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Bioactive Glasses in Dentistry: A Review

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Abstract

Bioactive glasses are silicate-based and can form a strong chemical bond with the tissues. These biomaterials are highly biocompatible and can form a hydroxyapatite layer when implanted in the body or soaked in the simulated body fluid. Due to several disadvantages, conventional glass processing method including melting of glass components, is replaced by sol-gel method with a large number of benefits such as low processing temperature, higher purity and homogeneity and therefore better control of bioactivity. Bioactive glasses have a wide range of applications, particularly in dentistry. These glasses can be used as particulates or monolithic shapes and porous or dense constructs in different applications such as remineralization or hypersensitivity treatment. Some properties of bioactive glasses such as antibacterial properties can be promoted by adding different elements into the glass. Bioactive glasses can also be used to modify different biocompatible materials that need to be bioactive. This study reviews the significant developments of bioactive glasses in clinical application, especially dentistry. Furthermore, we will discuss the field of bioactive glasses from beginning to the current developments, which includes processing methods, applications, and properties of these glasses.

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1. Introduction of bioactive glass

Bioactive glasses are a group of biomaterials which are used in the fields of dentistry and orthopedics. Forty five years ago, these glasses modified the functions and capabilities of biomaterials from bioinert to bioactive by stimulating a strong response after implanting in the human body (e.g. osteoproductivity) [1]. A material can be classified as bioactive if the above-mentioned biological response results in formation of a strong chemical bond between the implanted material and a soft or hard tissue [2]. Certain compositions of the silicate-based glasses, with calcium and phosphorus in proportions identical to those of natural bone, can form such a strong bond without an intervening fibrous layer [3]. When the glass contains more than 60% SiO_2, bonding to tissues is no longer observed [4]. On the other hand, it is expected that bioactivity increases with the amount of CaO in the composition, because the dissolution of the calcium ion from the glass plays an important role in formation of the chemical bond [5].

Results of in vivo implantation of bioactive glasses show that these materials produce no toxicity, no inflammation, and no foreign-body response [6]. In fact, these glasses bond with the bone through formation of a hydroxyapatite (HAp) layer. The same HAp layer is formed on the surfaces of these materials after soaking in the simulated body fluid (SBF) which has ion concentrations similar to the human blood plasma [7].

Hench at the University of Florida introduced the first bioactive glass in 1969 [3]. Those days, the available implant materials (metals and polymers) designed to be bioinert had a problem; they initiated fibrous encapsulation after implantation, rather than forming a

stable bond with the tissues. Hench began his work to overcome this problem by finding a material that could bond to the bone and survive the harsh environment of the human body. He tried making a degradable glass in the Na_2O-CaO-SiO_2-P_2O_5 system with high calcium content [3]. He discovered such glass with the composition of 46.1 mol.% SiO_2, 24.4 mol.% Na_2O, 26.9 mol.% CaO and 2.6 mol.% P_2O_5 (later termed 45S5 and Bioglass®) which formed a bond with the bone so tightly that it could not be removed without breaking the bone. In fact, this glass bonds with bone rapidly and stimulates bone growth away from the bone-implant interface. This bone bonding is the result of HAp layer formation on the surface of the glass, following initial glass dissolution [2]. This discovery was the introduction of the field of bioactive ceramics and the beginning of the formation of many new materials such as synthetic hydroxyapatite (HAp) and other calcium phosphates [8]. All glasses, glass-ceramics and ceramics that are used as implant materials are called "bioceramics" but "Bioglass®" is referred to as the original 45S5 composition and should not be used as a general term for bioactive glasses [9]. Table 1 presents the compositions of the bioactive glasses mentioned in this review.

Table 1: Compositions of three types of bioactive glasses.

