〔REVIEW〕

Network modifiers of bioactive glasses : a review

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Abstract

Bioactive glasses (BGs) are biomaterials intended for applications including hard-tissue regeneration (orthopedics, dentistry, and maxillofacial areas), coatings, wound healing, and drug delivery. Network formers (NFs), network modifiers (NMs), and intermediate oxides (IOs) play key roles in the *in vitro* and *in vivo* performances of BGs. Understanding the influence of BG NMs on dissolution rate, hydroxycarbonate apatite layer formation, and therapeutic activity is fundamental to the development of new BGs. Generic BGs designed by dipping in several active ions have been proposed. This review provides an overview of the effects of NMs (e.g., strontium, magnesium, zinc, and copper) on BG properties and characteristics. Understanding the effects of NMs is essential for the formulation of novel BGs.

Introduction

Bioactive glasses (BGs) are amorphous bioactive materials that were first reported by Hench (Hench, 2006 ; Hench et al., 1971 ; Hench & Paschall, 1973). The components of BGs can be classified into network formers (NFs), network modifiers (NMs), and intermediate oxides (IOs) (Brauer, 2015) Figure 1 illustrates the general BG structure. NFs are components that form a glass network without the involvement of other materials by forming tetrahedra and oxygen triangles ; they include B_2O_3, SiO_2, GeO_2, P_2O_5, As_2O_3, Sb_2O_3, In_2O_3, Ti_2O_3, SnO_2, PbO_2, and SeO_2 (Lakes, 2003). Of these, the most widely studied are silica (SiO_2), boron trioxide (B_2O_3), and phosphorous pentoxide (P_2O_5) (Brauer, 2015). NMs can change glass structure by creating terminal oxygens called nonbridging oxygen atoms (NBOs) breaking down the glass network, some of the most common are CaO, Na_2O, SrO, B_2O_3, P_2O_5, etc. While IOs are the components able to function as NMs or NFs depending on the glass composition the most common are MgO and Al_2O_3 (Brauer, 2015).

BGs have a three-dimensional (3D) tetrahedral network structure in which an NF is linked with oxygen atoms via four covalent bonds ; these are known as bridging oxygen atoms (BOs) (Brauer, 2015 ; Hupa & Karlson, 2017). An NM changes the structure by forming ionic bonds with oxygen, thereby changing BOs into NBOs (Brauer, 2015 ; Hupa & Karlson, 2017) (figure 2). BG properties depend on the extent of bonds with NBOs and BOs.

There are many possibilities to classify the glasses, in this review, they are classified according to their composition system.

Types of Bioactive glasses based on the network formers

a. Silicate-based glasses

Silica is the NF in silicate-based BGs. Silicate-based BGs were first discovered by Hench in the late 1960s and are the most widely studied for bone regeneration systems and drug carriers due to the high valence of silicon. Silicate-based BGs have a tetrahedral structure (Figure 3a) with BOs, NBOs.

Their bioactivity, surface area, porosity, and pore size make silicate-based BGs particularly interesting for scaffolds and grafts. Nevertheless, some of their mechanical properties are insufficient for clinical application (Hench and Jones, 2015).

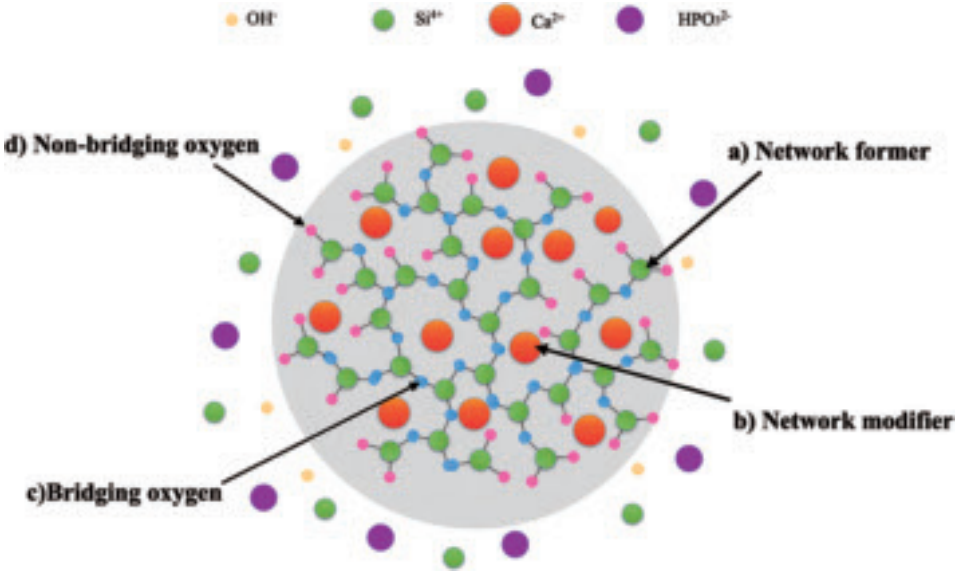

Figure 1 : Schematic representation of bioactive glass components. a) network former (NF), b) network modifier (NM), c) bridging oxygen atoms (BOs), and d) nonbridging oxygen atoms (NBOs).

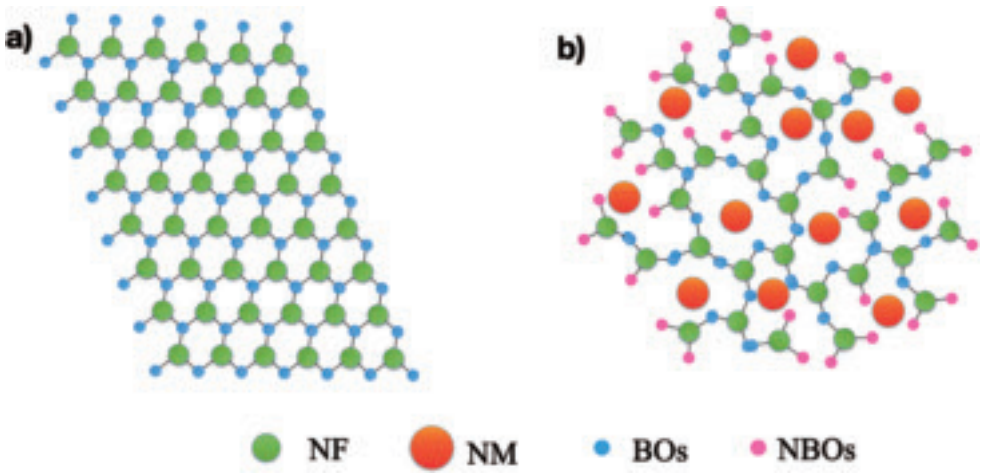

Figure 2 : Schematic representation of bioactive glass network structure a) tetrahedral structure without network modifiers and b) disruption of network by network modifier.

