Bioactive Glass in Medicine: A Mini-Review of Composition, Properties, Bioactivity Mechanisms, and Clinical Applications

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Abstract

From ancient civilizations using gold and silver for healing to the metal surgical instruments of the Renaissance, the introduction of anesthetic and antiseptic treatments in the 19th century, and the 20th century medical device revolution, the history of medical materials is an inventive one. Today, modern healthcare is being shaped by materials like bioglass.
Dr. Larry Hench invented bioglass in 1969, and it has since been used extensively in biological and medical application. This brief study covers composition, bioactivity mechanisms, and healthcare applications of bioglass. Bioglass has a wide range of applications, including bone regeneration, tissue engineering, implantable devices, and more thanks to its remarkable bioactivity, biocompatibility, and tissue bonding properties. The sol-gel synthesis method, offering lower processing temperatures and uniform compositions, has gained prominence. Although there are still issues with optimizing bioglass for various biomedical uses, current research and innovation show promise for the material's future advancement in healthcare.

Keywords: Bioglass Materials, Bioactivity, Tissue Engineering, Bioactive Glass.

1. Introduction

Bioglass, also known as bioactive glass (BG), represents a specialized type of glass with remarkable properties that make it invaluable in biomedical and healthcare applications. Dr. Larry Hench and his research group invented this revolutionary substance in 1969.[1] Their ground-breaking research intended to develop a substance that might interact well with living tissues. As a result, bioglass possesses distinctive attributes, including notable bioactivity, biocompatibility, and antibacterial properties. [2–8]The flagship bioactive glass, known as 45S5, boasts a composition of 45% SiO_2, 24.5% CaO, 24.5% Na_2O, and 6% P_2O_5 (wt.%).[1]This glass has been the parent composition for many bioactive glasses. These bioactive glasses develop strong bonds with the bone through the formation of hydroxyapatite (HA) or hydroxycarbonate apatite (HCA) layer on the surface by releasing Si, Ca, P and Na ions and stimulate the formation of bone tissues when implanted in the living body.[9]Bioglass primarily consists of silica (SiO_2) along with a blend of other oxides such as sodium oxide (Na_2O), calcium oxide (CaO), and phosphorus pentoxide (P_2O_5), with the precise composition varying based on intended applications and manufacturers.

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There are now several types of bioactive glass: the conventional silicates, such as Bioglass 45S5; phosphate-based glasses; borate-based glasses.[10] These bioactive glasses are able, following contact with body fluids, to form a film of bone-like mineral (crystalline calcium phosphate, or apatite) on their surface, following a rapid sequence of inorganic processes, involving ion release, hydrolysis, and partial dissolution. Bioglass 45S5 bonds with bone rapidly and also stimulates bone growth away from the bone–implant interface. After Hench's discovery, many bioactive glasses have been synthesized and used as artificial biomaterials for bone substitutes. Besides promoting rapid bonding with bone, this property has also been associated to the unique ability of a small range of BG compositions (centered around the BG45 one) to form bonds with soft tissues, such as muscles and ligaments, which is exploited in some clinical applications.[11]

In the past fifty years, melting and sol–gel have been the two main methods used for the synthesis of bioactive glasses. In the melting method, by heating a mixture of starting precursors following a special high-temperature regime, bioactive glasses can be quickly synthesized in large quantities.[12] Melting methods involve melting a mixture of oxides and additives at high temperatures, followed by grinding after cooling to yield glass particles.[13] Nevertheless, this technique presents challenges, including the need for elevated working temperatures and potential P_2O_5 evaporation.[13] In

contrast, the sol-gel technique has emerged as an attractive alternative, delivering purer glasses at lower densification temperatures and facilitating a diverse range of compositions.[14,15] Notably, in 1991, Li et al. showcased the superiority of the sol-gel method as a viable alternative for bioglass synthesis. This approach involves mixing metal salts and metalorganic precursors in an acidic or basic catalytic medium, followed by gelation through hydrolysis and polycondensation reactions [16–18]. Sol-gel-derived bioglasses have garnered significant attention for their potential in bone tissue regeneration due to their exceptional osteoconductivity, osteostimulation, and degradation rates. These glasses establish robust bonds with bone by forming hydroxyapatite (HA) or hydroxycarbonate apatite (HCA) layers when exposed to biological fluids, irrespective of composition, exhibiting faster HA formation rates compared to melt-derived 45S5 Bioglass® [2–5,13–21].

