Chapter

Incorporation of Novel Elements in Bioactive Glass Compositions to Enhance Implant Performance

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Abstract

Increasing popularities of bioactive-glasses and their potential medical applications have led to countless studies into improving their material characteristics and overall performance. Some scientists hope to create new bioactive-glass compositions, while others seek to merely modify existing ones such as the novel 45S5 bioactive-glass composition; created by Dr. Larry Hench. These modifications aim to address potential complications that may arise at a site following implantation such as bacterial infections. In other cases, the incorporation of a selected element or compound may aim to improve the implant functioning by increasing cell proliferation. Although possibilities are plentiful, researchers avoid compromising the typical bioactive glass characteristics when doping with elements such as silver, or gold to achieve additional properties. This chapter elaborates on the incorporation of popular elements by doping bioactive-glass compositions to introduce desired properties based on the implant application.

Keywords: doping, bioactive glass, hydroxyapatite, angiogenesis, osteogenesis, osteoconductive, biocompatibility, cell proliferation

1. Introduction

A bioactive material is one that is able to elicit a specific biological response at the interface of a material that results in bond formation between the body tissues and the material that they surround [1]. Common bioactive materials include bioactive glasses, and from that derived bioactive glass-ceramics and bioactive ceramics.

Bioactive glass was first introduced in the late 1960's by Dr. Larry Hench after an enlightening conversation with an army officer while attending a scientific conference. During their discussion, they connected on the common tragic injuries that the soldiers were experiencing during the Vietnam War that was occurring at that time. These types of injuries involved those to the limbs, and during that time, the treatment quite often involved amputation due to the absence of a material capable of effectively supporting the hands or the feet. Over the next few years, Hench and his students developed a soda-calcia-phosphate-silicate based glass composition, which was proven to stimulate bone [2]. The result of this development in 1969 was the well-known and copyrighted 45S5 Bioglass. This discovery was the beginning of a new generation of materials, acting

as temporary substrates for supporting damaged tissues [3], and since then launched products formed from variations of bioactive glasses and glass-cermaics such as calcium phosphates and synthetic hydroxyapatite [4–7].

The main purpose of such substrates was to create implants that react to the body's process unlike the implants that were in use at that time which were inert or unreactive. His continued study focused on revealing the mechanism on why his novel glass composition, 45S5, was able to interact with the body as a result of by-products from the dissolution of the glass components in the body [8, 9].

When a glass is designed to function as a potential implant and possess bioactive features, its behavior is monitored as certain criteria must be achieved before confirming bioactivity. This can be done by determining its surface type. There are five surface type characteristics of silica-based glasses. Type I surfaces undergo only a thin surface layer hydration when exposed to the bodily aqueous environment. In a case like that, the bulk composition is similar to that of the surface composition. Type II surfaces consists of a silica-rich protective film that occurs as a result of selective alkali ion removal. Type III surfaces are known for their ability to form dual surface layers, known to contribute to durability in both acidic and alkali solutions. Type III surface interactions are characteristic of an ideal bioactive glass. Type IV surfaces have the ability to form a silica-rich layer, however, the silica concentration is not high enough to protect the glass from further attack by network dissolution. Therefore, they are known to have poor durability. Glasses that undergo congruent dissolution with equivalent loss of alkali and silica exhibit that of a Type V glass surface [10].

2. What constitutes an effective bioactive glass?

The original purpose for creating a bioactive glass was to form a chemical bond with bone, and this was achieved by Dr. Larry Hench as stated prior. It is important to understand the mechanism of how this interaction became possible. According to Hench, further thermodynamic studies allowed us to understand that there is a formation of an organic structure being derived from an inorganic one. He was able to determine that the stability of Bioglass® came as a direct result of the formation of a Type III surface [10]. This usually occurs as the result of the presence of phosphorus pentoxide P_2O_5 in its composition or in some cases, aluminum(III) oxide Al_2O_3, forming an additional surface layer of either alumina-silicate or calcium-phosphate species on the surface of the silica-rich layer. This comes as a result of dealkalization, surface structural modifications or precipitation from solution [9, 10]. Glasses like these tend to be very durable in both acidic and alkaline solutions, which contribute to the formation of a hydroxyapatite layer capable of creating a bond with tissue.

Hench, his students, and his second wife, June Wilson, a clinical biologist, also noted that this mechanism contributed to 45S5 creating strong bonds to living tissue because of the expression of bone-growth genes [2, 11] in the body that was stimulated by the chemical byproducts of the glass components in the body due to Type III surface interaction [10].

2.1 Mechanism of bioactive glass as an implant and hydroxyapatite (HA) formation

The chemical mechanism that occurs once a bioactive glass is successfully introduced into the body as an implant involves a series of ion transfer reactions, as shown