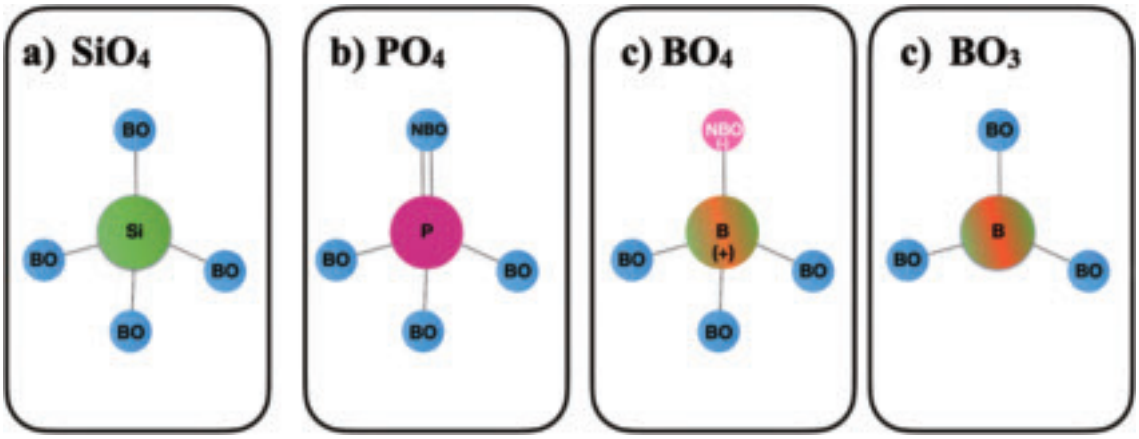

Figure 3 : Schematic representation of structure units that build up the silicate−(a), phosphate −(b), and borate− (c) glasses network.

b. Phosphate−based glasses

Phosphate−based BGs consist of an inorganic network of phosphate (PO_4^{3-}) tetrahedra, connected to a maximum of three other phosphate tetrahedra (figure 3b). Their synthesis is more challenging because the P_2O_5 precursor is very unstable and requires metal ions for stabilization (Jones, 2013 ; Skelton et al., 2007). The most used metal−oxides are Na_2O and CaO. The abilities of this class of glasses to completely dissolve and control the dissolution rate merit considerable interest (Deshmukh et al., 2020).

Phosphate−based BGs have applications in radiotherapy (Sene et al., 2008), hard−tissue regeneration, drug delivery, and wound healing (Mehrabi et al., 2020).

c. Borate−based glasses

Borate glasses comprise a network based on boron trioxide (B_2O_3). Their lower level of chemical stability results in faster dissolution and transformation into a hydroxycarbonate layer (HCA) (Deshmuck et al., 2020). HCA formation occurs by a process similar to that of silicate− and phosphate−based BGs. In contrast to silicate and phosphate−based glasses, the incorporation of modifier cations increases the network connectivity due to a transformation from neutral BO_3 into a negatively BO_4 balanced with the main cation (Hupa et al., 2017) (figure 3c). These glasses have a phenomenon called the “boron abnormally” referring to the no−linear change in network connectivity, meaning that an increase of oxide modifiers at some point increase the network connectivity, but higher addition will convert back into trigonal borate, decreasing the network connectivity (Hupa et al., 2017). Borate BGs can support cell proliferation and differentiation, exhibit high bioactivity (Lepry et al., 2015), and control dissolution rate (Fu et al., 2010). However, borate ion toxicity is the main concern of borate−based BGs ; some studies have noted that borate−based BGs are toxic in “static” *in vitro* conditions but not in “dynamic” *in vivo* conditions (Fu et al., 2010 ; Jung et al., 2012).

Bioactive glass’s structure

The structure of bioactive glass can be described in terms of network connectivity (NC). Network connectivity describes the short−range structure classified and represented by Q^n distribution, where Q symbolizes the network−forming polyhedron, and n corresponds to the number of bridging oxygens atoms connected to each polyhedron of the structure (0,1,2,3 and 4) Figure 4 schematically represent the NC values for silicate−, phosphate−, and borate−based BGs. The NC provides information concerning the degree of polymerization and enables the prediction of glass characteristics, such as crystallization tendency (Hill et al., 2011 ; O’Donnell, 2011), bioactivity (Eden, 2011 ; Hill et al., 2011), and polymerization (Eden, 2011). According to Deshmuhk (2020), a higher value of NC indicates a more connected network, although bioactivity properties diminish at higher NC values (Inert products have an NC value of Q^4). The desired value for good bioactivity is between Q^2

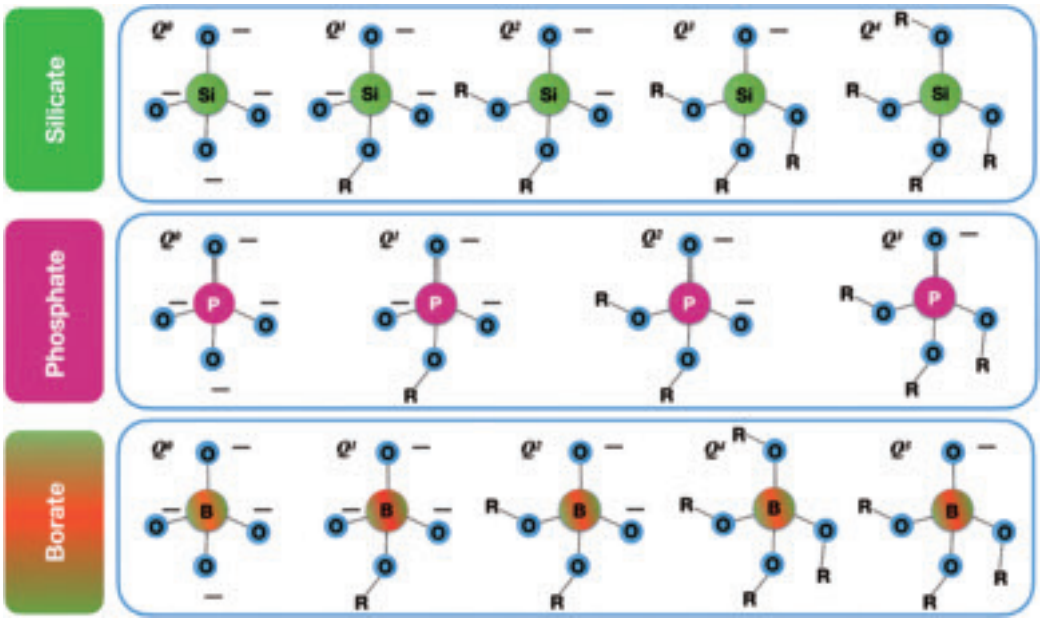

Figure 4 : Schematic representation of silicate−, phosphate−, and borate−based glasses structure unit in Qn..

and Q^3, a decrease in these values will weaken the 3D structure due to the small amount of bridging oxygen atoms, leading to easier disruption of the glass structure.

Since their discovery, many materials based on the original BG composition have been synthesized and extensive research has been conducted to understand their bioactivity mechanisms (Eden, 2011 ; Hench, 1991 ; 1998 ; 2015 ; Hench & Polak, 2002 ; Hench et al., 2004 ; Hill et al., 2011 ; Jones, 2013 ; O'Donnell, 2011).