2. Historical Background

Throughout history, biomaterials have primarily served the purpose of substituting for diseased or injured tissues. The first bioactive glass was invented by Larry Hench at the University of Florida in 1969. Professor Hench initiated his research into discovering a material capable of bonding with bone after an enlightening conversation during a bus ride with a US Army colonel. Freshly returned from the Vietnam War, the colonel inquired whether it was possible to develop materials that could withstand the harsh conditions within the human body. The challenge lay in the fact that all implant materials existing at that time, including metals and polymers engineered to be biologically inert, provoked fibrous encapsulation post-implantation instead of establishing a durable interface or bond with tissues.[1,12] Professor Hench decided to make a degradable glass in the $Na_2O–CaO–SiO_2–P_2O_5$ system, high in calcium content and with a composition close to a ternary eutectic in the $Na_2O–CaO$ SiO_2 diagram. The main discovery was that a glass of the composition 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 ®, formed a bond with bone so strong that it could not be removed without breaking the bone.[12] The University of Florida trademarked the term "Bioglass®" as the designated name for the original 45S5 composition. Originally, 45S5 Bioglass® was produced by melt-processing of oxides with high purity in a furnace at 1370 °C. The melt mixture is poured into water to quench, obtaining a frit. Next steps are drying and grounding, in order to obtain the appropriate particle size range. The Bioglass can be transferred into molds and rods or as-cast components can be produced.[20] This method is considered simple and suitable for higher quantities of products. However, the shortcoming of the method is the evaporation of P_2O_5 because of the high temperatures involved.[20] However, this technique incurs higher energy costs, and often results in partial devitrification with the formation of crystalline phases, which have reduced biological properties and are unsuitable for producing porous scaffolds.[18] Recent research has centered on the sol-gel technique, which operates at lower temperatures compared to traditional methods and offers the potential to achieve a uniform composition.[20] Sol–gel technique is the most dynamic, reliable and environmentally friendly bottom-up synthesis method which has received tremendous interest in diverse research fields such as nanotechnology, optoelectronics, semiconductors, medicines, biotechnology as well as separation science.[16] Fig. 1.A shows an X-ray micro tomography image of a bioactive glass sol-gel foam scaffold while Fig. 1.B shows an ICIE16 scaffold. Additionally, if clinical applications are considered, a method that will avoid contamination of the final product is preferred.[20]

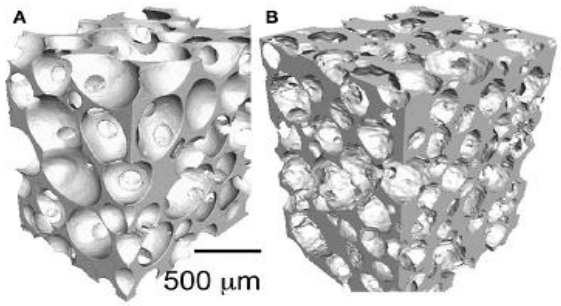

Fig. 1. X-ray microtomography images of bioactive glass scaffolds (A) sol–gel foam and (B) melt-derived gel-cast foam [20].

3. Bioglass Composition and PropertieS

The first BG (BioGlass) discovered by Hench et al. was BG 45S5, a quaternary system with a composition of 45 wt% SiO_2, 24.5 wt% CaO, 24.5 wt% Na_2O and 6 wt% P_2O_5. Since then, numerous other compositions have emerged which display similar levels of bioactivity, such as 50S BG (50 wt% SiO_2, 24.5 wt% Na_2O, 25 wt% CaO), 60S BG (60 wt% SiO_2, 36 wt% CaO, 4 wt% P_2O_5), and 76S BG (76 wt% SiO_2, 23 wt% CaO, 1 wt% P_2O_5).[17] BGs are mostly materials based on silica with calcium and phosphate as two necessary components.[22] In the quaternary formulation of $Na_2O–CaO–P_2O_5–SiO_2$- based bioactive glass (BG), the molar proportion of SiO_2 plays a pivotal role. Research has confirmed that bioactive glass enriched with up to 53% silica can establish bonds with both soft and hard tissues.[23]

In recent years, various studies have highlighted the unique properties of BGs, including osteoconduction and osteostimulation behavior, alongside their capacity to bond with both soft and hard tissues.[21] The typical physical and mechanical properties of BG have also been reported in the literature. The literature reports its mechanical strength to be 100-200 MPa, fracture toughness to be 1.2-2.6 MPa m1/2, hardness to be 458 HV, while the density of BG is approximately 2.45 g/cm3.[24] Generally, it is envisaged that the morphology and chemical compositions of sol–gel derived porous bioactive glasses significantly affect their biological properties.[16] The primary benefit of BG, which distinguishes it as a notable innovation includes its high surface speed reactivity that promotes the formation of quick networks in the tissues. Other benefits are its bioactivity, broad-spectrum antibacterial abilities, and biocompatibility. Nevertheless, every material has its impediments; BG's primary drawback is its limited mechanical strength.[25]

Since that the sol-gel method overcomes the drawbacks of the melting procedure, Table. 1. lists various studies done using the sol-gel method in which additional materials are added to bioglass and their influence on the bioglass's final qualities are discussed.