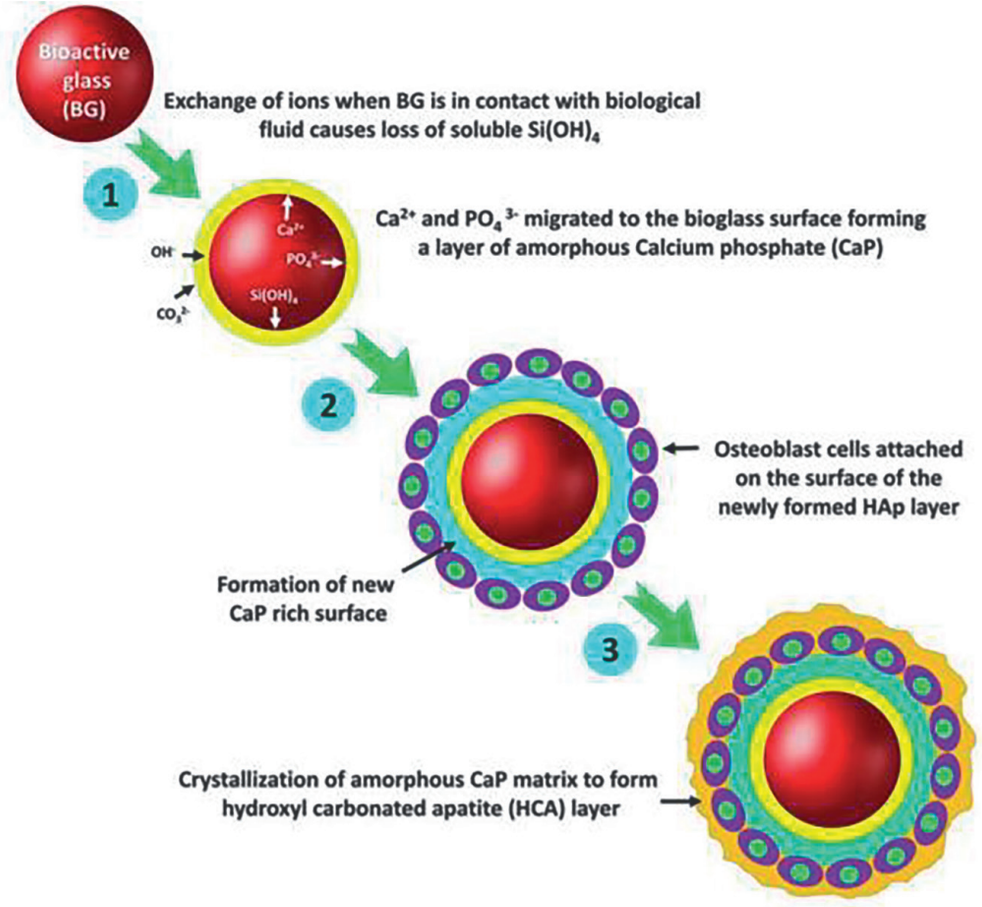

Figure 1.
Illustration of series of ion exchanges involved in the formation of HA [12].

in **Figure 1**, that result in the formation of hydroxyapatite (HA). The HA formation is required for the conformation of bioactivity. When a bioactive glass comes into contact with the bodily environment, a series of reactions occur to confirm bioactivity according to **Figure 1** in a 5-stage process:

1. Cation exchange involving the monovalent and bivalent cations present in the glass with the H^+ from the solution, leading to the formation of Si-OH (silanol) bonds on the glass surface and an increase in pH.

2. The pH continues to increase while Si-O-Si bonds are attacked by hydroxyl ions, causing soluble silica $Si(OH)_4$ to be lost in solution and increases the silanol concentration at the glass surface exposed to the fluid.

3. Condensation and polymerization of silanol groups occur, resulting in the formation of a silica-rich amorphous layer (silica gel).

4. Calcium and phosphate ions diffuse through the silica gel, forming and amorphous $CaO\text{-}P_2O_5$ rich film on the silica gel layer film which later crystalizes.

5. The crystallization of the $CaO\text{-}P_2O_5$ amorphous layer leads to the formation of HA.

Following the confirmation of bioactivity in stage 5, adsorption and desorption of growth factors, produced by the surrounding cells, are enhanced by the HA layers. Thereafter, macrophages prepare the implant site for tissue repair by the elimination of dead cells, followed by the attachment of osteoblast stem cells. The following stage involves the differentiation and proliferation of the osteoblast stem cells toward the mature osteoblast phenotype. This typically occurs within hours to weeks depending on the class of the bioactive material. Thereafter, generation of an extracellular matrix occurs as growth factors stimulate cell division and mitosis and the proteins required for the matrix development. The extracellular matrix becomes mineralized followed by the encasement of mature osteocytes in a collagen-HCA matrix, resulting in bone growth [13].

2.2 The original Bioglass® composition

The novel glass composition Bioglass 45S5 was of the Na_2O-CaO-SiO_2-P_2O_5 glass system and was known to possess a high calcium concentration with its composition close to a eutectic in the Na_2O-CaO-SiO_2 phase diagram [4, 5, 14]. Hench's novel discovery included this glass system in the following mol% concentration: 46.1%SiO_2, 24.4%Na_2O, 26.9%CaO, 2.6%P_2O_5. This glass composition was trademarked Bioglass® and since then has only been used in Ref. to the 45S5 composition and not for any other general bioactive glasses [14]. Its ability to create a bond to bone so strong that it could only be removed once the bone was broken.

2.3 Characterization and measurement of bioactivity

Figure 2 illustrates a ternary plot in increments of 10 wt% of the three base compounds with the addition on P_2O_5 for the formation of the novel Bioglass® composition, and for the design of other potential bioactive glasses and glass ceramics based on

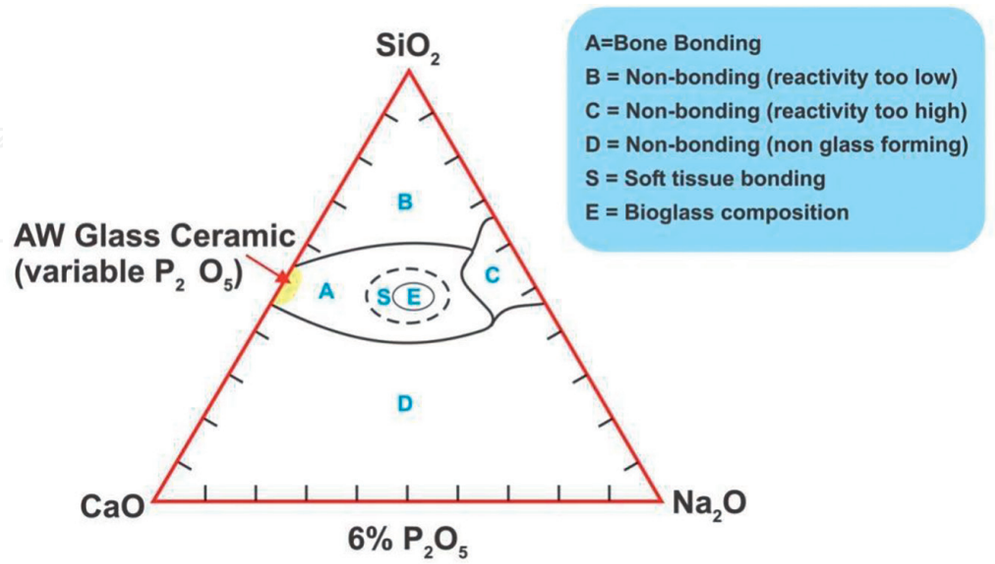

Figure 2.
Compositional dependence (wt%) of bone bonding and soft tissue bonding of bioactive glass and glass-ceramics. The compositions within region a have a constant 6%P_2O_5 apart from AW glass ceramic which consists of concentration of P_2O_5 greater than 6%. Regions S and E both have the ability to interact with and bond to soft tissue and within region E specifically lies the novel bioglass® composition reprinted with permission from [15].

