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BIOACTIVE GLASSES – APPLICATIONS, CHALLENGES

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ABSTRACT
Bioactive glasses are novel dental materials that are different from conventional glasses and are used in dentistry. Bioactive glasses are composed of calcium and phosphate which are present in a proportion that is similar to the bone hydroxyapatite. These glasses bond to the tissue and are biocompatible. They have a wide range of medical and dental applications and are currently used as bone grafts, scaffolds and coating material for dental implants. This article reviews various properties of bioactive glasses and their applications and also reviews the changes that can be made in their composition according to a desired application.

KEYWORDS: Bioactive glasses, Apatite formation, Glass transition temperature, Network connectivity, Clinical Applications, Grand challenges.

INTRODUCTION

A material is said to be bioactive, if it gives an appropriate biological response and results in the formation of a bond between material and the tissue. Bioactive glasses are silicate based, containing calcium and phosphate. Hench[1] was the first to develop bioactive glasses (1969) and these glasses were able to bond to tissues. Safety of these bioactive glasses was a concern, so various studies were performed to ensure that bioactive glasses are safe for clinical applications. Wilson et al[2] (1981) reviewed these studies and proposed that bioactive glasses are safe for clinical use. Bioactive glasses caused a revolution in healthcare and paved the way for modern biomaterial-driven regenerative medicine. The first 45S5 glass composition, invented by Larry Hench fifty years ago, was able to bond to living bone and to stimulate osteogenesis through the release of biologically-active ions. 45S5-based glass products have been successfully implanted in millions of patients worldwide, mainly to repair bone and dental defects and, over the years, many other bioactive glass compositions have been proposed for innovative biomedical applications, such as soft tissue repair and drug delivery. The full potential of bioactive glasses seems still yet to be fulfilled, and many of today's achievements were unthinkable when research began. As a result, the research involving bioactive glasses is highly stimulating and requires a cross-disciplinary collaboration among glass chemists, bioengineers, and clinicians. The need to replace damaged parts of the body in order to restore their physiological functionality has always been the driving force which has supported research into the discovery and the design of new biomaterials, in order to perform this task as efficiently as possible.

After the initial definition of biomaterial, based on the criterion of maximum biochemical/biological inertness in contact with body fluids (first-generation materials), the discovery of 45S5 Bioglass by Hench in 1969 constituted—for the first time in the story of biomaterials—an alternative. Since then, the concept of biocompatibility has been extended to all those materials which were able to promote a positive response of the living organism through the formation of a strong tissue-implant bond (second-generation materials) and the genetic activation of specific cell pathways (third-generation smart materials). 45S5 Bio glass represents the first example of a biomaterial belonging to the third generation, thanks to the biological role of its ionic dissolution products released into the physiological environment. The discovery of bioactive glasses (BGs) is attributed to Larry Hench, a Research Professor in the Department of Materials Science and Engineering at the University of Florida and then Director of the Bioglass Research Centre at the same University. As often happens when talking about scientific discoveries, the discovery of BGs also seems to be, only apparently, the result of a sequence of random events (serendipity). The foundations of this discovery are to be founded in a friendly conversation between Larry Hench and a U.S. Army colonel just returned from the Vietnam War in 1967. The topic of the talk was the rejection of polymeric

and metal implants, which were used at that time for the replacement of living tissues, as they were characterized by chemical inertness. However, after being put in contact with the physiological environment, these grafting materials were surrounded by a fibrous capsule of scar tissue that compromised their integration with the host tissue. After listening to some studies about gamma rays applied to vanadia-phosphate semiconductors conducted by Hench and his coworkers, the colonel's question was simple, but at the same time, very inspirational: "If you can make a material that will survive exposure to high energy radiation, can you make a material that will survive exposure to human body?".

Hench was fascinated by the colonel's question, also in the light of its social implication. In fact, once the war in Vietnam ended, the need for materials able to replace amputated limbs and compromised tissues, without them being rejected, was a matter of considerable importance, mainly aimed at the social reintegration of survivors. Hench based the so-called "hypothesis of bioactive glass" on two pillars: (i) metals and synthetic polymers elicited a "foreign body reaction" because their components were completely different from those that make up living tissues, and

(ii) a material that was capable of forming a bone-like hydroxyapatite layer on its surface should not be rejected by the body, as hydroxyapatite is the main mineral phase of natural bone tissue. From 1969 to 1971, Hench and his coworkers designed and studied different glass formulations based on the SiO_2–Na_2O–CaO–P_2O_5 oxide system, and they finally selected the composition $45SiO_2$–$24.5Na_2O$–24.5CaO–$6P_2O_5$ (wt %), characterized by high amounts of Na_2O and CaO, as well as a relatively high CaO/P_2O_5 ratio that makes the surface of the material very reactive in physiological environment. This glass composition, referred to as 45S5, also had the advantage of being extremely easy to melt, due to its proximity to the ternary eutectic. The name Bioglass was then trademarked by the University of Florida as the name for the original 45S5 composition and, therefore, it should be used only with reference to that composition and not generally to indicate BGs.