Name	Composition
45S5 (Bioglass®)	46.1 mol.% SiO_2, 24.4 mol.% Na_2O, 26.9 mol.% CaO and 2.6 mol.% P_2O_5
58S (Sol-gel derived)	60 mol.% SiO_2, 36 mol.% CaO and 4 mol.% P_2O_5
S53P4	53 mol.% SiO_2, 23 mol.% Na_2O, 20 mol.% CaO and 4 mol.% P_2O_5

2. The mechanism of HAp layer formation on bioactive glasses

Hydroxyapatite is similar to the bone mineral and can interact with collagen fibrils of damaged bone to bond with it. Protein adsorption, incorporation of collagen fibrils, attachment of bone progenitor cells, cell differentiation, the excretion of bone extracellular matrix and its mineralization are involved in the formation of HAp layer-bone bond. Osteogenesis, due to the dissolution products of the glass on osteoprogenitor cells, stimulates new bone growth [10].

The mechanism of HAp layer formation on bioactive glasses has been widely studied in vitro and in vivo. This process involves different stages; calcium ions dissolve from the bioactive glass into the body fluid while a silica-rich interlayer forms on the glass surfaces. The nucleation of HAp is now possible because the surrounding fluid is supersaturated with respect to HAp due to the dissolution of the calcium ions. In addition, silica-rich interlayer dissolves a considerable amount of silicate ion and provides favorable sites for the nucleation. The process of nucleation and growth of the HAp layer continues by the reactions of the calcium, phosphate, and hydroxide ions. It is possible that carbonate or fluoride anions incorporate in the reactions, as well [3,9,11].

In 1980, Hench showed that the in vivo formation of the HAp layer can be reproduced in Tris buffer solution at pH 7.4. Later, Kokubo and Hench independently confirmed that apatite can form on the surface of Bioglass® in SBF. In 1991, it was suggested that a simulated body fluid (SBF) which has the ion concentrations equal to human blood plasma can reproduce HAp formation [3]. Thin film X-ray diffraction (TF-XRD), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were used to confirm the similarity of the composition and structure of HAp formed in SBF to the bone mineral [12]. Hence, immersion in SBF can be used for in vivo bone bioactivity prediction before animal testing; this reduces the number of animals used and the duration of experiments and, therefore, increases the possibility of the development of new types of bioactive materials [3].

SBF is a solution that simulates human blood plasma with ion compositions similar to human blood, but without any proteins, hormones, glucose, or vitamins [13]. During immersion in SBF, different processes occur simultaneously which result in structural and chemical changes to the surface of the material. These processes are leaching, degradation, and precipitation [14]. In the leaching process, through the exchange of the cations H^+ and H_3O^+, metal ions like Na^+ and Ca^{2+} are released and the pH at the interface increases up to 7.4. In parallel, hydroxyl ions locally break the silica-oxygen bonding. Then, silicon as silicic acid, $Si(OH)_4$, is released into the solution. The hydrated silicic acid on the surface is surrounded by at least one hydroxy group; subsequently, a silicic acid gel layer forms. Simultaneously, the glass releases calcium and phosphorus and an amorphous calcium phosphate-rich phase is formed on the surface. The CaP phase then crystallizes into a hydroxyapatite (HAp) structure [14].

3. Processing methods

For years, conventional glass technology has been used to produce bioactive glasses. Mixture of oxides or carbonates grains, as the glass components, are melted in a platinum crucible and homogenized at high temperatures up to 1250-1400°C. Then, to produce a bulk implant, the molten glass is cast into steel or graphite mold. For the required tolerance, a final grind and polish is often necessary. Sometimes, bioactive glass powders are required for some clinical applications such as treatment of periodontal lesions. In conventional glass technology, the molten glass is poured into water or other liquid medium to produce small fragments. To achieve powders with specific size ranges for periodontal treatment, subsequent grinding is necessary [4].

Producing bioactive glasses by conventional glass technology has several disadvantages as listed below (***A-D***). ***A:*** Very high purity is necessary for optimal bioactivity which is difficult to maintain in this method due to the high temperatures of processing, the low

silica and high alkali content of the traditional bioactive glass compositions. Such glasses are very reactive and can dissolve platinum and take other multiple cations as impurities [4]. Gross and Strunz [15] have shown that M^{3+}, M^{4+}, and M^{5+} impurity cations in bioactive glasses have considerable effects on tissue bonding. Greenspan and Hench [16] have revealed how bone bonding is sensitive to a small amount of $A1^{3+}$ in bioactive glasses. Evaporation of P_2O_5 at high temperatures may also result in composition uncertainty in the conventional method [17]. ***B:*** Bioactive powders are exposed to contaminants during the conventional glass processing which exerts negative effects on bioactivity. ***C:*** Conventional method imposes a compositional limitation on bioactive glasses; this is because of very high liquidus temperature of SiO_2 and very high viscosity of silicate melts with high SiO_2 content. ***D:*** The increased production costs of this method is considerable which is due to high-temperature processing in platinum crucibles, multiple handling steps, capital equipment, labor, maintenance, quality assurance, and quality control [4].