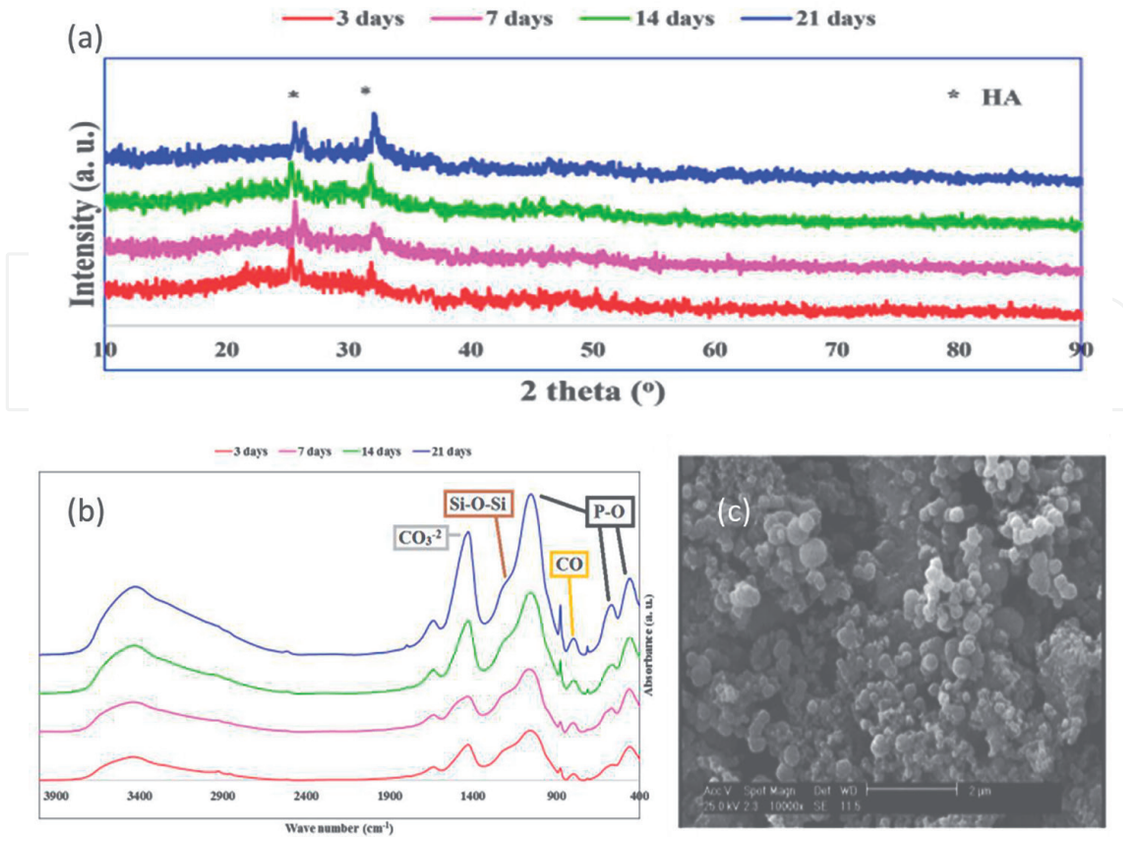

Figure 3.
(a) XRD analysis and identification of HA formation through starred peaks after glass composition S4-Z1 is immersed in SBF solution for 3,7, 14 and 21 days respectively. (b) FTIR analysis of S4-Z1 after immersion in SBF for 3. 7, 14, and 21 days respectively. (c) HA formation identified via SEM analysis after immersion in SBF solution for 21 days. Reprinted with permission [19].

the wt% of each component. Within it identifies regions of bonding type as it relates to the ability to bond to hard or soft tissue. This is a good tool to predict the bioactive behavior of glass compositions within the SiO_2-Na_2O-CaO series and other potential series depending on the compounds involved in the desired composition.

The index of bioactivity, I_B, is used to indicate the measurement of the bioactivity of any material. Introduced by Hench, $I_B = 100/t_{0.5bb}$, where $t_{0.5bb}$ is the time for more than 50% of the implant interface to be bonded to bone [16]. Bioactivity increases as the I_B increases.

Since 1994, bioactive materials were classified into Class A and Class B types. Class A bioactive materials were determined to be osteoproductive materials which elicit both intracellular and extracellular responses at its interface. Therefore, Class A bioactive glasses have the ability to bond with both bone and soft tissue. Class B materials are known as osterconductive materials which elicit only an extracellular response at its interface. Therefore, osteoconductive implants provide a biocompatible interface along which bone migrates. Bioglass® is both osteoproductive and osteoconductive and has an I_B of 10 [17]. Region D in **Figure 2** has an I_B of 0 while there is an I_B of 2 at region A, and it increases as the composition becomes more central on the ternary plot [18].

Experimental processes known to test for bioactivity include *in vivo* or *in vitro* studies. However, many scientists have performed *in vitro* studies such as Simulated Body Fluid (SBF) testing followed by Fourier Transform infrared spectroscopy (FTIR), Scanning electron microscopy (SEM), and X-ray diffraction (XRD). FTIR analysis is performed to detect the presence of HA formation by identifying and

evaluating bond bending and stretching inherent to particular functional groups. XRD analysis is possible through the evaluation of phase analysis and identification of peaks absorbed at certain wavelengths, while SEM analysis is used to evaluate the morphology and microstructure of the HA formation. These are indicated in the following **Figure 3** for the analysis of a bioactive glass composition S4-Z1 after submersion in SBF solution at room temperature for 3, 7, 14, and 21 days respectively.

3. Development throughout the years

As Hench's introduction of the novel 45S5 Bioglass® to the medical and engineering era became popular, it birthed future opportunities and advancements for bioactive glasses as researchers sought to make targeted improvements with it to further their knowledge about their applications. Additionally, toxicity of the glasses and environmental factors such as temperature, pressure, and pH must be considered when designing a particular bioactive glass for medical applications. Throughout the years, bioactive glasses have been used in the following areas: dental fillings and treatment, scaffold production, incorporation into other materials such as polymers and for hard and soft bone tissue engineering [20]. Further exploration and experimentation with bioactive glass compositions, led to the formation of many different compositions intended for specific purposes which were achieved by incorporating other compounds to customize them based of the desired characteristics. A few base compositions that have been created overtime is listed in the following **Table 1**.