COMPOSITION

Bioactive glasses have different families and each family has a different composition. Some classes of bioactive glasses, like Bioglass™ (45S5), are now being used intraorally as bone grafting material after gaining FDA approval.45S5 bioactive glass is composed of SiO_2 (46.1 mol%), CaO (26.9 mol%), Na_2O (24.4 mol%) and P_2O_5 (2.6 mol%).[5] 45S5 is able to form HCAP (hydroxycarbonated apatite) in less than 2 hours and binds to tissues.

Process of Formation

Bioacitve glasses were initially obtained via melting at higher temperatures. Two common processes for the formation of bioactive glasses are melting and sol-gel process. Rounan Li et al[3] (1991) demonstrated that the formation of bioactive glasses with a composition of SiO_2- CaO-P_2O_5 by sol-gel processing and it was observed that glasses made from the sol-gel process required lower temperatures as compared to conventional melting method. It has also been suggested by Peltola T et al[4] (1999) that glasses made from sol-gel processing have increased bioactivity.[7]

Mechanism of Action of Bioactive Glasses and Apatite Formation

When a bioactive glass is present in an aqueous solution, it reacts with it. As a result of this reaction, a change in the structure and chemical composition of bioactive glass occurs which causes its dissolution and HCAP is formed. Different glass compositions were used by Kokubo et al[5] (1990) to study the growth of apatite in simulated body fluid (SBF). It was observed that calcium ions of the glass dissolve and apatite's ion activity product is greater than before. The silica network which acts as a place for apatite nucleation, gets disrupted. The growth of the apatite is therefore based on utilization of calcium and phosphate ions from SBF.

Glass Transition Temperature of a Bioactive Glass

Glass transition temperature (Tg) is a range of transfor-mation when an amorphous solid is changed into a super cooled liquid on heating. Properties like dissolution rate and strength of different glasses can be compared with the help of Tg.

Tg and peak crystallization temperature are two very important properties of a glass. A big processing window between these two makes sure that the glass sinters without crystallization. If a bioactive glass crystallizes, it becomes less bioactive because the ion exchange between the glass and aqueous solution is resisted by the crystalline phases.

Network Connectivity of a Bioactive Glass

The number of bridging oxygen atoms are responsible for the network connectivity (NC) because these bridging oxygen atoms join the two neighboring polyhedra. NC can be utilized to assess the bioactivity, surface reactivity and solubility of a glass. A decreased NC shows that the glass has low Tg but higher solubility and higher reactivity and vice versa. Therefore, NC is an important tool for designing new glasses with different compositions for different applications

Relationship between Tg and Hardness

A linear relationship exists between Tg and hardness of a bioactive glass. A decreased Tg of a bioactive glass predicts that the glass has reduced hardness. A similar relation between hardness and Tg of a bioactive glass was explained by Baesso et al[6] (1999), where hardness was found to be decreasing with a decreasing Tg.

Current Clinical Applications of BGs—Where Are We?