Low-temperature sol-gel processing offers a favorable alternative to conventional glass processing, which considerably reduces the costs due to lowering the processing temperatures [4]. This process has become an attractive research field during 1980s [18]. Mixing the metal alkoxides in the solution to synthesize an inorganic network, hydrolysis, gelation, and low-temperature firing are the steps for producing a sol-gel derived glass [19]. The microscopic structure of such glass can be modified by controlling monomer precursor, reaction temperatures, water to alkoxide ratio, and catalyst [5]. In sol-gel process, many disadvantages of conventional method can be eliminated and the purity which is resulted from processing at low temperatures (600-700ºC) can be controlled. The advantages of this method include ease of powder production, a broader range and a better control of bioactivity, high homogeneity, good control of particles size and morphology and the easy preparation of thin films and coatings [4,5].

The sol-gel derived bioactive glass has a porous structure which increases its specific surface area by two orders of magnitude compared to a melt-derived glass of a similar composition. Therefore, the rate of the surface of HAp formation for the sol-gel based materials is more rapid. The recognition that the high surface-area is favorable for the formation of the HAp layer bonding led to application of the sol-gel process to create bioactive glasses [5]. A ternary bioactive glass with a starting surface area greater than 150 m^2/g was produced by Li *et al.*, [4] and used for bone graft applications. Greenspan *et al.* [20] demonstrated that bioactive glasses with surface areas greater than 50 m^2/g could bond to the bone and soft tissue within 24 h of in vitro experiment.

Production of a two (CaO and SiO_2), three (SiO_2–CaO–P_2O_5 , SiO_2–CaO–Na_2O , P_2O_5–CaO–Na_2O) or even four (SiO_2–CaO–P_2O_5–Ag_2O) component bioactive glass has been conducted through sol-gel method [21]. Sol-gel method allows the production of other glass ceramics such as SiO_2–CaO–P_2O_5, SiO_2–P_2O_5–Al_2O_3–CaO–Na_2O–K_2O [22]. On the surface of these glasses, the formation and the rapid increase of the thickness of HAp layer were observed as a result of contact with Tris buffer and simulated body fluid (SBF). This is an indication of the high bioactivity of the gel-derived glasses [23].

Difficulty to obtain crack-free bioactive glass monoliths, greater than 1 cm in diameter, is the disadvantage of sol–gel synthesis. The large shrinkage during drying stage and the evaporation of the liquid by-products are two reasons of the cracking. The vapor must pass through the interconnected pore network from inside to the surface, which can create capillary stresses and, therefore, cracking. For powders, these stresses are small because the path of evaporation is short and the material can accommodate the stresses. For monoliths, the path from the center to the surface is long and twisty, and the drying stresses can lead to fracture. Narrow distribution pores with increasing size can reduce this problem [9].

4. The applications of bioactive glass

In 1986, a bioactive glass was successfully used as middle ear prosthesis to repair conductive hearing loss and it was the first clinical application of such material. In tooth extraction, bioactive glasses have been used to preserve the height of the alveolar ridge [24]. Bioactive glasses also have been used for spinal fusion, reconstruction of the iliac crest following autograft harvesting, and for filling bony defects in a number of orthopedic procedures. These early clinical applications confirmed the benefits of this material as highly compatible implants [25]. More recent application of bioactive glasses include coatings for orthopedic metallic implants, trabecular coatings, bone replacement, periodontology, endodontology, scaffolds for bone tissue engineering, regenerative medicine, and composite based scaffolds [26,27].