Most of the bioactive glass compositions in **Table 1** consists of the following four compounds: SiO_2, Na_2O, CaO, and P_2O_5. The original 45S5 composition served to identify which combinations of compounds produced a glass with ideal bioactive properties. While the S53P4 composition comprised of a slight variation of Hench's original 45S5 composition, the 13-93 and 13-93B1 compositions include compounds not found in Hench's original composition. Although these deviations from the 45S5 composition reduces their bioactive potential, other benefits are gained. For example, S53P4 bioactive glass is more stable than the 45S5 composition and borate-based bioactive glasses stimulate faster hydroxyapatite (HA) formation rates. Magnesium ions have been shown to increase bioactive glass antibacterial properties and synergize well with host Mg ions in the body during the bone formation process. Furthermore, the "addition of borate ions into the glass matrix has been proven to increase apatite

	Composition (wt%)									
Name	**SiO_2**	**Na_2O**	**CaO**	**P_2O_5**	**K_2O**	**MgO**	**B_2O_3**	**ZnO**	**CuO**	**Source**
45S5	45.0	24.5	24.5	6.0	•	•	•	•	•	[20]
S53P4	53.0	23.0	20.0	4.0	•	•	•	•	•	[20]
13-93	53.0	6.0	20.0	4.0	12.0	5.0	•	•	•	[20]
13-93B1	34.4	5.8	19.5	3.8	11.7	4.9	19.9	•	•	[20]
13-93B3	•	6.0	20.0	4.0	12.0	5.0	53.0	•	•	[22]
GL1605	•	6.4	20.0	4.0	12.0	5.0	51.6	1.0	0.4	[22]

Table 1.
Composition of various silicate-based bioactive glasses [20].

formation rates" on bioactive glass surfaces. This in turn opens the potential for a faster bone remodeling process [21].

The continuous evolution of bioactive glasses is also revealed through their clinical applications. Silica-base bioactive glasses such as the nominal 45S5 and the S53P4 composition were the original accepted standard in the implantation industry. Their rapid surface reaction time and comparatively low softening temperatures allow for optimal conditions for bone remodeling. Recently, though, borate-based bioactive glasses have gained a foothold in the tissue engineering market. Having been approved in 2016 and 2018 respectively, the 13-93B3 and GL1605 compositions represent the newer borate bioactive glass compositions. Borate glasses on average have been shown to release Na and Ca ions at a faster rate than their silica-based counterparts [22]. They are also responsible for slower regional pH increases than silica glasses due to reduced concentrations of alkali ions and the presence of boron. Whether these features are improvements to silica-based glasses or not is up to researchers and their intended applications, but nevertheless, borate glasses have contributed to the expansion of the bioactive glass market.

3.1 Limitations of bioactive glasses

Like all materials, researchers are continuously testing and expanding the limitations of the base bioactive compositions. For example, some base compositions are more appropriate for environments under constant load while others for those of brief, high load amplitudes. Another factor to consider is the alkalinization of regions introduced to bioactive glasses. While this may not be significant at lower concentrations, it hinders the extent that base bioactive glass compositions can be incorporated into the body since large pH changes can be detrimental to human health. Researchers in response have to determine viable methods of retaining the beneficial effects bioactive glasses present while lessening their control over regional pH. Likewise, the intrinsic brittle nature of bioactive glasses has prompted researchers to consider alternative methods of incorporating them into the body that maintain their biological benefits while increasing their strain to failure nature [23–25]. Rather than diverting valuable resources toward synthesizing different base bioactive glass compositions for singular uses, researchers are now looking to expand base properties through a variety of methods. The goal is to synthesize inorganic bioactive glasses that feature similar properties to materials found within the human body (**Table 2**).

Material	Compressive Modulus (GPa)	Bending Strength (MPa)	Compressive Strength (MPa)	Fracture Toughness (MPa $m^{1/2}$)	Vickers Hardness (MPa)	Structure	Source
HA	35–120	60–120	100–150	0.8–1.2	90–140	Ceramic	[20]
Bioglass® 45S5	60	40	•	0.6	•	Glass	[20]
Bioglass 52S4.6	60	40	•	•	•	Glass	[20]
Trabecular Bone	0.05–0.6	10–20	1.5–7.5	0.1–0.8	40–60	•	[20]
Cortical Bone	7–30	50–150	100–135	2–12	60–75	•	[20]

Table 2.
Mechanical properties of various bioactive glasses, ceramics, and human bones [20].

3.2 Doping-glass performance and manipulation

Customization and improvement of bioactive glasses can be achieved through doping. Doping involves the introduction of impurities or other elements into a base composition that would result in the enhancement in properties (mechanical, biological, structural, thermal, electrical, optical) of the particular product. Wetzel *et al* indicated a limitation of Bioglass® where it easily crystalized during high temperature processing. They deduced that the addition of Mg or Zn on the form of MgO or ZnO even at low concentrations improved the thermal behavior of Bioglass® [24]. Although doping is relatively simple to accomplish, the doping technique implemented can affect the extent of doping taking place. Likewise, there are various parameters one must consider when doping a material or bioglass in this instance. As previously stated, a doping technique must be selected under the assumption that some techniques are more applicable under certain conditions than others. For example, the standard melting technique is relatively straightforward, but the P_2O_5 within the bioactive glass has a much lower melting temperature than the other components [24–26]. A higher temperature processing can lead to the evaporation of a portion of the substance composition, therefore decreasing the overall bioactive potential of the glass along with other properties. Moreover, concentration of dopant material should be determined.

The CaO present in the Bioglass® composition increases its durability. Studies have shown that "when 10 mol% of CaO was substituted with 10 mol% SiO_2 to form 20%Na_2O-10%CaO-70%SiO_2", it exhibited a slower Na^+ dissolution, and a more stabilized SiO_2-rich surface film when compared to the binary 20%Na_2O-80%SiO_2. This is due to the presence of CaO acts as a modifier that increases the coupling reactions between Si-O-Si and NS bonds, stabilizing the SiO_2 rich film by filling the micro voids that form as a result of the Na dissolution, satisfies the bond in this film and prevents any further loss of Na ions [10]. The presence of P_2O_5 allows for the formation of a secondary calcium phosphate film that develops on the side that is in contact with the organic fluid environment.