Table. 1. Various studies aim to add additional elements to bioglass using the sol-gel process.

Ion/ Element	Formation of Hydroxyapatite and Bioactivity	Effects	Ref
Silver oxide (Ag_2O), Zinc oxide (ZnO)	growth of a crystalline hydroxyapatite layer on the surface, excellent in vitro bioactivity	fine-tuning of the material's properties, such as its antibacterial characteristics and its ability to support hydroxyapatite formation.	[26]
Iron oxide (Fe_2O_3)	showed the formation of a crystalline HAp layer on its surface , in vitro bioactivity	The addition of iron oxide influenced the specific surface area, pH values, and bioactivity of the material, with higher iron oxide content leading to decreased bioactivity.	[27]
aluminum oxide (Al_2O_3)	samples exhibited the formation of a hydroxyl carbonate apatite (HCA) layer on their surfaces, in vitro bioactivity	The addition of Al_2O_3 increased the density of the glass samples due to increased network compactness. he thermal expansion coefficient decreased with the addition of Al_2O_3.	[28]
Copper (Cu)	it forms an apatite layer on its surface, in vitro bioactivity	The release of copper ions from the material into SBF has an antimicrobial effect.	[29]

4. Bioactivity Mechanisms

In this context, a bioactive material is defined as a material that stimulates a beneficial response from the body, particularly bonding to host tissue (usually bone). A bioactive glass is one that elicits a particular biological reaction at the interface of the material, which stimulates cell proliferation, gene response and the formation of a bond between living tissues and the material.[26]

Sol–gel based bioactive glasses have been extensively explored as a promising and highly porous scaffold material for bone tissue regeneration applications owing to their exceptional osteoconductivity, osteostimulation and degradation rate. These bioactive glasses develop strong bonds with the bone through the formation of hydroxyapatite (HA) or hydroxycarbonate apatite (HCA) layer on the surface by releasing Si, Ca, P and Na ions and stimulate the formation of bone tissues.[30]

Fig. 2. shows the disordered structure of a glass in the SiO_2–CaO–Na_2O system. This disordered structure, enhanced by the presence of lattice modifiers, results in high reactivity in an aqueous environment of these glasses.[31]

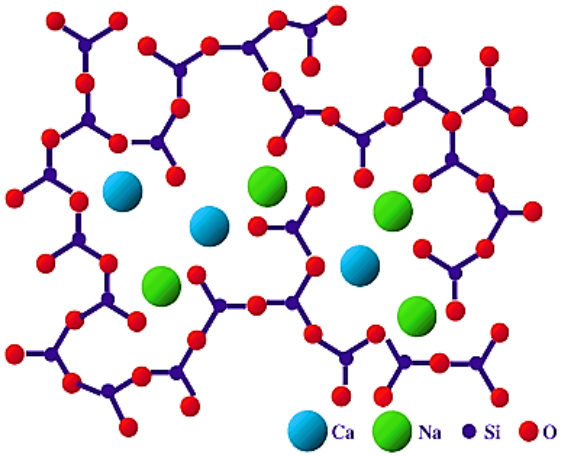

Fig. 2. Molecular Structure of Bioglass [31].

The strong bioactive response of BG is a consequence of two mechanisms: i) BG rapidly develops hydroxycarbonate apatite (HCA) layer that promotes the attachment and proliferation of osteogenic cells [24] and ii) the ionic dissolution products from BG up-regulate gene expression in human osteoblast cells promoting osteoblast metabolism and resulting in the rapid regeneration of bones.[24]

The integration of Bioglass with bone is shown in the Fig. 3. The reaction with surrounding physiological fluid at the surface of Bioglass is shown in first two steps, and the formation of new bone is shown in the last two stages.