BG bioactivity is strictly linked to partial dissolution of the network and surface reactivity. Partial dissolution leads to ion release and HCA layer formation on the surface. The HCA layer bonds with hard and soft tissues (Hench, 1991 ; 1998 ; 2015 ; Hench & Polak, 2002 ; Hench et al., 2004 ; Jones, 2013 ; Vichery et al., 2016). Figure 5 describes the mechanism of HCA layer formation.

Hitherto, the term "BG bioactivity" was exclusively used in the context of the repair and regeneration of hard tissue (Mehrabi et al., 2020). More recently, this concept has been broadened with potential applications to soft-tissue regeneration, such as wound healing (Gillete et al., 2001), spinal cord (Joo et al., 2012), muscle (Shah et al., 2005), and ligament repair (Bitar et al., 2005), lung tissue engineering (Verrier et al., 2004), gastrointestinal applications (Boccaccini et al., 2005), cardiac tissue regeneration (Chen et al., 2020), embolization of uterine fibroids (Kehoe et al., 2012), and cancer treatment (Chauhan et al., 2019).

BGs can be synthesized by methods such as melt quench (Hench et al., 1971), sol-gel (Deshmukh et al., 2020), sol-gel with coprecipitation (Jones et al., 2013), and sol-gel with irradiation (Deshmukh et al., 2020). The use of wet chemistry has provided a broader range of bioactive BGs with unique morphologies, sizes, porosities, and compositions (adding active ions) (Deshmukh et al., 2020).

The incorporation of active ions *via* intermediate oxides (IOs) influences the crystallization, morphology, crystallinity, solubility, thermal stability, and dissolution behavior of BGs. These IOs are also known as doping agents (DAs) ; they improve the mechanical characteristics of BGs and add therapeutic effects, allowing DA-doped BGs to serve as versatile tools for dentistry. Rigorous study and design of new compositions and *in vitro* testing of existing compositions are warranted.

Effect of doping agent on the bioactive glasses

During BGs synthesis, cationic DAs with ionic bonds to NBOs function as NMs. Following network modification, the dissolution rate changes according to the NC value (Figure 4). For the Q^1 case, the dissolution rate increases dramatically due to the weakness of the 3D BG structure. As the value approaches Q^4, the dissolution rate, and bioactivity decrease. Cations modify the internal structure and environment surrounding BGs particles. The size of each DA interferes with the 3D structure (opening or closing the network structure), thereby increasing or decreasing the glass dissolution rate. Table 1 proportionate a brief description of the DA

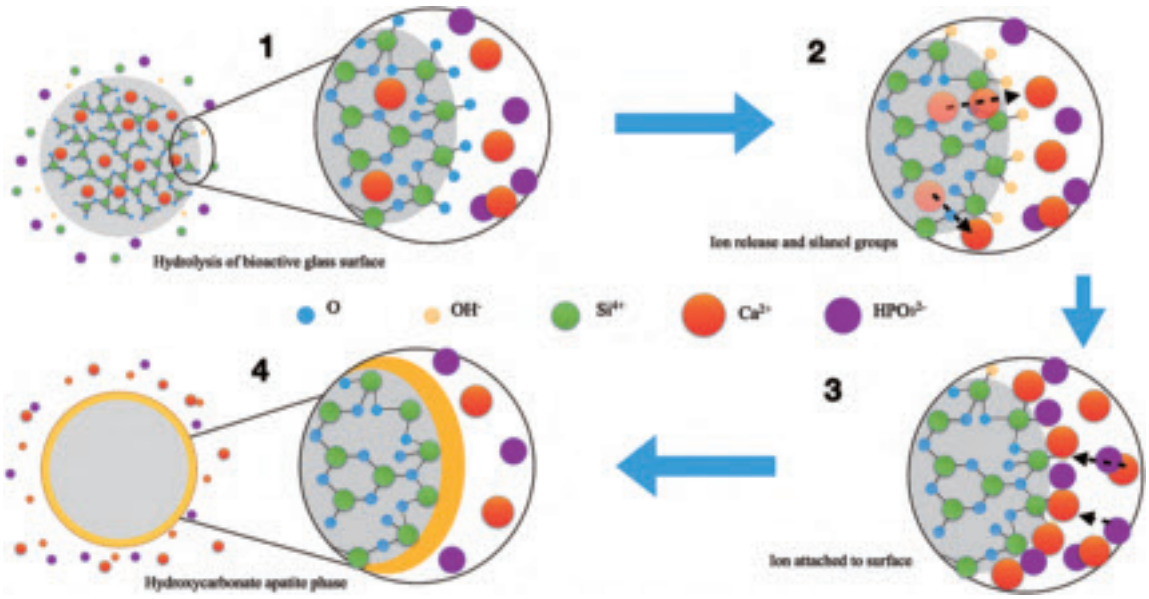

Figure 5 : Schematic illustration of hydroxycarbonate apatite layer formation on the surface of silica-based bioactive glass.

Table 1 : Doping agents' effects on bioactive glass network, cells, and tissues.

Ions	Function	Effect on BGs	Effect *in-vitro & in-vivo*	Reference
Calcium	NM	Disrupt Network bonding Forms octacalcium-phosphate	Osteogenesis Angiogenesis	Schumachaer et al., 2021
Phosphate	NM, NF	Network stability Forms octacalcium-phosphate	Osteogenesis Angiogenesis	Arcos et al., 2010
Sodium	NM	Hydroscopic behavior Bioactivity	pH control	Chen et al., 2017 Crovace et al., 2021.
Boron	NM, NF	Bioactivity Properties (Size pore, surface area)	Antibacterial Osteogenesis Vascular occlusion	Chang et al., 2020
Strontium	NM, IO	Bioactivity Decrease HCA in high quantities	Osteogenesis Antibacterial effect	Bauer et al., 2012
Zinc	NM, NF, IO	Decrease bioactivity Decrease surface area and pore size	Antibacterial Osteogenesis	Oudadesse et al., 2011 Aina et al., 2019
Cooper	NM, IO	No effect bioactivity	Antibacterial Osteogenesis Angiogenic	Moila et al., 2014 Akhtach et al., 2021 El-fiqui et al., 2021
Mangnesium	NM, IO	Decrease bioactivity	Osteogenesis Angiogenesis	Jodati et al., 2020.
Cobalt	NM, IO	Hardness surface	Angiogenesis Osteogenesis Antibacterial efect	Chattopadhyay et al., 2006 Lung et al., 2021
Silver	NM, IO	Hardness surface Maintain bioactivity	Antibacterial activity Osteogenesis	Zhu et al., 2014 Kazemian et al., 2021
Titanium	NM, NF	Exothermal temperature Endotermal temperature Enhances crystallization	Osteogenesis	Geol et al., 2007 Mahdy et al., 2021
Cerium	NM, IO	Bioactivity Nanoparticles agglomeration Wettability decreased	Osteogenesis Neuro-protective Antioxidant Angiogenesis Anti-inflammatory	Mahapatra et al., 2017 Lie et al., 2018 Saatchi et al., 2021

and its behavior in BGs. Overall, NM-doped BGs display a wide range of therapeutic effects, and applying wet chemistry for structural modification has extended the types of bioactive materials available. However, many challenges remain. Some of the most common DAs and their functions are described below.