Different forms of bioactive glasses including particles, porous scaffolds, or dense constructs have been used in clinical applications, such as dentistry [9]. In the following section, some applications and products of the original Bioglass®, as the first introduced bioactive glass, will be discussed. Table 2, presents these products and some of their applications.

** Medical Devices with Monolithic shape*

In 1988, a simple cone of Bioglass®, termed the Endosseous Ridge Maintenance Implant (ERMI®), was the commercial Bioglass® device in dentistry. To repair the tooth roots and to provide a stable ridge for dentures, such devices were inserted into fresh tooth extraction sites. They were highly stable and much better than HAp tooth root implants. However, this product did not gain commercial success because surgeons prefer to be able to cut the implant to shape rather than be limited to cones of fixed size.

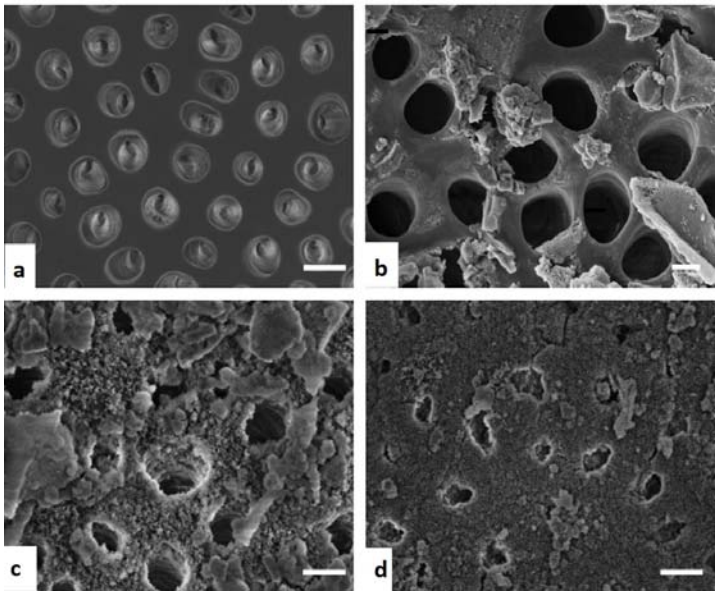

Figure 1. SEM micrographs of human dentine (bar = 1 µm): (a) untreated, (b) immediately after application of NovaMin® in artificial saliva (AS); (c) 24 h after application of NovaMin® in AS; (d) 5 days after application. SEM images are adapted from Earl *et al.* [39].

Internationally, products based on particles rather than monolithic shapes are in commercial use [24].

* *Particulates of Bioactive Glass*

Surgeons and dentists often prefer to use particles or granules instead of monoliths, as they can press them easily to fill a defect. In 1993, Perio-Glas® (NovaBone Products LLC, Alachua, Florida) as the first particulate bioactive glass with the particle sizes of 90–710 µm was introduced for the repair of bony defects of the jaw and bone loss arising from periodontal disease. In vivo and clinical studies [28-30] showed a great success of Perio-Glas® in treatments of defects filled with new bone compared to controls. The regenerative properties for infra-bony defects can be enhanced with low-level laser therapy postoperatively [31]. Another application of Perio-Glas® is in "guided tissue regeneration", which has been used with polymeric membranes [32]. Perio-Glas® can also be used to produce bioactive glass slurry with applications in root canal sterilization tools prior to insertion of implants and raising pH to bactericidal levels in addition to its bioactive properties [33]. Other products, which have been used as bone graft in dentistry and orthopaedic, are Biogran® (BIOMET 3i, Palm Beach Gardens, Florida) and BonAlive® (BonAlive Biomaterials, Turku, Finland) [9,34].

**Using Bioactive Glass for Treatment of Hypersensitivity*

A very fine Bioglass® particulate called NovaMin® (NovaMin Technology, GlaxoSmithKline, Florida, UK), with a particle size of ~18 µm is used as an active repair agent in toothpaste. This material mineralizes tiny holes in the dentine and reduces the sensitivity of the tooth. Dentin hypersensitivity (DH) is an oral problem which is attributed to the root surface exposure due to periodontal disease, toothbrush abrasion or cyclic loading fatigue of the thin enamel near the cemento-enamel junction [35]. The hydrodynamic theory about DH mechanism proposes that when external stimuli such as cold, hot, tactile or osmotic pressure are applied to the exposed dentin, they cause fluid movement within the dentinal tubules. These open tubules allow the fluid to flow through the tubules, which may result in pressure changes that excite the nerve endings in the dental pulp and DH occurs [36].