In some bioactive glass and dopant compositions, low dopant concentrations may not produce the desired properties while high concentrations can. On the other hand, high dopant concentrations may have disadvantages associated with them such as cytotoxic and carcinogenic effects while low concentrations minimize them and provide protection from these drawbacks. Additionally, the application that a bioactive glass will be used for must also be taken into account when doping.

Other functional variables such as load, fatigue, temperature, and the substances that a bioactive glass will experience in its application are essential in the selection of a desired bioactive glass composition. While a doped bioactive glass may function well under minimal stress at room temperature, its properties may not be ideal in its environment of use. Therefore, it is important to consider the dopant material, concentration, and its application to ensure the promotion of ideal properties and the minimization of those that are not wanted.

Transition metals currently make up a large proportion of suitable dopants due to the medical benefits they provide. Elements like iron (Fe), copper (Cu), magnesium (Mg), and zinc (Zn) that already play vital roles within the human body are the focus of these studies [21, 26–30]. Similar interest has also been directed toward the rare earth elements. Various elements like Gadolinium (Gd), Erbium (Er), and Holmium (Ho) that are extensively used in a wide range of medical treatments are attractive avenues for researchers to explore [31–33]. While these make up most target dopant

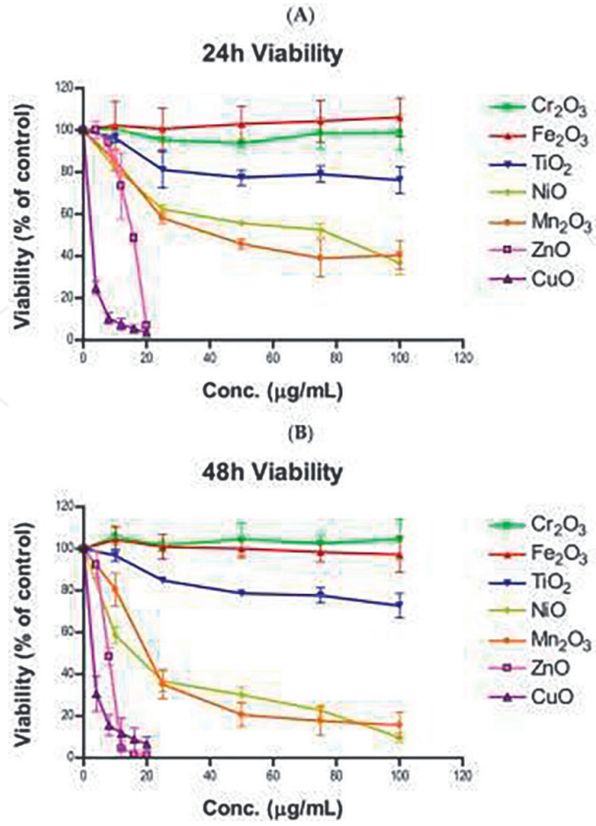

Figure 4.
Cell viability of various transition metal oxides on A549 cells. **Figure 1A** *and* **B** *Model the importance of researchers understanding the biological effects dopant compounds have on the human body. Cell viabilities below 70% are considered to be cytotoxic. While Cr_2O_3 and Fe_2O_3 caused little to no change in cellular viability, the same cannot be said for the oxides of Cu, Zn, Mn, and Ni. However, these ions are also key contributors to various vital functions in the human body [28].*

materials, much work is needed to understand the effects that doping a bioactive glass with one of these compounds will have and their extent. **Figure 4** reveals the cytotoxic effects that various transition element doping oxides have on cell lines. While some compounds may increase desired bioactive glass components, their biocompatibility should also be assessed before wide-spread usage.

3.2.1 Boron oxide (B_2O_5)

It has been experimentally revealed that borate glass systems exhibit greater hydroxyapatite (HA) formation and dissolution rates than their silicate-based relatives (ex: 45S5, 13-19, S53P4). Furthermore, borate glasses have been used for healing applications by medical professionals due to the borate ions possessing inherent antibacterial capabilities. When bioactive glasses are doped with borate ions, there was a "gradual increase in surface apatite formation rates" with increased concentration. [34] Additionally, the antibacterial properties of borate doped glass composition increased with greater doping concentrations. This trend is repeated microstructurally as the glass transition temperature, T_g, decreases with increasing borate concentrations. Moreover, the glass stability factor and crystallization peak temperature, T_p, gradually increased with increasing borate concentrations before decreasing once a concentration threshold is surpassed. This pattern is mirrored in cell proliferation studies and antibacterial tests concerning borate-doped bioactive glasses. Therefore, it is important for researchers to weigh the importance of enhanced HA formation

against decreased glass stability, cell proliferation, and antibacterial properties at greater borate concentrations. As with all materials, the conditions these bioactive glasses will be performing in will determine the importance researchers place on these material properties.

3.2.2 Copper (Cu)

Cu is another metallic ion that researchers have incorporated into bioactive glass matrices and scaffolds to increase biological performance. Researchers are drawn to it because of its positive effects on endothelial cells and blood vessel maturation. Cu is also an essential ion in the human body and plays a pivotal role in angiogenesis, so doping bioactive glasses with it serves to enhance these benefits [28, 29]. This is upheld in Cu-doped calcium phosphates and bioactive glass scaffolds that reveal enhanced angiogenesis and stimulated osteogenesis in Cu-doped bioactive glass scaffolds. The Cu^{2+} ion also possesses natural antibacterial properties and works in conjunction with the Ca^{2+} ions in BGs to increase this property. Cu-doped bioactive glasses and scaffolds have also been shown to increase the differentiation levels of mesenchymal stem cells (MSCs) and act as catalyzing agents in endothelial cell proliferation. On the other hand, bioactive glasses and scaffolds doped with Cu are less suitable at elevated temperatures than their non-doped base compositions. This is due to Cu weakening the BG matrix when it is doped which leads to a decreased glass transition temperature, T_g. While this may not change the benefits doping bioactive glasses with Cu provides, it does limit the applications of Cu-doped bioactive glasses and scaffolds.