a. Boron

Boron Oxide (B_2O_3) is an NM that can also function as an NF. The addition of boron increases the glass network connectivity by forming 4-coordinates BO_4. As an NM the increase of boron has shown to decrease the specific surface area, thus maybe related to the diminished contribution by micropores blocking of the glass network. Therefore, the increase of mechanical stability and bioactivity (Deilmann et al., 2020). *In vitro* studies established that boron (B) was toxic to cell cultures, but no toxicity was detected during *in vivo* studies on rats (Fu et al., 2010 ; Jung et al., 2012). B-doped BGs enhanced HCA layer formation (bioactivity), improved the antibacterial effect, promoted cell proliferation (human periodontal ligament cells ; Bai et al., 2020), and increased alkaline phosphatase activity. Adding 2 mol% of B_2O_3 to BGs enhanced biocompatibility with endothelial cells (Haro Durand et al., 2014) and showed a pre-osteoblastic cells (MC3T3-E1) inhibition of > 46.1% (Brown et al., 2009). Chang et al. (2020) used B-doped BGs as a component for composite bone cement. They found direct relationships of boron content with specific surface area, average pore size and volume, and compressive strength. Zhang et al. (2020) used 3D-printed borosilicates (in which the concentrations of B_2O_3 were 19.4 mol% and 38.8 mol%) and sodium alginate implants for mandible reconstruction in rats ; the borosilicates were almost fully degraded within 28 days. Moreover, they reported good mechanical properties, excellent biocompatibility, and promotion of bone regeneration. Notably, borosilicate spheres have been used to enhance lesion targeting and simulate temporary vascular occlusion to treat conditions such as hemorrhages of hyper-vascular tumors in pigs (Doucet et al., 2021).

b. Sodium

Sodium oxide (Na_2O) is an NM that disrupts the silica network by bonding with NBOs. Hench in 1971 noted that sodium (Na) is critical for network dissolution and BG bioactivity. However, high amounts of Na_2O can produce hygroscopicity, which affects BG stability and mechanical properties. Chen et al. (2017) demonstrated that Na is not essential for BGs bioactivity. They compared Na-free BG with high-Na-content (29.6 mol% and 28.3 mol%) BGs. The Na-free BGs were highly bioactive. Crovace et al. (2021) reported that substituting Na_2O to K_2O in BGs increased the densification rate ; this was attributed to a higher tendency to crystallize.

c. Magnesium

Magnesium (Mg) has important roles in muscle metabolism and bone formation (Rath et al., 2014). The incorporation of magnesium into bioactive glasses takes place through magnesium oxide (MgO). MgO can behave as an NF or NM. As NM, reduces the bioactivity in-vitro due to a small ionic radii making a more compact glass structure (Jodati et al., 2020 and Azevedo et al., 2010). However, as NF, increase the surface reactivity (bioactivity) and osteogenic activity (osteoblast proliferation) due to the substitution of Si-O-Si by Si-O-Mg which is weaker (Azevedo et al., 2010).

d. Phosphorous

Phosphorous pentoxide (P_2O_5) can behave as an NF or as an NM, its role as NM, is very complex in BGs. Li et al. (2021), confirmed that a high content of phosphate increased the bioactivity and enhance the proliferation of cells (5.07 mol%) (Li et al. 2021), however more than 10 mol% phosphate content in a silica-based BG reportedly resulted in a non-bioactive composition (Arcos et al., 2010).

e. Calcium

The calcium cation (Ca^{2+})plays a primary role in the formation of hydroxyapatite, which is the main component of the human body´s hard tissues (teeth and bones). It is found throughout the human body and participates in various metabolic processes. In bioactive glasses calcium is a typical NM, it is added to BGs as calcium oxide (CaO). It is needed to enhance the formation of an HCA layer. In the initial phases of dissolution, Ca^{2+} deposits in the superficial layer of BGs, forming Ca–PO clusters that eventually form an HCA layer (Schumacher et al., 2021). Therefore, Ca^{2+} has a critical role in BG bioactivity.

f. Titanium

Titanium oxide (TiO_2) is an IO that can function as an NF or an NM according to its concentration in the glass. As NF, it increases the glass crystallization temperature, because it is incorporated as TiO_2 into the glass structure (Geol et al., 2007). Titanium ion tetrahedrally coordinates with SiO_2 and BO. Mahdy et al. (2021), reported an increase in glass stability (i.e., reduced ion leaching) after doping 5% and 10% of TiO_2 into BGs (Mahdy et al., 2021). The stability was attributed to the formation of a $CaTiSiO_5$ phase (Deer et al., 1992) and its incorporation as an NF. As an NM TiO_2 enhances crystallization (Park et al., 2008) without changing glass shape or morphology (Mahdy et al., 2021). Furthermore, in 2021 lung reported an increase of surface hardness on titanium (Ti), silver (Ag), cobalt (Co) doped bioactive glass coatings, maybe related that TiO_2, CoO, and Ag nanoparticles could act as nano-filler particles (Lung et al., 2021). The addition of 4% TiO_2 reduces the rate of amorphous calcium phosphate (ACP) / HCA layer formation in vitro, but in more physiological condition (adding of proteins) an enhancement of HA formation was observed (Asif et al., 2014). The good biocompatibility displayed by Ti-doped BGs makes them suitable candidates for tissue regeneration (Mahdy et al., 2021).

g. Cobalt

Cobalt Oxide (CoO) as NM, delays the formation of the HCA layer in a Co concentration-dependent manner. Lung et al. (2021), used All56s a multi-ion-doped (Ti, Co, and Ag) reporting enhanced angiogenesis and osteogenesis related to cobalt ion (Co^{2+}). All56s BG showed good biocompatibility, which contrasts with the cytotoxicity detected in MC3T3-E1 mouse osteoblast-like cells (Fleury et al., 2006), and cell viability reduction of a line derived from osteosarcoma cells (MG63) due to oxidative stress (Chattopadhyay et al., 2015) by Co-doped BGs. The All56s multi-ion BGs, synthesized by Lung et al. (2021), had greater antibacterial activity against *Porphyromonas gingivalis*, compared with individual ion-doped BGs (except Ag-doped BGs).

h. Copper

Copper (Cu) is an essential element in collagen synthesis, which plays a crucial role in bone formation and healing. Interest to use Copper Oxide as an NM is based on its abilities to stimulate angiogenesis and osteogenesis (Miola et al., 2014). An *in vitro* study of 1.5 mol% CuO in BGs found inhibition of *S. aureus* growth, highlighting the potential of the material to avoid post-surgical infections and enhance hard-tissue regeneration (Akhtach et al., 2021). El-Fiqi et al. (2021), studied a nano-delivery system based on Cu-doped BGs loaded with epidermal growth factor. The system displayed angiogenic and antibacterial effects toward *Enterococcus faecalis*. Moreover, epidermal growth factor-Cu-doped BGs produced a regenerative effect on human dental pulp stem cells. The introduction of CuO in BGs with different compositions had no negative effect on bioactivity. However, dose-dependent cytotoxicity toward 3T3 fibroblasts was observed at copper ion (Cu^{2+}) concentrations > 10 mg/L for biocomposites of Cu-doped BGs and nanofibrillated cellulose used for wound-healing applications. The antibacterial, angiogenic, and osteogenic properties of Cu-doped BGs make them potentially suitable materials for orthopedic and dental applications (Wang et al., 2016).