When these kinds of toothpastes are used, Bioglass® particles adhere to the dentine and form an HAp layer; therefore, blocking of the tubules relieves the pain for longer periods. In a clinical trial of 100 volunteers who brushed twice daily with a NovaMin®-containing toothpaste over the 6-week period, gingival bleeding and plaque growth reduced 58.8% and 16.4% respectively in comparison with the control groups who used normal toothpaste [37]. Another clinical trial has shown improved pain relief when brushing with a NovaMin®-containing toothpaste for 2-6 weeks compared to brushing with a toothpaste containing potassium nitrate [38].

Despite brushing only for a few minutes a day, the Bioglass® particles stimulate long-term repair, which results from the fact that these particles attach to the dentine. For in vitro trials, human dentine is lightly etched to reveal the tubules. Figure 1-b shows the dentine immediately after the application of NovaMin®. After 24 h, the particles are attached to the dentine and HAp layer covers the surface. This shows that NovaMin® stimulates the deposition of calcium phosphate over the dentine tubules. In fact, the glass dissolution products stimulate the mineralization. Dissolution of the glass in the mouth raises pH, which leads to promotion of HAp deposition [39].

The sol-gel derived bioactive particles are also us-

ed in treatment of hypersensitivity. The trials have shown that 24 h after using toothpaste containing the sol–gel and after washing with cola, juice, coffee and further brushing, the tubules remain occluded [40].

Toothpaste is not the only dental care application of Bioglass®; NovaMin® can repair the enamel sensitivity due to bleaching treatments of the teeth [39]. For whitening the teeth, dentists use air polishing using particles as abrasives to remove the stains. Air polishing with Bioglass® can stimulate mineralization of the dentine tubules in a similar mechanism to that of NovaMin®-containing toothpaste, which resulted in 44% reduction of tooth sensitivity compared to other air polishing powders, such as sodium bicarbonate. Teeth treated with the Bioglass® were also whiter than those
treated with sodium bicarbonate [41].

**Remineralization Using Bioactive Glass*

Demineralization and remineralization are natural processes which continuously occur for teeth. Physiological processes as well as bacterial acids and foods cause demineralization, while remineralization results from the deposition of mineral (calcium and phosphorous) from saliva or oral fluid. Since natural remineralization is not enough for having strong enamel, bioactive glasses are used to augment the process. Bioactive glasses have unique remineralizing properties and are generally introduced into various dentifrices as very fine particles to provide calcium and phosphorus to the tooth surface [42].

The first study on dentin remineralization by a bioactive glass was conducted by Wang *et al.* [43]. In this study, after artificial demineralization with EDTA (ethylene-diamine-tetraacetic acid), the treatment with nanoparticulate bioactive glass was compared to the treatment with conventional, micron-sized material (PerioGlas®). The results showed that nanoparticulate bioactive glass resulted in a noticeable increase in mineral content suggested a rapid remineralization of the samples. This result confirmed the critical role of particle size and specific surface area. However, these samples are mechanically unstable, unless the precipitated mineral forms a composite material with the collagen matrix of the samples [43]. In addition, investigations on bioactive glass-containing toothpaste show significant reduction in dentine permeability and excellent resistance to acid challenge which can be beneficial for hypersensitivity and remineralization treatments [44].

In 2014, Mehta *et al.* showed that bioactive glass (Novamin®) and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) successfully remineralized early enamel caries. However, Novamin® remineralized the carious lesion more effectively. CPP-ACP had an amorphous nature and couldn't properly adhere to the enamel surface. This also led to lower hardness value for CPP-ACP, while Novamin® showed higher values of hardness because it attached to the surface more compactly [45]. In another study, it was confirmed that bioactive glass is an effective remineralizing agent as the effects of bioactive-containing products were investigated on remineralization of artificial induced carious enamel lesion [46].