3.2.3 Gold (Au)

Bioactive glasses doped with gold nanoparticles (AuNPs) have also garnered interest among researchers. This is because AuNPs possess a wide range of biomedical applications like therapy, hygiene, diagnostics, and prevention. It is important to note that AuNPs with small diameters (1–2 nm) are toxic in the human body because they cause damage to cell structures when absorbed [35]. However, particle diameters from 3 to 100 nm appear to not have any toxic effect on cellular structures. Not only does doping with AuNPs increase a BG's biocompatibility, but they also increase the rate of the calcium phosphate layer on the surface, bettering its osteoconductive properties. Greater amplitudes in zeta potentials are also positively correlated with increasing dopant concentrations of AuNPs. In other words, increasing the dopant concentration of AuNP corresponds to greater long-term stability for the bioactive glasses. Interestingly, researchers have also discovered that AuNPs have the possibility of being released into nearby organs from the bioactive glasses they were doped with. This has led some to pursue methods of treatment delivery to specific regions of the body.

3.2.4 Iron (Fe)

Iron was one of the initial elements that were incorporated into bioactive glasses to increase their bioactivity and antibacterial properties [28]. Fe ions have been revealed to enhance the bone metabolism process which is why they were considered as potential doping candidates into bioactive glasses. Fe-doped bioactive glasses have characteristically lower crystallization temperatures than their non-doped counterparts and also have greater storage modulus values [27]. This is turn correlates to larger elastic modulus

values for Fe-doped bioactive glasses, making them more suitable for implantation applications into the human body [25]. Likewise, scaffolds created from Fe-doped bioactive glasses have much greater degrees of formability than their base compositions. On the other hand, cytotoxic risks must be considered when doping with high concentrations of Fe which can have detrimental effects within patients and their environment. Interestingly, the magnetic properties present in Fe^{2+} ions are transferred into the base composition they are doped into. Researchers hope to take advantage of this magnetic behavior by expanding upon existing targeted therapeutic treatments.

3.2.5 Magnesium (Mg)

Magnesium is an important trace element in the human body, which is what makes it an excellent candidate for doping into bioactive glasses. The integral role Mg plays in bone development and maintenance drew researchers to include it among the first wave of transition metals to be considered as a suitable doping agent. Bioactive glasses doped with Mg have shown increased rates of HA formation on their surfaces and enhanced bioactive and antibacterial capabilities in comparison to their base concentrations [21]. Additionally, these bioactive glasses have exhibited superior long-term osteoconductive and biocompatibility properties. This is important because researchers are continuously seeking methods to increase biomedical implant lifespans since the percentage of individuals outliving their implants is increasing. Furthermore, Mg-doped bioactive glasses have promising applications in skeletal tissue regeneration due to their lower ionic release rates which do not affect the cellular environment to the extent of those with elevated rates.

3.2.6 Rare earth elements (REE)

Many REE ions have practical medical applications including but not limited to imaging techniques, cancer treatments, and pain relief [32]. Therefore, it is not surprising that some of these elements are viable options for therapeutic bioactive glasses. REE have been shown to promote bone repair and increase osteogenesis rates [31]. This is due to their ability to mimic calcium's role in the bone repair process and open the door to bone density disorder treatments. There are concerns about their cytotoxicity to both patients and the environment (**Table 3**), but that is for researchers to determine what level of risk is acceptable while achieving sought-after results [33]. Furthermore, the sustainability of REE's use as a whole is in question since demand for these naturally occurring elements will soon outweigh their supply. Solutions ranging from increased research into REE recycling and replacement are viable options to consider. However, one may also decide that the resources spent in developing a solution can be otherwise diverted to additional research into other dopant materials.

3.2.7 Silicon nitride (Si_3N_4)

Greater quantities of bone tissue around bioactive glasses have been observed with Si_3N_4-doped BGs [23]. This compound's high strength, fracture toughness, low friction wear, and biocompatibility make it an ideal doping substance for bioactive glasses designed for load-bearing purposes. It is also important to note that Si_3N_4 is an osteoconductive biomaterial with the potential to catalyze osteogenesis. In other words, this compound increases the rate of bone formation by reducing the time it takes bone-forming cells to reach their target regions. Like other viable dopants,

Compound	3 T3 NRU cytotoxicity test		Test *T. tubifex*			Source
	IC_{50} (μg/ mL)	Calculated LD_{50} (mg/ kg b.w.)	EC_{50} (g/ L)	EC_{50} (mol/ L)	$IgEC_{50}$ (mol/ L)	[33]
Erbium (III) chloride hexahydrate	613.1	1135.2	31.6	0.0827	- 1.08	[33]
Lanthanum (III) chloride heptahydrate	379.4	962.6	28.2	0.076	- 1.12	[33]
Praseodymium (III) chloride hydrate	532.4	1085.1	18.7	0.0755	- 1.12	[33]
Europium (III) chloride hexahydrate	530.3	1078.4	26.9	0.0734	- 1.13	[33]
Gadolinium (III) chloride hexahydrate	571.2	1120.7	27.4	0.0736	- 1.13	[33]
Ytterbium (III) chloride hexahydrate	423.1	1001.3	31.0	0.0801	- 1.10	[33]
Samarium (III) chloride hexahydrate	575.6	1124.0	25.1	0.0689	- 1.16	[33]
Thulium (III) chloride anhydrous	440.7	1015.0	22.7	0.0825	- 1.08	[33]
Dysprosium (III) chloride hexahydrate	931.8	1264.0	31.5	0.0836	- 1.08	[33]
Terbium (III) chloride hexahydrate	397.4	979.2	31.6	0.0846	- 1.07	[33]
Holmium (III) chloride hexahydrate	963.6	1205.3	27.1	0.0714	- 1.15	[33]
Lutetium (III) chloride hexahydrate	580.2	1066.5	34.3	0.088	- 1.06	[33]
Yttrium (III) chloride hexahydrate	377.0	959.6	31.0	0.0801	- 1.10	[33]
Neodymium (III) chloride hexahydrate	418.5	966.2	25.8	0.072	- 1.14	[33]
Cerium (III) chloride heptahydrate	501.9	1067.1	31.7	0.0852	- 1.07	[33]
Barium Chloride	661.5	1184.0	15.6	0.075	- 1.12	[33]
Cadmium chloride	0.252	62.7	16.5	0.09	- 1.05	[33]

Table 3.
Cytotoxicity and Ecotoxicity of rare earth compounds [33].