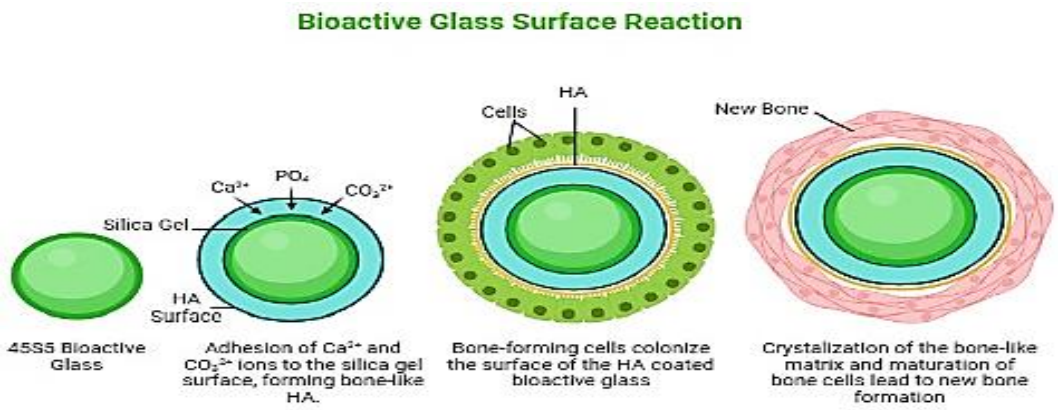

Fig. 3. A step by step image of the integration of bioactive glass with bone.

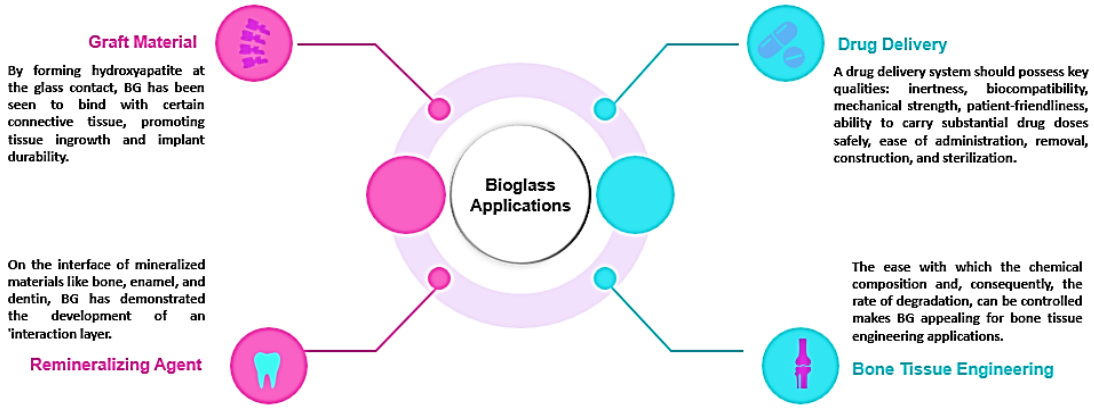

Fig. 4. Applications of bioglass in medicine.[33]

5. Applications of Bioglass

During the last decade, the demand for the biomaterials have grown significantly and the intense research interest is attributed to their wide range of applications in the healthcare and medical industries, for example; in regenerative medicines, implantable devices, wound healing therapies, tissue engineering, plastic surgeries, drug delivery systems and orthopedic disorders.[21] Bioactive glasses (BGs) possess the capacity to induce a specific in-vivo biological response at the interface while also establishing robust chemical bonds with both bone and soft tissues. overall results indicate that the proposed material is very promising for biomedical applications in bone regeneration and tissue engineering. However, the mechanical properties of these glasses have severely limited their clinical applications,[21] optimizing both the pore architecture and morphology of BGs is important to enhance their functionality for tissue engineering applications.[32] More applications of bioglass are shown in Fig. 4.

4.Conclusion

Over the past 50 years, bioactive glasses have been developed. This time period has seen significant study on the unique qualities of bioactive glasses. However, despite increasing research activity, bioactive glasses have not yet reached their full application potential. This both a challenge and a prospect for the future design of bioactive glasses.

The glass mesh can also contain numerous trace elements to obtain promising qualities that aid in bone regeneration. Bioactivity is one of the many qualities that can be affected by changing the composition of the glass. This presents an opportunity for strategic glass composition design to address multiple challenges simultaneously.

Preclinical in vivo investigations, optimizing for hard tissue, optimizing for soft tissue, getting the perfect composite combination, providing optimal biological performance, and obtaining suitable mechanical properties are some of the upcoming challenges for Bioglass.

The majority of the materials given have demonstrated acceptable biocompatibility and minimal cytotoxicity, paving the door for in vivo studies. However, considerable work still needs to be done in order to build materials ideally meeting biomedical goals.

This mini-review briefly discusses a study of bioglass, emphasizing its structure, characteristics, bioactivity, and medical uses. It emphasizes the important role that bioglass plays in promoting strong tissue connections and the importance of bioglass in the medical industry.

There are still many challenges ahead for the clinical use of bioactive glasses, requiring continued innovation.

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