**Bioactive Glass Coatings*

As metals are bioinert, the metallic implants are encapsulated with fibrous tissue after implantation and cannot attach to tissue which shows serious need of such implants to bioactive coatings. The hydroxyapatite layer forms on bioactive glass coatings as a result of dissolution and improves the bonding of implants to the host bone. The problem is that a highly bioactive coating may degrade over time and result in instability of the metallic implant in the long term. Perhaps, the dental field is the best application for bioactive glass coatings, e.g. on titanium implants with screw threads. However, it should be noted that the thermal expansion coefficient of the glass and the metal must match to prevent the glass pulling away from the metal during the processing [47]. For instance, the thermal expansion coefficient of the Bioglass® and titanium don't match. In order to address such problem, for example, in the SiO_2–CaO–MgO–Na_2O–K_2O–P_2O_5 system, the Na_2O and CaO are replaced with K_2O and MgO, respectively to modify the thermal expansion coefficient [48]. Another example is coating with the following composition (by weight): 53% SiO_2, 6% Na_2O, 22% CaO, 11% K_2O, 5% MgO, 2% P_2O_5, and 1% B2O3 on titanium implants, which were first tested in rabbit femurs [49]. Compared to non-coated implants, more bone grew on the coated implants. By using appropriate compositions, the mismatch of thermal expansion coefficients doesn't make any problem and bioactive glasses can successfully be used as coatings.

Table 2: Name and application of some products of the original Bioglass® and their applications

Product	Applications
ERMI®	Repair of the tooth roots and providing a stable ridge for dentures
Perio-Glas®	Repair of bony defects of the jaw and bone loss arising from periodontal disease- Guided tissue regeneration- Root canal sterilization tools
Biogran®	Bone graft
BonAlive®	Bone graft
NovaMin®	Active repair agent in toothpaste for hypersensitivity treatment- Repair of the enamel sensitivity due to bleaching treatments of the teeth- Remineralizing agent

5. Antibacterial properties

During dissolution of bioactive glass, the pH rises due to cation release and such condition can kill the microbes [1]. For instance, an in vitro study showed that S53P4, as one kind of bioactive glass, can kill pathogens connected with enamel caries (Streptococcus mutans), root caries (Actinomyces naeslundii, S. mutans) and periodontitis (e.g. Actinobacillus actinomycetemcomitas) [50]. S53P4 and other compo-

sitions of bioactive glass with concentrations higher than 50 mg ml^{-1} in the broth cultures of 16 different bacteria showed antibacterial properties due to the pH increase [50]. It is postulated that an ideal bioactive glass material includes antibacterial elements which prevent infections and reduce the post-operative sensitivity. The widely considered elements for this purpose are metals which have bioactivity against microorganisms and can overcome the problems related with the low stability of other organic antimicrobial compounds during the biomaterial processing [51].

Silver is one of the elements known as antimicrobial. Silver ions can easily be introduced into a glass and then released during dissolution. The sol-gel-derived composition of 76 % SiO_2, 19% CaO, 2% P_2O_5 and 3% Ag_2O (by weight) is the first antibacterial glass which contains silver [52]. Less than 1 mg ml^{-1} of this glass in culture is needed to kill bacteria such as Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus, compared to 50 mg ml^{-1} of silver-free glasses to be bactericidal. It is noteworthy that the low concentrations of the sol-gel glass that can be bactericidal are not toxic to human osteoblasts [53]. Silver-containing sol-gel glasses have a limitation in their synthesis as it must be conducted under infrared radiation and the glass must be stored in the dark to prevent the silver nitrate precursor and Ag_2O reducing to silver metal. This not only increases the cost of production, but also complicates the surgical procedures. Silver-doped melt-derived glasses have also improved bactericidal properties compared to silver-free equivalent glasses. Nanoparticles of Bioglass® can kill Enterococcus faecalis, a micro-organism associated with failed root canal treatments [54].