Si_3N_4 promotes MSC differentiation into osteoblasts and improves their adhesion to organic material. This in turn leads to an increased production of collagen and mineralization, enhancing the bone formation process. The increased bone formation also corresponds with an increase in environment pH. This is due to the Na^+ and Ca^{2+} ions being released during bone formation that create hydroxides which contribute to an increase in regional pH. This phenomenon is shared among most bioactive glass compositions, and there are a multitude of methods to negate potential detrimental effects to patients.

3.2.8 Silver (Ag)

Silver was one of the first transition metals that researchers attempted to dope bioactive glasses with. This is due to its inherent antibacterial capability that covers a wide array of diseases. Medical professionals have enjoyed its benefits in surgical applications and researchers sought to expand upon their success. It has been observed that Ag-doped bioactive glasses have greater bioactive and antibacterial capabilities than their non-doped bioactive glass counterparts [28]. Furthermore, Ag particles are able to diffuse uniformly throughout the bioactive glasses in which they are doped. The feature of not forming a separate Ag layer at the glass surface is important because some unintended and potentially dangerous cellular responses can occur [36]. Likewise, the antibacterial and bioactive benefits Ag particles present are countered by their possible cytotoxic effects in the human body at high concentrations. Therefore, researchers' margin of error and the specific application of these bioactive glasses play key roles in determining the extent they are doped with Ag particles.

3.2.9 Zinc (Zn) and strontium (Sr)

Zinc and Strontium have been doped separately and together into bioactive glass compositions to optimize their properties. Zn is responsible for promoting bone formation while Sr. has been found to limit bone resorption and promote bone remodeling [30]. Bioactive glasses, MSC proliferation and differentiation processes are also increased by the doping of Zn and Sr. When Zn is doped into the glass matrix, it is distributed uniformly, and the surface matrix experiences an accelerated growth of its apatite layer. This in turn corresponds to an overall increase in bioactivity. It is important to note that doping the bioactive glass with too much Zn will increase the potential of cytotoxic effects and a create a lower degradation profile. Additionally, solely doping a bioactive glass with Sr. has been found to limit the formation of the apatite layer on the glass surface. Furthermore, the Sr-glass network is looser than the base glass and Zn-glass networks due to Sr's ionic radius being larger than those of Ca, the element being substituted with the dopant material, and Zn. Although extensive research has been done regarding these differences in glass networks, there do not seem to be any significant effects in BG properties when low doping concentrations are used. Likewise, it has been experimentally determined that small molar concentrations of Zn (~2%) and Sr. (~5%) produce optimum cell proliferation and differentiation properties, minimizing negative effects associated with elevated doping concentrations. Co-doping the bioactive glass composition with both Zn and Sr. results in a combination of the two dopant effects. The (Zn + Sr)-glass network promotes cell proliferation and differentiation while also limiting the formation of the glass's surface apatite formation and bone resorption. These represent a few of the various elements and their effects that are considered throughout the glass doping process.

4. Conclusion

Over the past few decades, since the discovery of Bioglass® in 1969, hundreds of other bioactive glass compositions have been derived or attempted, all with the hopes of either improving properties of existing applications such as metal implants, or to personalize a specific composition for a unique application. For instance, using a bioactive glass composition to coat a particular metal alloy for implantation. Over the

years, researchers have introduced elements in the form of compounds into base compositions with the aim of achieving distinct properties such as increased bioactivity, anti-bacterial behavior, bone proliferation, etc. Therefore, they have since seen promising outcome when incorporating elements such as magnesium, copper, zinc, boron, and strontium, just to name a few. The evolution of bioactive glasses has already shown promising progress and is expected to be become a staple prat in medical devices and applications within the near future. However, this journey has yet to continue. It is important to evaluate the biological response to the newly developed bioactive glass compositions to fully understand their risks and benefits. We are curious to see where this field is leading us in the next years.

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Conflict of interest

The authors declare no conflict of interest.

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References

[1] Hench LL, Kokubo T. Properties of bioactive glasses and glass-ceramics. In: Handbook of Biomaterial Properties [Internet]. Springer US; 1998 [cited 2021 Jun 10]. p. 355-63. Available from: https://link.springer.com/chapter/10.1007/978-1-4615-5801-9_22

[2] Simmons JH, JNCS. The Professional Life of Larry L. Hench – a true renaissance scientist/engineer. J Non Cryst Solids. 2016 Mar 15;436:58-61.

[3] Karlsson KH, Hupa L. Thirty-five years of guided tissue engineering. J Non Cryst Solids. 2008 Jan 15;354(2-9):717-21.

[4] Jones JR. Reprint of: Review of bioactive glass: From Hench to hybrids. Vol. 23, Acta Biomaterialia. Elsevier Ltd; 2015. p. S53-82.

[5] Hench LL. The story of Bioglass®. In: Journal of Materials Science: Materials in Medicine. 2006. p. 967-78.

[6] Kokubo T. Bioactive glass ceramics: properties and applications. Biomaterials. 1991 Mar 1;12(2):155-63.

[7] Hench LL, Splinter RJ, Allen WC, Greenlee TK. Bonding mechanisms at the interface of ceramic prosthetic materials. J Biomed Mater Res [Internet]. 1971 Nov 1 [cited 2021 Jun 10];5(6):117-41. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jbm.820050611

[8] Wilson J, Pigott GH, Schoen FJ, Hench LL. Toxicology and biocompatibility of bioglasses. J Biomed Mater Res [Internet]. 1981 Nov 1 [cited 2021 May 23];15(6):805-17. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jbm.820150605

[9] Clark AE, Hench LL, Paschall HA. The influence of surface chemistry on implant interface histology: A theoretical basis for implant materials selection. J Biomed Mater Res [Internet]. 1976 Mar 1 [cited 2021 May 23];10(2):161-74. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jbm.820100202

[10] Hench LL. Physical chemistry of glass surfaces. J Non Cryst Solids. 1977 Sep 8;25(1-3):343-69.

[11] Hench LL, Wilson J. Surface-active biomaterials. Vol. 226, Science. 1984. p. 630-6.

[12] Oliver J anne N, Su Y, Lu X, Kuo PH, Du J, Zhu D. Bioactive glass coatings on metallic implants for biomedical applications. Vol. 4, Bioactive Materials. KeAi Communications Co.; 2019. p. 261-70.

