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Chapter

New Trends in Bioactive Glasses for Bone Tissue: A Review

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Abstract

Bioactive glasses are very attractive materials, used for tissue engineering materials, usually to fill and restore bone defects. This category of biomaterials, show considerable potential for orthopaedic surgery because they can promote bone tissue regeneration. Many trace elements have been incorporated in the glass network, an example is metallic glasses to obtain the desired properties. Because of tolerable mechanical properties, and because they are able to bond to living bone and stimulate its regeneration, this bioactive glasses have a particular interest and are in a continuous research and improvement. The chapter presents the history of bioactive glasses, classification, include a summary of common fabrication methods, applications, surface coatings, applications and future trends in relation to human bone. This review highlight new trends and areas of future research for bioactive glasses.

Keywords: bioactive glasses, bioactivity, glass-ceramics, biodegradable, melt-derived glasses, bone, applications, tissue engineering

1. Introduction

Research in the field of materials science and engineering has expanded greatly in recent decades, especially in the field of biocompatible materials. This is because, on the one hand, medicine is constantly looking for solutions to remedy many health problems, and on the other hand, certain classes of materials have already proven useful in alleviating or even curing certain human suffering [1, 2].

The development of biocompatible materials research is an evolving process driven by the increase in the number of accidents and many health problems, but also by the desire to increase the average life expectancy in humans. As research in the field of biomaterials science advances at the laboratory level, the incidence of serious diseases is increasing in the global human community. The World population is getting larger and the percent of elder persons is increasing and influencing the increase of chronic illness, like cancer or cardiovascular diseases. Next to this on large scale other infectious diseases are getting more common like: HIV/AIDS, tuberculosis or gastrointestinal

issues. On this reason the focus of the research in the field of medical materials and instruments should prepare for the request on the market [3].

While traditional biomaterials were based on polymers, ceramics and metals, now the latest generation of biomaterials incorporates biomolecules, therapeutic drugs and even living cells. At present, biomaterials are a special category of materials, indispensable for raising the quality of human life and extending its duration [4].

Biomaterials are generally intended to be implanted in a living organism to restore the shape and function of a part of a tissue destroyed by disease or trauma.

The introduction of a biomaterial into the human body determines an implant versus tissue interaction, which can generate conflicting reactions. They can be toxic, mechanical, and electrochemical biological. It can even lead to serious damage to the bone or adjacent tissue, or assembly used. Due to these phenomena, depending on the quality of the biomaterial, the place of implantation and other causes, corrosion occurs on the surface of the implant, with loss of quality his.

Depending on the medical application for which it is suitable, a biomaterial must have one or more of the properties presented in **Figure 1**. These factors are very important and have a close correlation between them: to be biologically compatible with the host tissue (for example, it does not have to causes rejection, inflammation and immune responses); Easily achieve direct bio-chemical attachment to the host tissue; The biodegradation time must be adjusted to suit the time of natural bone formation; Degradation mode: Surface or depth erosion; Ability to support the growth of germinal capillaries, tissues perivascular mesenchymal and osteoprogenitor cells from host in the three-dimensional structure of the graft that acts as a support; Needed to maximize space for grip and growth cellular, revascularization, proper nutrition and oxygen supply; For support in the process of cell growth and in the transport of nutrients and oxygen [5].

A material suitable for use in medicine must have, where appropriate, certain characteristics special and offer a number of advantages: mechanical integrity of the tissues acting as a support for growth living tissue; control of the biological response, by promoting dynamic interactions with tissues surrounding; behaving as a space for the survival of host cells, facilitating the transport of nutrients and metabolites, by maximizing the biological and / or pharmaceutical response; good biocompatibility / biodegradability, with adequate degradation kinetics; new tissue formation, thus minimizing both tissue and response toxicity systemic; feasibility in production [6, 7].

Of all the factors, biocompatibility is the most important feature to be taken into account consideration in the clinical applications of a biomaterial and which is related to

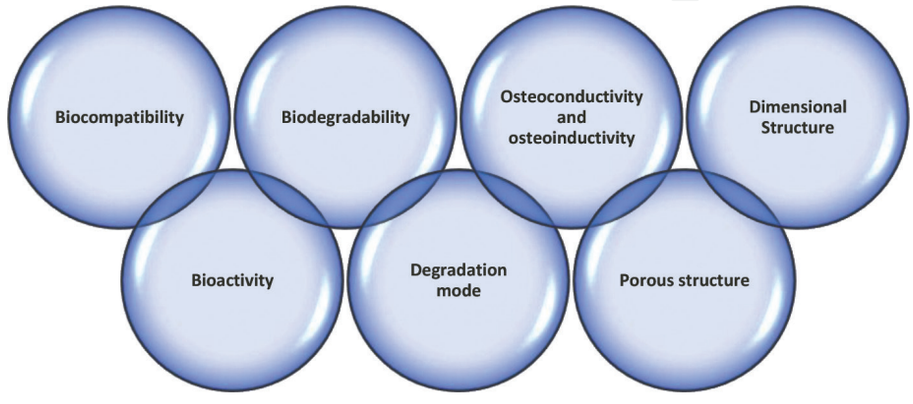


Figure 1.
The main characteristics of biomaterials.

behavior biomaterials in various contexts. Biocompatibility is correlated with the appearance of a response weak immune system in contact with a particular biomaterial [8, 9].

The most complex unit is the human body, having many levels of tissues, organs and systems. If we speak about tissues these can be soft or hard, after that being classified in ones in contact with blood or not, in contact with the biomaterials or not [10].

