appears to be disrupted by the presence of sodium and calcium ions that have also been referred to as “network-modifying cations” as they introduce the non-bridging oxygen bonds, and therefore, cause the dissolution of BG in aqueous environments^{19,23}. Another constituent of BG is phosphorus pentoxide (P_2O_5). It has been shown by nuclear magnetic resonance (^{31}P MAS-NMR), that phosphorus in BG can be associated with sodium or calcium ions, existing as either monophosphate or diphosphate complexes or both²⁴ and is not bound with the silica component²⁵. Furthermore, phosphate is not a key requirement for the bioactivity of BG; it mainly acts as a nucleation site for the crystallization of amorphous calcium phosphate. It has been shown by studies that BGs without phosphate exhibit both in-vitro and in-vivo bioactivity¹⁹.

The bioactivity of BG depends on various factors and the rate at which a given bioactive glass degrades in aqueous solutions depends on its composition. Bioactive glasses with a silica content greater than 60 mol% exhibit bio-inert behavior^{2,19,26}. It has been observed that the bioactivity of BG increases with the addition of phosphate²⁴ mainly because phosphate influences the ability of BG to form apatite in living tissues²⁵. The compositional characteristics responsible for the bioactivity of 45S5 BG are a low content of silicon oxide, high content of network modifiers (sodium and calcium oxides) as well as a high calcium oxide-phosphorus pentoxide ratio³. The composition of the 45S5 BG has been compared with those of the other bioactive glasses in Table 2.

Recent research has also shown that phosphate plays a significant role in enhancing the formation of fluorapatite (FAP) when incorporated in novel bioactive glasses containing fluoride²⁷. The bioactivity is also influenced by structural parameters such as network connectivity (NC), which has been described as the number of bridging bonds per silicon atom²³. Network connectivity (NC) of BG determines its solubility, which, in turn, impacts on the release of calcium and phosphate ions in solution²⁵.

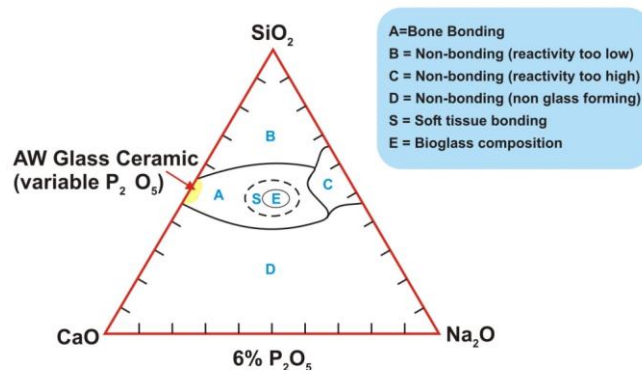


Fig. (2). Diagram illustrating the bioactivity of BG in terms of its composition².

The ability of BG to bond to bone and soft tissues has been illustrated by Hench in terms of a ternary phase diagram (Fig. 2)². It explains the bioactivity of BG and its bone and soft tissue bonding in relation to the relative compositions of silicon oxide, sodium oxide and calcium oxide while the percentage of phosphorus pentoxide is kept constant². It has been shown that the bioactive glass compositions corresponding to about 30-60 mol% silica, 10-50 mol% calcium oxide, 5-40 mol% sodium oxide and a constant phosphorus pentoxide content of 6 mol% are bioactive¹⁹. The composition of the original 45S5 Bioglass lies within the above mentioned parameters, shown by the region “E” in the ternary phase diagram².

DISSOLUTION OF BIOACTIVE GLASS IN PHYSIOLOGICAL ENVIRONMENTS

It has been explained that the bonding of 45S5 BG to bone occurs as a result of a layer of hydroxyl-carbonated apatite (HCA) that forms on the surface of BG when it comes into contact with living tissues^{3,28}. Hench has described a series of reactions that take place on the surface of a BG bone implant leading to the formation of hydroxyl-carbonated apatite (HCA)³. The reactions involve the

Table 2. Compositions of different bioactive glasses³.

	Na ₂ O	K ₂ O	MgO	CaO	SiO ₂	P ₂ O ₅	B ₂ O ₃
45S5	24.5	0	0	24.5	45.0	6.0	0
13-93	6.0	12.0	5.0	20.0	53.0	4.0	0
6P53B	10.3	2.8	10.2	18.0	52.7	6.0	0
58S	0	0	0	32.6	58.2	9.2	0
70S30C	0	0	0	28.6	71.4	0	0
13-93B1	5.8	11.7	4.9	19.5	34.4	3.8	19.9
13-93B1	5.5	11.1	4.6	18.5	0	3.7	56.6
P ₃₀ C ₃₅ N ₁₅	9.3	0	0	19.7	0	71.0	0

formation of silanol (Si-OH) groups on the BG surface, dissolution of silica and the formation of a layer of amorphous calcium phosphate (ACP), which, in turn, crystallizes as hydroxyl-carbonated apatite (HCA) due to the incorporation of hydroxyl and carbonate ions³. Adsorption of biological molecules such as growth factors takes place in the newly formed layer of hydroxyl-carbonated apatite (HCA). This is followed by the introduction of macrophages which prepare the site of BG implant for tissue repair. Attachment of osteoblast precursor cells takes place on the implant site leading to the differentiation of osteoblasts and resultantly new bone formation takes place^{14,29}.

Two classes of bioactivity of BG have been described²⁹. These depend on the type and the rate of response of host tissues towards the bioactive implant. Bioactive glasses that exhibit the fastest rate of bonding to bone correspond to Class A bioactivity and have been termed as “osteopductive”^{14,29}. In comparison, bioactive materials corresponding to Class B bioactivity have been termed “osteoconductive” and require more time to elicit host cellular response¹⁴.