i. Zinc

Zinc (Zn) is needed for the formation of bones in the human body. It plays a role in bone metabolism and has antibacterial effects (Balasubramanian et al., 2015). ZnO is an excellent stabilizer, improving glass properties, and is an excellent biocide. It can function as an NF or NM. As an NM, it reduces the surface area and pore size of BGs because its ionic radii is smaller than that of Ca^{2+}, which results in a more compact and tightly bonded glass network, increasing the strength of glass, thus decreasing their solubility (Anand et al., 2014). Miola et al. (2014), found that the precipitation of crystalline hydroxyapatite from a highly Zn-doped (20 mol%) BG only occurred after 1 month of immersion in simulated body fluid. Other authors confirmed that the introduction of ZnO reduced the solubility and leaching rate of ions, thereby delaying hydroxycarbonate layer formation (Aina et al., 2009 ; Lusvardi, 2009 ; Oudadesse et al., 2011). Esteban-Tejeda et al. (2015), evaluated the effect of ZnO content in BGs on *Escherichia coli* and *Staphylococcus aureus*, which revealed that Zn^{2+} could be attached to microorganism membranes via electrostatic forces. Hence, Zn^{2+} could trigger membrane electrochemical potential to provoke cell death. The biocidal activity was directly related to Zn content.

j. Strontium

Strontium (Sr) is a bone-seeking element (similar to calcium). In the human body, is found in the skeleton (98%), liver, muscles, and sites of high metabolic turnover (D'Haese et al., 1997 ; Dahl et al., 2001). Strontium can function as NM, incorporated into the glass as strontium oxide (SrO). Strontium ions (Sr^{2+}) upregulate osteoblast activity (enhancing bone formation) and downregulates osteoclast activity (inhibiting resorption) (Mao et al., 2017). Brauer (2012) demonstrated the antibacterial effect of Sr upon injection into bone defects to stabilize the bone structure. The feasibility of Sr^{2+} as a substitute for Ca^{2+} in hydroxyapatite has increased interest in Sr-doped BGs. Furthermore, Sr-doped bioactive glasses are "highly appealing for treatment of bone pathologies" (Mao et al., 2017).

Sr-doped BGs enhance the HCA layer formation due to the larger size of Sr^{2+}, compared with Ca^{2+} (Wei et al., 2014). The expanded BG network displays improved bioactivity (Taherkhani et al., 2016). However, if the percentage is increased over 10% of Sr content, the HCA layer formation is inhibited due to Sr^{2+} inhibition of octacalcium-phosphate formation (Wei et al., 2014). Additionally, the release of Sr^{2+} from BGs stimulates osteogenic differentiation in bone marrow mesenchymal stem cells (Mosqueira et al., 2021). These studies are consistent with the findings of Fei et al. (2021), who showed that the optimal concentration of Sr could enhance bioactivity and osteoblast activity. Fiorilli et al. (2021) found that Sr-doped BGs functionalized with ICOS-Fc decreased bone resorption (Fiorilli et al., 2021).

k. Silver

Silver (Ag) is an IO and NM. Ag-doped BGs display bactericidal and bacteriostatic properties. The bactericidal effect of silver ion (Ag^{+}) results from its interaction with the cell membrane (altering membrane permeability), its inhibition of adenosine triphosphate production (disrupting cell protein and enzyme synthesis), and interference in DNA replication. The antibacterial effect of Ag-doped BGs has been evaluated in Gram-positive and Gram-negative bacterias, including *E. coli* and *S. aureus* (Kazemian et al., 2021 ; Zhu et al., 2014).

Kazemian et al. (2021), synthesized Ag-doped BGs that formed an HCA layer after one day of immersion in simulated body fluid. Their procedure improved the bioactivity, compared with a previous study where an HCA layer formed only after three days of immersion (El-Rashidy et al., 2018). Additionally, Kazemian et al. (2021), observed good biocompatibility of Ag-doped BGs below a concentration of 250 μg/mL. These results are consistent with the findings of Zhu et al. (2014), that Ag-doped BGs were a good matrix for osteoblast growth. Ag-doped BGs are thus a promising material for bone regeneration.

l. Cerium

Cerium (Ce) is a rare earth element also of interest as a BG dopant. It promotes bone formation (positive effect *in vitro* toward mouse osteoblasts ; Zhang et al., 2010) and is effective as an implant coating (Li et al., 2018). The behavior of Ce as a neuroprotective agent is related to its antioxidant activity (Schubert et al., 2006). The antioxidant property derives from its ability to quench free radicals by switching between Ce^{4+} and Ce^{3+} and adjusting the oxygen saturation of its microenvironment. Ce induces anti-inflammatory effects, enhances osteogenesis, and angiogenesis (Celardo et al., 2011 ; Li et al., 2018 ; Mahapatra et al., 2017 ; Nethi et al., 2017). Ce doped in BGs does not affect the morphology or structure of BG particles (Atkinson et al., 2019). Zheng et al. (2020), synthesized Ce-mesoporous BG nanoparticles, which were noncytotoxic *in vitro*, and downregulated the expression levels of pro-inflammatory genes (IL-1β, IL-6, and TNF-α) and oxidative stress-related genes (NOS2 and MMP9) in macrophages. Ce-doped BGs had a higher gene expression level of OPG than RANKL, suggesting improved osteogenesis. Ce-doped BGs were incorporated into electrospin chitosan/polyethylene oxide nano-fiber scaffolds for use in soft-tissue engineering. However, increasing the Ce content led to nanoparticle agglomeration ; and wettability was reduced when the content exceeded 10 wt.% (Saatchi et al., 2021).

Concluding remarks and challenges regarding bioactive glasses

Hench suggested that the era of innovation in BGs spans the period 2005–2025, during which time a wide range of gene-targeting BGs would be developed. However, many challenges must be addressed before the clinical use of BGs (Hench et al., 2015). A notable frontier involves the material-based guidance of stem cells. More rigorous studies are needed concerning the interference of ions in the upregulation and downregulation of genes before gene-targeting BGs can reach clinical applications.

Immediate challenges for BGs involve improvement of mechanical properties ; development of reliable coatings, soft-tissue engineering applications, interfacial tissue engineering applications, reliable *in vitro* and *in vivo* testing methodologies ; and controlled release of therapeutic ions and biomolecules (Baino et al., 2018).

In dentistry, BGs have been used primarily for enamel remineralization, as a coating, and bone regeneration (Kawaguchi et al., 2017). However, novel approaches with new bioactive formulations and modifications are needed before clinically approved products are manufactured.

Conflict of Interest

The authors declare that there is no conflict of interest.

References

Aina V, Malavasi G, Fiorio Pla A, Munaron L, Morterra C. Zinc-containing bioactive glasses : surface reactivity and behavior towards endothelial cells. Acta Biomater 5 : 1211-1222, 2009.