Copper and its alloys, such as brass, bronz, copper-nickel and copper-nickel-zinc can also be used in antimicrobial applications. The strong antimicrobial ions of copper can be doped to different matrices such as polymers or ceramics [55,56]. Copper not only is an excellent antimicrobial agent but also has an essential role in bone formation and healing. This metal can also stimulate wound healing responses and improves the vascular density in and around subcutaneously implanted allografts and hyaluronan based hydrogel. Copper sulfate can induce the formation of cord-like and tubular structures and potentiate the effect of endogenous growth factors, which makes it a perfect additive for blood vessel ingrowth [57]. Cellular copper can be regarded as an angiogenic agent because of its remarkable distributions in human endothelial cells during their angiogenesis. This ion can also stimulate the endothelial cell proliferation and suppress osteoclast activity [58]. Moreover, elastin matrix deposition can be stimulated by this metal because elastin fibrils can aggregate into mature fibers when copper ions are released from nanoparticles [59].

Zinc is another metal which is thought to have antibacterial properties and beneficial cellular response, but it can also cause toxicity [60]. Because of anti-inflammatory and antimicrobial properties, dentifrices with 2% zinc citrate have been used in the treatment of poor gingival health [61].

6. Mechanical properties

The application of bioactive glasses, due to their low mechanical strength and inherent brittleness, has been limited to non-load-bearing parts such as ossicles in the middle ear. Incorporation of nitrogen into the silicate network can address the problem of low strength in glasses. When oxygen is replaced by nitrogen in alumino-silicate glasses, elastic modulus and hardness increase linearly with nitrogen content; however, glass transition temperature increases, as well. Incorporation of nitrogen also results in greater slow crack growth resistance, modest gains in fracture resistance, and increased viscosities [62]. Addition of both fluorine and nitrogen can increase the mechanical properties as fluorine induces considerable reductions in both glass melting temperatures (T_m) and glass transition temperatures (T_g) while elastic modulus and hardness increase with nitrogen incorporation but they are unaffected by fluorine incorporation. The dissolution of nitrogen into the glass melt is also facilitated by fluorine [63].

7. Effects of different ion doping on other properties of bioactive glass

In addition to antibacterial and mechanical properties of bioactive glass, other properties can also be affected by adding different ions which make the material more compatible for different clinical applications.

**Effect of strontium*

Strontium is a bone-seeking agent, able to impact bone cells which can be substituted for calcium in bioactive glass for better bone bonding and osteoblast stimulation, with anabolic and anti-catabolic properties. For treatment of osteoporosis, strontium ranelate and strontium chloride can be used. Osteoblast proliferation can be promoted by strontium-substituted Bioglass® which also decreases the osteoclast activity in the cell culture [64].

**Effect of phosphate*

Increasing phosphate which is present in bioactive glasses as orthophosphate, aids in maintaining the network connectivity. In fluoride-containing glasses, the formation of flourapatite at low pH is favored by increasing P_2O_5 and this is more favorable for clinical applications of dentistry and orthopedics [65].

**Effect of fluoride*

Fluoride can inhibit the demineralization of the enamel and dentin, enhance remineralization, and inhibit bacterial enzyme; hence, it prevents dental decay and improves the oral health [66].

**Effect of zinc*

Zinc is a fundamental ion that improves bone-bonding of glass, inhibits bone resorption, controls cell growth, differentiation, and development and stimulates protein synthesis. Slow skeletal growth and alterations in bone calcification can result from zinc deficiency [60].

8. Modification of dental ceramics with a bioactive glass

Dental ceramics should have specific properties, such as high strength, fracture toughness, wear resistance, similarity with natural tooth structure and long life in the oral environment, in order to be used in restorative dentistry. To successfully place the fixed restorations in the oral environment, it is necessary to keep periodontal tissues healthy. Fixed restorations increase the local plaque accumulation, especially with poor oral hygiene, and lead to inflammation, loss of attachment and eventually periodontal tissue's breakdown. Existence of a marginal gap between the tooth and restoration which is exposed to oral bacteria results in pulp irritation or necrosis, secondary caries and cement dissolution, all being the common reasons of fixed prosthetic restoration failure [67].