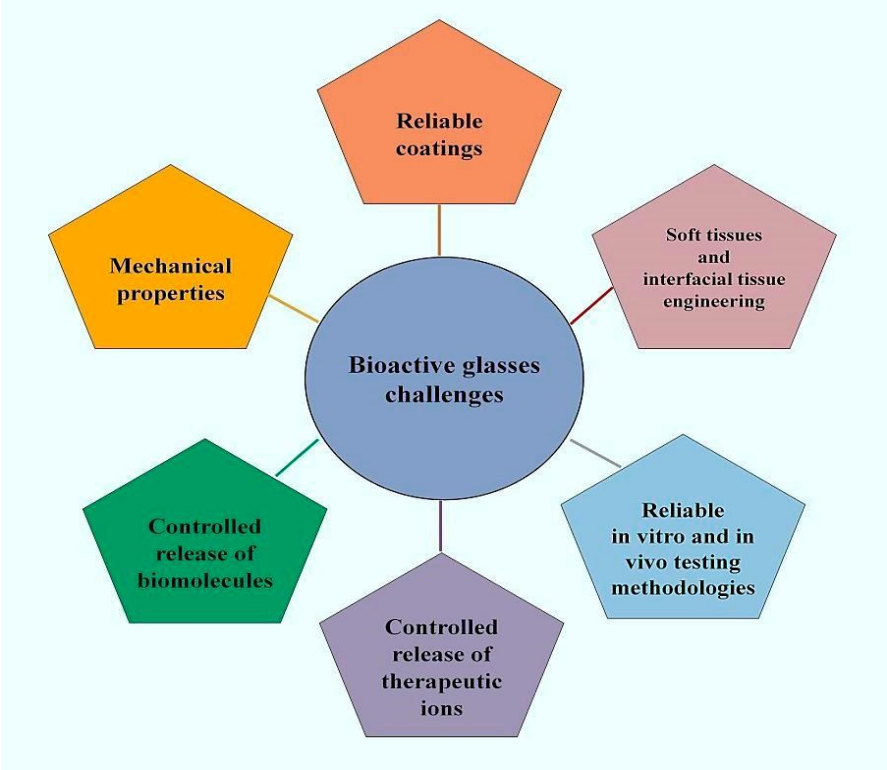
BGs are not only able to form a hydroxyapatite-like surface layer after being put in contact with biological fluids, thus promoting a stable bond to living bone (osteoconduction), but also osteoinductive, i.e., they are able to stimulate bone cells towards a path of regeneration and self-repair, thus significantly accelerating tissue healing kinetics. It has been estimated that over about 30 years, from 1985 (FDA approval) to 2016, Hench's original 45S5 Bioglass has been implanted in 1.5 millions of patients to repair bone and dental defects. Other glass and glass-ceramic products have also made available to surgeons for clinical use; a summary of the main applications of BGs, along with some of today's commercial products, is reported in Table.

Grand Challenges for the Future—Where Are We Going?

The impressive experimental research carried out over fifty years—since Hench's early study in 1969 to date—has clearly demonstrated the great suitability and versatility of BGs in medicine, and has led to the development of many clinical products that improved the patient's well-being and rehabilitation. This background of accumulated knowledge is expected to stimulate scientists to continue research and discover new applications for BGs in the effort to cope with the challenges of today's society.

Table: Chronology of the key applications of bioactive glasses in biomedicine.

Year(First Experimental Use)	Achievement Application
1969	Invention of the 45S5 glass composition (45S5 Bioglass)
1977	Treatment of ear diseases by using Ceravital glass-ceramics (replacement of middle ear small bones)
1978	Ocular implant (biocompatibility with corneal tissue)
1985	Approval by Food and Drug Administration (FDA) of the first 45S5 glass implant (MEP implant for middle ear ossicular repair)
1987	Treatment of liver cancer (radioactive glasses)
1988	Clinical use of the 45S5 Bioglass-based Endosseous Ridge Maintenance Implant (ERMI) in human patients
1993	FDA approval of PerioGlass(45S5 Bioglass particulate used for bone & dental repair)
1998	Peripheral nerve repair
1999	FDA approval of radioactive glasses (TheraSphere)for cancer treatment
2000	Wound healing
2002	FDA approval of Medpor-Plus^{TM} (polyethylene/45S5 Bioglass composite porous orbital implants).
2003	Antibacterial (Zn-containing) bone/dental cements
2004	Lung tissue engineering
2004	Use of mesoporous bioactive glass (MBG) as a drug delivery system
2005	Skeletal muscle and ligament repair
2005	Treatment of gastrointestinal ulcers
2010	Cardiac tissue engineering
2011	Commercialization of a cotton-candy borate bioactive glass for wound healing in veterinarian medicine. FDA approval is pending.
2012	Embolization of uterine fibroids
2012	Spinal cord repair
2018	Use of radioactive glasses (TheraSphere) in patients with metastatic colorectal carcinoma of the liver



The most Important challenges Proposed for Bioactive Glasses (BGs) in Medicine

Some examples of commercially produced glasses available on the market.

CONCLUSION

Bioactive glasses with various compositions are now used for wide range of applications. Bioactive glasses have become an area of interest for researchers and research is still continuing on various aspects of these glasses. With their current applications, a bright future of these glasses in the field of medicine and dentistry can be easily predicted. The abundant literature published until now on BGs witnesses the extraordinary versatility of these biomaterials, which primarily depends on the flexibility of their composition. BG properties can also be tailored by acting on the fabrication process to produce, for example, macroporous scaffolds, mesoporous materials exhibiting drug release ability, or composite and multilayered constructs for interfacial tissue engineering. In summary, we forecast a bright future for the use of BGs in medicine, which will further expand the Glass Age.

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