Akhtach S, Tabia Z, Mabrouk KE, Bricha M, Belkhou R. A comprehensive study on copper incorporated bio-glass matrix for its potential antimicrobial applications. Ceram Int 47 : 424-433, 2021.

Anand V, Singh KJ, Kaur K. Evaluation of zinc and magnesium doped 45S5 mesoporous bioactive glass system for the growth of hydroxyl apatite layer. J. Non Cryst Solids. 406 : 88-94, 2014.

Arcos D, Vallet-Regi M. Sol-gel silica-based biomaterials and bone tissue regeneration. Acta Biomater 6 : 2874-2888, 2010.

Asif IM, shelton RM, cooper PR, Addison O, Martin RA. In vitro bioactivity of titanium-doped bioglass. J Mater Sci : Mater Med : 1-9, 2014.

Atkinson I, Anghel EM, Petrescu S, Secui AM, Stefan LM, Mocioiu. Cerium - containing mesoporous bioactive glasses : material characterization, in vitro bioactivity, biocompatibility, and cytotoxicity evaluation. Micropor Mesopor Mater. 276 : 76-88, 2019.

Azevedo MM, Jell G, O´Donnell MD, Law RV, Hill RG,

Stevens MM. Synthesis and characterization of hypoxia−mimicking bioactive glasses for skeletal regeneration. J Mater Chem. 20 : 8854−8864, 2010.

Bai N, Chen W, Luo L, Tong W, Wen C, Zhan X, Sa B. Effect of B_2O_3 on the structural and in vitro biological assessment of mesoporous bioactive glass nanospheres. J Am Ceram Soc. 1 : 1−15, 2020.

Baino F, Hamzahlou S, Kargozar S. Bioactive glasses : Where are we and where are we going? J Funct Biomater 9 : 1−26, 2018.

Balasubramanian P, Strobel LA, Knesset U, Boccaccini AR. Zinc−containing bioactive glasses for bone regeneration, dental and orthopedic applications. Biomed Glasses 1 : 51−69, 2015.

Bitar MC, Knowles J, Lewis MP, Salih V. Soluble Phosphate glass fibers for repair of bone ligament interface. J Mater Sci Mater Med 16(12) : 1131−1136, 2005.

Boccaccini AR, Blaker JJ, Maquet V, Day RM, Jéróme R. Preparation and characterization of Poly (Lactide−Co−Grycolide) (PLGA) and PLGA/bioglass composite tubular foam scaffolds fo tissue engineering applications. Mater Sci Eng 25 (1) : 23−31, 2005.

Brauer DS. Bioactive glasses−structure and properties. Angew Chemie Int Ed 54 : 2−24, 2015.

Brauer DS, Karpuhkina N, Media G, Bhat A, Law RV, Radecka I, Hill RG. Bactericidal strontium−releasing injectable bone cements based on bioactive glasses. J R Soc Interface 10 : 1−8, 2012.

Brown RF, Rahaman MN, Dwilewicz AB, Huang W, Day DE, Li Y, Mal Sonny B. Effect of borate glass composition on its conversion to hydroxyapatite and on the proliferation of MC3T3−E1 cells. J Biomed Mater Res A 88 (2) : 392−400, 2009.

Celardo I, Pedersen JZ, Traversa E, Ghibelli L. Pharmacological potential of cerium oxide nanoparticles. Nanoscale 3 : 1411−1420, 2011.

Chang Y, Lin Z, Xie X, Wu Z, Yao A, Ye S, Lin J, Wang D, Cui X. An injectable composite bone cement based on mesoporous Borosilicate Bioactive Glass spheres. Journal of Inorganic Materials 35 (12) : 1398−1406, 2020.

Chattopadhyay S, Dash SK, Tripathy S, Das B, Mandal D, Pramanik P, Roy S. Toxicity of cobalt oxide nanoparticles to normal cells ; an in vitro and in vivo study. Chem Biol Interact 226 : 58−71, 2015.

Chauhan N, Mulcahy MF, Salem R, Benson AB, III Boucher E, Bukovcan J, Cosgrove D, Laframboise C, Lewandowski RJ, Master F, El−Rayes B, Strosberg JR, Sze DY, Sharme RA. Therasphere Yttrium−90 Glass Microspheres combined with chemotherapy versus chemotherapy alone in second−line treatment of patients with metazoic colorectal carcinomaof the liver. Protocol for the EPOCH phase 3 radomized clinical trial JMIR Res Protoc 8 (1) : e11545, 2019.

Chen Q, Jin L, Cook WD, Mohn D, Lagerqvist EL, Elliot DA, Haynes JM, Boyd N, Stark WJ, Pouton CW, Stainley EG, Elefanty AG. Elastomeric Nanocomposites as Cell delivery vehicles and cardiac support devices. Soft Mater 6(19) : 4715−4726, 2020.

Chen X, Chen X, Brauer SD, Wilson MR, Law MR, Law VR, Hill GR, Karpukhina N. Sodium is not essential for high Bioactivity of Glasses. Int J Appl Glass Sci 8 (4) : 428−437, 2017.

Crovace MC, Soares VO, Rodrigues ACM, Peitl O, Raucci LMSC, De Oliveira PT, Zanotto ED. Understanding the mixed alkali effect on the sinterability and in vitro performance of bioactive glasses. J Eur Ceram Soc, 2021.

Dahl SG, Allain P, Marie PJ, Mauras Y, Boivin G, Ammann P, Tsouderos Y, Delmas PD, Christiansen C. Incorporation and distribution of strontium in bone. Bone 28 : 446−453, 2001.

Deer W, Howie R, Zussman A. An introduction to the rock−forming minerals, Third ELBS impression, Printing press Ltd, Hong Kong, 1992. Common Wealth.

Deilmann L, Winter O, Cerrutti B, Bradtmüller H, Herzig C, Limbeck A, Lahayne O, Hellmich C, Eckert H, Eder D. Effect of boron incorporation on the bioactivity, structure, and mechanical properties of ordered mesoporous bioactive glasses. J Mater Chem 8 : 1456, 2020.

Deshmukh K, Kovárik T, Krenek T, Docheva D, Stich T, Pola J. Recent advances and future perspectives of sol−gel derived porous bioactive glasses : a review. RCS Adv 10 : 33782−33835, 2020.

D´Haese PC, Van Landeghem GF, Lamberts LV, Bekaert VA, Schrooten I, De Bore ME. Measurement of strontium in serum, urine, bone and soft tissues by Zeeman atomic absorption spectrometry. Coin Chem 43 : 121−128, 1997.

Doucet J, MacDonald K, Lee C, Hana RA, Soulez G, Boyd D. The feasibility of degradable glass microspheres as transient embolic medical devices. J Biomater Appl 35 (6) : 615−632, 2021.

Eden M. The split network analysis for exploring composition structure correlations in multicomponent glasses : I Rationalizing bioactivity−composition trends of bioactive glasses. J Non−Cryst Solids 357 : 1595−1602, 2011.

El−Fiqi A, Mandakhbayar N, Jo SB, Knowles JC, Lee JH, Kim HW. Nanotherapeutics for regeneration of degenerated tissue infected by bacteria through the multiple delivery of bioactive ions and growth factor with antibacterial/angiogenic and osteogenic/odontogenic capacity. Bioact Mater 6 : 123−136, 2021.