It is impossible for ceramic materials to develop new attachment on their surface. Therefore, in spite of the ability of fixed ceramic restorations to regenerate the morphology and function of the damaged structure, they cannot completely attach to the periodontal tissue. In fact, conventional dental ceramics are biocompatible but not bioactive. Consequently, if these ceramics would be modified in a way that they could stimulate bioactive behavior around the fixed restorations margins and provide a bioactive surface, through the tissue regenerative techniques, they could develop periodontal tissue attachment and create complete sealing of the marginal gap. This sealing could prevent the failure of fixed ceramic restorations by eliminating secondary caries, micropenetration of the oral bacteria and their adhesion on cement surface [68].

It is expected that utilization of guided tissue regeneration techniques in the field of dental ceramics can provide solutions to address fixed prosthetic restorations failure. This technique can result in formation of new attachments on the tooth surfaces (e.g. cementum) or on implant surfaces (Titanium, hydroxyapatite, etc.). Therefore, if dental ceramics could exhibit a cement-like behavior, the biological surface required for attachment of the cells would be provided and tissue attachment would be promoted. Formation of apatite on the dental ceramic surface can enhance the tissue attachment because cementum consists of biological hydroxyapatite [69].

As mentioned before, bioactive glasses can restore osseous defects and develop a new attachment on tooth surfaces. The strong and stable bonding results from development of a hydroxyapatite layer, similar to that of the bone, on the surface after inclusion into biological environment. Sometimes, biological apatites include traces of inorganic elements that can be substituted in the apatite lattice or adsorbed on the apatite surface. Bioactive materials can form this biological apatite on their surface in vitro under various soaking conditions [7].

Development of apatite on the dental ceramic surfaces through modification with bioactive glasses has been tried by several researchers. In 2003, a dental ceramic was coated by a bioactive glass and after immersion in SBF, the growth of a well-attached apatite layer on the surface was observed [70]. Moreover, it was reported that the attachment and proliferation of human periodontal ligament cells can be supported by dental ceramic–bioactive glass mixtures [71].

As expected, sol-gel method can create a more porous surface which raises the dissolution rate and promotes apatite formation, so dental ceramic-bioactive glass mixture prepared by such method can accelerate the onset of HAp formation [72]. In 2010, two sol–gel derived materials were successfully produced for dental applications: a novel ceramic and a bioactive mixture (ceramic 30 wt.%-bioactive glass 58S 70 wt.%) with better control of composition, microstructure and properties due to high homogeneity provided by the sol-gel method, compared to melt-derived ceramics [22].

In melting powder preparation techniques, the surface reactivity of ceramics has been weakened by high reaction temperature, which results in high heterogeneity and loss of porosity and their surface area depends only on the particle size of the powders [21]. On the other hand, the sol-gel method provides control over the textural properties (specific surface area and porosity) and crystal structure which develops an optimized bioactive surface and also maintains the surface bioactivity over a wider composition range of silica content [73].

Conclusions

Bioactive glasses are able to bond to both soft and hard tissue and promote the bone growth. The bioactivity behavior of these glasses is related to the formation of a biologically active hydroxyapatite 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. These glasses are produced via two main methods, melting and sol-gel processing. The latter has many advantages which make it a favorable method in order to provide glasses with fine porous textures and enhanced bioactivity. Bioactive glasses have a wide range of applications, such as bone grafts, scaffolds, coating materials, and are used for hypersensitivity treatment. One of the most important properties of bioactive glasses is their ability to exhibit antibacterial activity, which creates a bacteria-free environment while healing and regenerating the defect area. The promotion of this ability is possible by doping antibacterial elements, such as silver, copper or zinc to such glasses. Another property of bioactive glasses is mechanical property which can be improved by introducing nitrogen and fluorine to the silicate network of the glasses. The other properties of bioactive glasses can also be altered by incorporation of different ions such as strontium and phosphates. These potentials of bioactive glass make it a unique material to be widely used in dentistry. For example,

modification of dental ceramics with sol-gel derives bioactive glasses is one of the most attractive applications of these glasses in dentistry. Such materials can stimulate bioactive behavior around the fixed restorations margins and provide a bioactive surface. Therefore, they can develop periodontal tissue attachment and create complete sealing of the marginal gap. This sealing can prevent the failure of fixed ceramic restorations by eliminating the secondary caries, micropenetration of oral bacteria and their adhesion on the cement surface.

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