FABRICATION OF BIOACTIVE GLASS (BG)

Mainly two different methods have been employed to synthesize BG for various applications¹⁸. Traditionally Bioactive glasses have been synthesized using the melt-quenching technique²³. The constituent oxides are melt in a platinum crucible at high temperatures (1300-1400°C) and are then quenched in water, dried and ground^{21,23,30}. In 1991 (Table 1), a chemical technique to synthesize BG was developed¹⁴. In the so-called “sol-gel route”, precursors such as tetraethyl orthosilicate (TEOS) and calcium nitrate (CN) have been used to form a gel consisting of BG nanoparticles (Fig. 2) at lower temperatures using green chemistry route²³. Bioactive glasses produced in this way have a more porous

structure and greater pore volumes. The greater surface area improves surface activity^{31,32} that is a practical advantage in addition to the lower temperatures.

BIO-DENTAL APPLICATIONS OF BIOACTIVE GLASS (BG)

Bioactive glasses possess wide ranging clinical applications in the field of medicine and dentistry. In medicine, it is commonly being used as a bone graft to promote osteogenesis whereas, in dentistry, it is frequently being used in dentifrices to treat dentin hypersensitivity (DH) and as a coating material of dental implants^{33,34}. Few of the common uses of BGs are explained here.

Bone Grafts

Bone grafts are used to substitute bone which has been lost due to infection, trauma or a disease process³⁵. BG has been used as a bone graft for over two decades now. It has superior osteoconductive properties and stimulates new bone growth over its surface³⁶. Previously, Oonshi *et al.*, conducted a study to compare the properties of hydroxyapatite (HA) and BG, when they are used as a bone graft in an animal model and it was concluded that BG is not only easier to manipulate, but also restores the bone within 2 weeks as compared to HAP, which took 12 weeks to generate an equivalent response³⁷. In another extensive literature review which reported results from various long-term follow up studies, it was also concluded that the use of BG as a bone graft demonstrated excellent bone healing properties³⁸.

Bone Regeneration

BGs have got an admirable ability to regenerate bone and many studies have provided evidence of this. Felipe *et al.* performed a study in dogs and reported that the use of BG

initiated mineralized bone formation³⁹. In another histological study, two different composition of BG (PerioGlas and BioGran) were used to evaluate bone formation in surgically created defects in the tibiae of rats⁴⁰. It was concluded from the results of this study that both compositions of BG promoted comparable bone formation demonstrating their excellent osteoconductive properties.

Antimicrobial Agent and Disinfectant

Antimicrobial agents are commonly used for various dental procedure such as endodontic^{41,42} and periodontic treatments^{43,44}. The use of BG can increase the pH of the aqueous solution and generate antimicrobial effects. It has been previously reported that BG can be inserted into periodontal defects and it inhibits bacterial colonization by providing calcium ions to the defective area and by raising pH⁴⁵. During endodontic procedures, BG can be also be used as a topical disinfectant and this use has demonstrated no adverse effects on dentin stability⁴⁶.

Coating for Dental Implants

Bioactive implant coatings are commonly used to enhance the osseointegration with alveolar bone. For instance, HA is usually sprayed onto the external surface of dental implants to promote osseointegration but its adherence to the metal surface of implant is not perfect⁴⁷. The use of BG as a coating material for dental implants has produced better results in terms of adherence to the metal surface of implant and bone regeneration⁴⁸, but still, more research is needed in this area.

Treating Dentin Hypersensitivity (DH)

One of the most common treatment options to manage DH is to block the exposed dentinal tubules with a material which can endure environmental adversities. Since human bone and dentin are very similar in composition, it can be anticipated that a material which forms an intimate bond with the bone will also form the same with the dentin⁴⁹. A recent in-vitro scanning electron microscope (SEM) study conducted on human dentin discs has demonstrated superior tubule occlusion properties of BG as compared to the regular fluoride containing dentifrice, both pre- and post-citric acid challenge⁵⁰.

Treating Gingivitis

Many researchers are interested in the anti-gingivitis role of BG. It has been demonstrated previously in an in-vivo study that BG dentifrice demonstrated superior anti-plaque and anti-gingivitis effects and decreased gingival bleeding as compared to a placebo dentifrice⁵¹. In another study

conducted on human subjects having gingivitis, the topical application of BG reduced the signs of gingival inflammation⁵².

Abrasive Material in Dental air Abrasion Machine

Alumina particles used in the dental air abrasion system could be toxic if inhaled⁵³. It has been demonstrated earlier that inhalation of BG causes insignificant pulmonary changes and the particles are also safely excreted⁵⁴. BG has got the ability to replace alumina in the air abrasion machine and its use produces less damage of dental enamel⁵⁵. Previously, Farooq I *et al.*, synthesized different new compositions of melt derived BGs containing fluoride and demonstrated comparable cutting results of alumina and new BGs, when they were used in air abrasion machine to cut human enamel⁵⁶. In addition to cutting, the apatite formation for these new compositions of BGs in Tris buffer within 6 h, implicating their potential to promote tooth remineralization⁵⁶.

CONCLUSIONS

Research concerning bioactive glass has been successful and reliable for clinical applications. The bioactivity resulted in an improved interaction of these materials while performing in the biological environment; for example, potential to induce remineralization, improved osseointegration and cellular activity during regenerative dentistry. In order to improve the properties of existing bioactive materials and enhance their potentials clinical applications in dentistry, more *in vivo* research and clinical trials are required.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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