El−Rashidy AA, Way G, Gad A, Azza A, Balasubramanian P, Kaya S, Boccaccini AR, Sami I. Preparation in vitro characterization of silver−doped bioactive glass nanoparticles fabricated sin a sol−gel process and modified Stober method. J Non−Cryst Solids 483 : 26−36, 2018.

Esteban −Tejeda L, Prado C, Cabal B, Ramón Torrecillas JS, Moya Serafín J. Antibacterial and antifungical activity of ZnO containing glasses. PLoS ONE 10 : 1 − 17, 2015.

Fei YC, Chen LG, Kuo CK, Chou YJ. Influence of strontium dopant on bioactivity and osteoblast activity of spray pyrolyzes strontium−doped mesoporous bioactive glasses. J Asian Ceram Soc 9 : 221−228, 2021.

Fiorilli S, Pagani M, Boggio E, Gigliotti LC, Dianzani C, Gauthier R, Pontremoli C, Montalbano G, Dianzani U, Vitale−Brovarone C. Sr−Containing mesoporous bioactive glasses bio−functionalized with recombinant ICOS−FC : an in vitro study. Nanomater 11 : 1−23, 2021.

Fleury C, Petit A, Mwale F, Antoniou J, Zukor DJ, Tabrizian M, Huk OL. Effect of cobalt and chromium ions on human MG−63 osteoblasts in vitro : Morphology, cytotoxicity, and oxidative stress. J Non−Cryst Solids 27 : 3351−3360, 2006.

Fu Q, Rahaman MN, Fu H, Liu X. Bioactive glass scaffolds with controllable degradation rates for bone tissue engineering applications, I. Preparation and in Vitro degradation. J Biomed Mater Res 95A : 164−171, 2010.

Fu Q, Rahaman MN, Bal BS, Bonewald LF, Kuroki K, Brown RF. Bioactive glass scaffolds with controllable degradation rates for bone tissue engineering applications, II in vitro and in vivo biological evaluation. J Biomed Mater Res 95A : 172−179, 2010.

Geol A., Shaaban ER, Melo FCL, Ribeiro MJ, Ferreira JMF. Non.−isothermal crystallization kinetic studies on Mg−Al_2O_3−SiO_2−TiO_2 glass. J Non−Cryst Solids 353 (24−25) : 2382−2391, 2007.

Gillette RL, Swaim SF, Satin EA, Bradley DM, Coolman SL. Effects of a Bioactive Glass on healing of closed skin wounds in dogs. Am J Vet Res 62 (7) : 1149−1153, 2001.

Haro Durand LA, Góngora A, Porto López JM, Boccaccini AR, Zago MP, Baldi A, Gorustovich A. In vitro endothelial cell response to ionic dissolution products from boron −doped bioactive glass in the SiO_2−CaO−P_2O_5−Na_2O system. J Mater Chem B 2(43) : 7620−7630, 2014.

Hench LL. Bioceramics : from concept to clinic. J Am Ceram Soc 74 : 1487, 1991

Hench LL. Bioactive materials : The potential for tissue regeneration. J Biomed Mater Res C 41 : 511, 1998

Hench LL. The story of Bioglass. J Mater Sci Mater Med 17 : 967−978, 2006.

Hench LL, Jones JR. Bioactive glasses : Frontiers and challenges. Frotniers in Bioingeniering and biotechnology 3 : 1−12, 2015.

Hench LL, Paschall HA. Direct chemical bond of bioactive glass−ceramic implants to bone and muscles. J Biomed Mats Res Symp 4 : 1−25, 1973

Hench LL, Polak JM. Third−generation biomedical materials. sciencemag.org 294 : 1016−1017, 2002.

Hench LL, Splinter RJ, Greenlee HF, Allen WC. Mechanism of interfacial bonding between ceramics and bone. J Biomed Mater Res 117 : 8−10,1971

Hench LL, Wilson J, Greenspan DC. Bioglass : a short history and bibliography. J Aust Ceram Soc 40 : 1, 2004

Hill RG, Brauer DS. Predicting the bioactivity of glasses using the network connectivity or split network models. J Non−Cryst Solids 356 : 517−524, 2010.

Hupa L, Karlsson H. Tailoring of the bioactive glasses, in bioactive glasses−fundamentals, technology and applications, ed A.R. Boccaccinni, D.S. Brauer and L Hupa, The Royal Society of Chemistry, pp 136−160, 2017.

Jodati H, Güner B, Evis Z, Keskin D, Tezcaner A. Synthesis and Characterization of magnesium−lanthanum dual doped bioactive glasses. Ceramic Int 50 : 1−9, 2020.

Joo NY, Knowles JC, Lee GS, Kim JW, Kim HW, Son YJ, Hyun JK. Effects of phosphate glass fiber−collagen scaffolds on functional recovery of completely transected rat spinal cords. Acta Biomater 8(5) : 1802−1812, 2012.

Jones J. Review of Bioactive glass : from Hench to Hybrids. Acta Biomater 9(1) : 2013.

Jones J, Ehrenfried L, Saravanapan P, Hench L. Control-

ling ion release form bioactive glass foam scaffolds with antibacterial properties. J Mater Sci Mate Med 17 : 989−996, 2006.

Jung SB, Day DE, Brown RF, Bonewald LF. Potential toxicity of bioactive borate glasses in−vitro and in−vivo. Advances in bioceramics and porous ceramics V ; Narayan R, Colombo RP, Halbing M, Mathur S, Eds. ; John Wiley & Sons, Inc. : Hoboken, NJ, USA, 2012.

Karasu B, Yanar AAO, Koçak A, Kısacık Ö. Bioactive Glasses. El−Cezerî Fen ve Mühendislik Dergisi 4(•) : 436−471, 2017.

Kawaguchi K, Iijima M, Endo K, Mizoguchi I. Electrodeposition as a new bioactive glass coating process for orthodontic stainless steel. Coatings 7 : 3−13, 2017.

Kazemian Z, Varzandeh M, Labbaf S. A facile synthesis of monodispersed spherical silver doped bioactive glass nanoparticle. J Mater Sci : Mater Med 32 : 1−29, 2021.

Kehoe S, Abraham R, tonkopi E, Boyd D, Abstract NO. 74 : Novel radiopaque embolic agent for uterine fribroid embolization : determination of radiopacity adn biological evaluation ; cytocompatibility, intracutaneous reactivity and local effects after implantation. J Vasc INterv Radiol 23(3) : s33, 2012.

Lakes R. Composite Materials in Biomaterials. Principles and applications. Boca Rton, London, Nuee York, Washington DC, CRC Press, pp 79−93, 2003.

Lepry WC, Nazhat SN. Highly bioactive sol−gel−derived borate glasses. Am Chem Mater 27 : 4821−4831, 2015.

Li J, Wen J, Li B, Li W, Qiao W, Shen J, Jin W, Jian X, Yeung KW, Chu PK. Valence State manipulation of Cerium Oxide nanoparticles on a titanium surface for modulating cell fate and bone formation. Adv Sci 5 : 2018.