[13] Hench LL, Best SM. Ceramics, Glasses, and Glass-Ceramics: Basic Principles. In: Biomaterials Science: An Introduction to Materials: Third Edition. Elsevier Inc.; 2013. p. 128-51.

[14] Jones JR. Review of bioactive glass: From Hench to hybrids. Vol. 9, Acta Biomaterialia. 2013. p. 4457-86.

[15] Baino F. Bioactive glasses – When glass science and technology meet regenerative medicine. Vol. 44, Ceramics International. Elsevier Ltd; 2018. p. 14953-66.

[16] Koga N, Strnad Z, Šesták J, Strnad J. Journal of Thermal A nalysis and Calorimetry, V ol. Vol. 71. 2003.

[17] Cao W, Hench LL. Bioactive materials. Ceram Int. 1996 Jan 1;22(6):493-507.

[18] Hench LL. Bioglass: 10 milestones from concept to commerce. J Non Cryst Solids. 2016 Jan 15;432:2-8.

[19] Goudarzi Z, Parvin N, Sharifianjazi F. Formation of hydroxyapatite on surface of SiO2–P2O5–CaO–SrO–ZnO bioactive glass synthesized through sol-gel route. Ceram Int. 2019 Oct 15;45(15):19323-30.

[20] Verrier S, Blaker JJ, Maquet V, Hench LL, Boccaccini AR. PDLLA/Bioglass® composites for soft-tissue and hard-tissue engineering: An in vitro cell biology assessment. Biomaterials. 2004 Jul 1;25(15):3013-21.

[21] Wetzel R, Bartzok O, Hupa L, Brauer DS. Low Mg or Zn substitution for improved thermal properties of Bioglass 45S5. Mater Lett. 2019 Dec 1;256:126599.

[22] Jung S, Day T, Boone T, Buziak B, Omar A. Anti-biofilm activity of two novel, borate based, bioactive glass wound dressings. Biomed Glas [Internet]. 2019 Jan 1 [cited 2021 May 25];5(1):67-75. Available from: https://doi.org/10.1515/bglass-2019-0006

[23] Marin E, Adachi T, Boschetto F, Zanocco M, Rondinella A, Zhu W, et al. Biological response of human osteo-sarcoma cells to Si3N4-doped Bioglasses. Mater Des. 2018 Dec 5;159:79-89.

[24] Fu Q, Rahaman MN, Sonny Bal B, Brown RF, Day DE. Mechanical and in vitro performance of 13-93 bioactive glass scaffolds prepared by a polymer foam replication technique. Acta Biomater [Internet]. 2008;4:1854-64. Available from: www.sciencedirect.com

[25] Saxena V, Kumar V, Singh A, Singh VK. Effect of reinforcing S53P4 bioactive glass on physio-mechanical and biological properties of Ti-8Nb-2Fe alloy. 2019; Available from: https://doi.org/10.1016/j.ceramint.2019.07.184

[26] Balamurugan A, Balossier G, Kannan S, Michel J, Rebelo AHS, Ferreira JMF. Development and in vitro characterization of sol-gel derived CaO-P 2 O 5-SiO 2-ZnO bioglass. Available from: www.actamat-journals.com

[27] Chiu K-Y, Chen K-K, Wang Y-H, Lin F-H, Huang J-Y. Formability of Fe-doped bioglass scaffold via selective laser sintering. 2020; Available from: https://doi.org/10.1016/j.ceramint.2020.03.216

[28] Gupta N, Santhiya D, Murugavel S, Kumar A, Aditya A, Ganguli M, et al. Effects of transition metal ion dopants (Ag, Cu and Fe) on the structural, mechanical and antibacterial properties of bioactive glass. 2017; Available from: https://doi.org/10.1016/j.colsurfa.2017.11.023

[29] Hoppe A, Meszaros R, Stähli C, Romeis S, Schmidt J, Peukert W, et al. In vitro reactivity of Cu doped 45S5 Bioglassâ derived scaffolds for bone tissue engineering. [cited 2021 Apr 21]; Available from: www.rsc.org/MaterialsB

[30] Wu X, Meng G, Wang S, Wu F, Huang W, Gu Z. Zn and Sr incorporated 64S bioglasses: Material characterization, in-vitro bioactivity and mesenchymal stem cell responses. Mater Sci Eng C. 2015 Jul 1;52:242-50.

[31] Zhu D-Y, lu B, Yin J, Ke Q-F, Xu he, Zhang chang-Q, et al. gadolinium-doped bioglass scaffolds promote osteogenic differentiation of hjBMsc via the akt/gsK3β pathway and facilitate bone repair in vivo. Int J Nanomedicine [Internet]. 2019 [cited 2021 Apr 21];14:1085-100. Available from: http://dx.doi.org/10.2147/IJN.s193576

[32] Giese E. Rare Earth Elements: therapeutic and diagnostic applications in modern medicine. Clin Med Reports. 2018;2(1).

[33] Rucki M, Kejlova K, Vlkova A, Jirova D, Dvorakova M, Svobodova L, et al. Evaluation of toxicity profiles of rare earth elements salts (lanthanides) *. 2020; Available from: https://doi.org/10.1016/j.jre.2020.02.011

[34] Prasad S. S, Datta S, Adarsh T, Diwan P, Annapurna K, Kundu B, et al. Effect of boron oxide addition on structural, thermal, in vitro bioactivity and antibacterial properties of bioactive glasses in the base S53P4 composition. J Non Cryst Solids [Internet]. 2018; 498(May):204-15. Available from: https://doi.org/10.1016/j.jnoncrysol.2018.06.027

[35] Magyari K, Nagy-Simon T, Vulpoi A, Popescu RA, Licarete E, Stefan R, et al. Novel bioactive glass-AuNP composites for biomedical applications. 2017 [cited 2021 May 19]; Available from: http://dx.doi.org/10.1016/j.msec.2017.03.138

[36] Kozon D, Zheng K, Boccardi E, Liu Y, Liverani L, Boccaccini AR. Synthesis of monodispersed Ag-doped bioactive glass nanoparticles via surface modification. Materials (Basel) [Internet]. 2016 [cited 2021 May 20];9(4). Available from: /pmc/articles/PMC5502798/