Li Y, Chen L, Chen X, Hill R, Zou S, Wang M, Liu Y, Wang J, Chen X. High phosphate content in bioactive glasses promotes osteogenesis in vitro and in vivo. Dent Mater 37 : 272−283, 2021.

Lung YKC, Abdalle MM, Chu CH, Yin I, Got SR, Matinlinna JP. A multielement−dopped porous bioactive glass coating for implant applications. Materials 14 (4) : 961, 2021.

Lusvardi G, Zaffe D, Menace L, Bertoldi C, Malavasi G, Consolo U. In vitro and in vivo behaviour of zinc−doped phosphosilicate glasses. Acta Biomater 5 : 419−428, 2009.

Mahapatra C, Singh RK, Lee JH, Jung J, Hyun JK, Kim HW. Nano−shaped varied cerium oxide nanomaterials rescue human dental stem cells from oxidative insult throughout intracellular or extracellular actions. Acta Biomater 50 : 142−153, 2017.

Mahdy E, Sahbal KM, Mostafa M, Beherei HH, Abdel−Monem YK. Enhancement of glass−ceramic performance by TiO_2 doping : In vitro cell viability, proliferation, and differentiation. Ceram Int 47 : 6251−6261, 2021.

Mao L, Xia L, Chang J, Liu J, Jiang L, Wu C. The synergistic effects of Sr and Si bioactive ions on osteogenesis, osteoclastogenesis and angiogenesis for osteoporotic bones regeneration. Acta Biomater 61 : 217−232, 2017.

Mehrabi T, Messbar AS, Mohammadi Z. Bioactive glasses : A promising therapeutic ion release strategy for enhancing wound healing. ACS Biomater Sci Eng 6 : 5399−5430, 2020.

Miola M, Brovarone V, Maina G, Rossi F, Bergandi L, Ghigo D, Saracino S, Maggiora M, Canuto RA, Muzio G, Vernè E. In vitro study of manganese−doped bioactive glasses for bone regeneration. Mater Sci Eng C 38 : 107−118, 2014.

Mosqueira L, Barrioni BR, Martins T, Ocarino NM, Serakides R, Pereira MM. In vitro effects of the co−release of Icariin and strontium from bioactive glass sub−micron spheres on the reduced osteogenic potential of rat osteoporotic bone marrow mesenchymal stem cells. Biomed Mater 15 (5) : 1−23, 2020.

Nethi SK, Nanda HS, Steele TWJ, Patra CR. Functionalized nanoceria exhibit improved angiogenic properties. J Mater Chem B 5 : 9371−9383, 2017.

O´Donnel MD. Predicting bioactive glass properties from the molecular chemical composition : glass transition temperature. Acta Biomater 7 : 2264−2269, 2011.

Oudadesse H, Dietrich E, Gal YL, Pellen P, BureauB, Mostafa AA, Cathelineau G. Apatite forming ability and cytocompatibility of pure and Zn−doped bioactive glasses. Biomed Mater 6 : 1−9, 2011.

Park J, Ozturk A. Effect of TiO_2 addition on the crystallization and tribological properties of $MgO−CaO−SiO_2−P_2O_5−F$ glasses, Thermochim. Acta 470 (1−2) : 60−66, 2008.

Saatchi A, Arani AR, Moghanian A, Mozafari M. Synthesis and characterization of electrospun cerium−doped bioactive glass/chitosan/polyethylene oxide composite scaffolds for tissue engineering applications. Ceram Int 47 : 260−271, 2021.

Schumacher M, Habibovic P, Van rijt S. Mesoporous bio-

active glass composition effects on degradation and bioactivity. Bioactive mater 6 : 1921−1931, 2021.

Schubert D, Dargush R, Raitano J, Chan SW. Cerium and yttrium oxide nanoparticles are neuroprotective. Biochem Biophys Res Commun 342 : 86−91, 2006.

Sene FF, Martinelli JR, Okumo E. Synthesis and characterization of phosphate glass microspheres for radiography applications. J Non−Cryst solids 354 : 4889−4893, 2008.

Sepp B, Kunzmann T. The stability of clinopyroxene in the system CaO−MgO−SiO2−TiO2 (CMST). Am Mineral 86 (3) : 265−270, 2001.

Shah R, Sinanan ACM, Kowles JC, Hunt NP, Lewis MP. Craniofacial muscle engineering using a 3−dimensional phosphate glass fibre construct. Biomater 26(13) : 1497−1405, 2005.

Skelton KL, Glenn JV, Clarke SA, Georgia G, Valappil SP, Knowles JC, Nazhat SN, Jordan GR. Effect of ternary phosphate−based glass compositions on osteoblast and osteoclast−like proliferation, differentiation and death in vitro. Acta Biomater. 3 : 563−572, 2007.

Taherkhani S, Moztarzadeh F. Influence od strontium on the structure and biological properties of sol−gel −derived mesoporous bioactive glass (MBG) powder. J Sol−Gel Sci Technol 9 : 1−12, 2016.

Verrier S, Blanker JJ, Marquet V, Hench LL, Boccaccini AR. PDLLA/Bioglass composites for soft tissue and hard −tissue engineering : an in vitro cell biology assesment. Biomaterials 25 (15) : 3013−3021, 2004.

Vichery C, Nedelec JM. Bioactive glass nanoparticles : from synthesis to materials design for biomedical applications. Materials 9 : 1−17, 2016.

Wei L, Ke J, Prasadam I, Miron RJ, Lin S, Xiao J. A comparative study of Sr−incorporated mesoporous bioactive glass scaffolds for regeneration of osteopenia bone defects. Osteop Int 25 : 2089−2096, 2014.

Wang X, Cheng F, Liu J, Smått J, Gepperth D, Lastusaari M, Xu C, Hupa L. Composites of Copper−containing mesoporous bioactive glass and nano−fibrillated cellulose : biocompatibility and angiogenic promotion in chronic wound healing application. Acta Biomater 46 : 286−298, 2016.

Zhang J, Cuilian L, Yaping L, Jing S, Peng W, Kequian D, Zhao Y. Effect of cerium ion on the proliferation, differentiation, and mineralization function of primary mouse osteoblast in vitro. J Rare Earths 28 : 138−142, 2010.

Zhang P, Yang K, Zhou Z, Zhu X, Li W, Cao C, Zhou K, Liao L. Customized Borosilicate Bioglass Scaffolds with excellent biodegradation and osteogenesis for mandible reconstruction. Frontiers in Bioengineering and Biotechnology 8 (18) : 610284, 2020.

Zheng K, Torre Elisa, Bari A, Taccardi N, Cassinelli C, Morra Marco, Fiorilli S, Vitale−Drovarone C, Iviglia G, Boccaccini A. Antioxidant mesoporous Ce−doped bioactive glass nanoparticles with anti−inflammatory and pro−osteogenic activities. Mater Today Bio 5 : 1−14, 2020.

Zhu H, Hu C, Zhang F, Feng X, Li J, Lui T, Chen J, Zhang J. Preparation and antibacterial property of silver−containing mesoporous 58S bioactive glass. Materials Science and Engineering : C 42 : 22−30, 2014.

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