On biomaterials the classification can vary, according to the composing materials and their use; the origin – natural or synthetic, simple or mixed composite and so on. Regarding the composition these can be metallic, ceramic, polymeric, composite and of natural origin.

According to every biomaterial, the advantages and disadvantages can influence their use, being induced by the characteristics of biomaterials and by the functional requirements of implants.

Bioglass (BGs) is a chemical compound that is part of a compositional family known to have the best bioactivity properties. This are osteoconductive and osteoinductive as well biocompatible and highly bioactive, as demonstrated by the connection with living tissues in a short time to just a few hours [11].

This new class of biomaterials, based on an amorphous mixture of oxides (SiO_2-Na_2O-K_2O-CaOMgO-P_2O_5), was patented in 1968 by Larry Hench by preparing the well-known Bioglass 45S5.

Depending on the percentage of SiO_2 mainly, these biomaterials can be bioinert, bioactive or bioresorbable. Hench and Clark were the first researchers to observe the bioactivity of this material in vitro and in vivo and demonstrated its osteointegrative potential [12].

At the same time, the antimicrobial and anti-inflammatory properties and the possibility to easily control the crystallinity by applying heat treatments corresponding to the glassy phase present in the bioglass structure were noted. All these are additional arguments for this class of biomaterials to be a first objective in research in the field [13].

L.L. Hench developed the concept of using a material based on silicon dioxide, calcium oxide and phosphorus pentoxide, in a proportion similar to that of natural bone, to make implants, which have the property of developing a bond with the bone. In **Figure 2** is presented the Hench Diagram. The level of biocompatibility of a material can be correlated with the time in which it was performed bone binding for more than 50% of implant surface ($t_{0.5bb}$) [15].

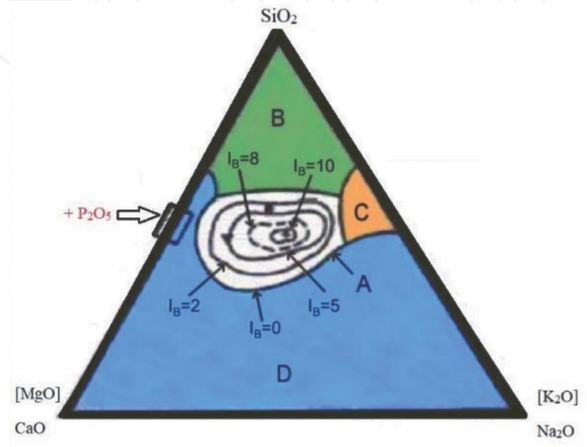


Figure 2.
*Hench diagram [14]. *notations: A - bioactive materials, B - inert materials, C - absorbable materials, D - cannot be obtain bioglasses, la = 0 the limit of the compositions that allow the binding to the hard tissues, l_a = 8 is the limit of the compositions that allow the binding of soft tissues.*

The bioactivity index is defined by the following formula:

$$I_B = \frac{100}{t_{0.5bb}} \quad (1)$$

Because some studies show that the GBs are fragile and exhibit poor mechanical properties, this limiting the involvement in load-bearing applications, another way to represent a feasible solution, is to incorporate the bioactive glasses into gelatine matrices and to fabricate composites [16, 17].

2. History - current level of development

Although 40 years have passed since the patenting of this material, until now it has been intensively used only in the form of large diameter particles (~ 100 μm), grouped in blocks with different geometries, with applications in regenerative orthopedic surgery (bone fillers).

Enamel-glazing and flame / plasma spray are used as commercial methods to obtain bioglass thin films at the commercial level, and in recent years' intensive research has been carried out in many biomaterials research laboratories to find alternative methods to the traditional ones, which lead to thick coatings with low mechanical strength.

Although their superficial properties are interesting, their development is limited due to: high fragility and reduced mechanical resistance to static fatigue. However, they are used to make middle ear bones, alveolar reconstructions, dental implants, films for total coverage of prostheses (alumina or titanium alloy), for modern cancer treatments.

For all these applications, the bioglasess have seen a spectacular development, as shown in **Table 1**.

Due to the high fragility and low mechanical strength of bioglasses as well as the toxicity of metal ions that can occur from metal alloys used in internal prostheses, the study of metal orthopedic prostheses coated with thin bioglasses films was studied.

Their use is motivated, among other things, by the porosity characteristics of the bioglasses, which allow a very intimate propagation of the tissues, thus ensuring a perfect connection with the implant. Thus, these structures have the advantage of combining the bioactive properties of the coating material with the mechanical strength of the support (**Figure 3**).

Bioglasses are superficially active, they have the property of binding mechanically or biochemically to bone tissue or collagen fibers in contact with soft, living tissue.

It has been shown that the connection between the bioglass and the bone is achieved by the formation of a superficially active interface based on hydroxyapatite, which further determines the reconstruction action of the tissue cells; such a mechanism is stimulated by a slightly basic pH, caused by ion exchanges between the bioglass and the tissue.

Materials with limited reactivity, such as dense hydroxyapatite, have a weaker effect than biosticles in the healing process of bone tissue.

All classes of the biomaterials are used throughout the human body, for this purpose, physical, chemical and biological properties of materials are exploited, often new or improved properties, and the resulting structures can interact faster at the biomolecular level, both on the surface and inside the cell.

Year	Stage/Achievement/Application
1969	Highlighting the binding (binding) of the bone with the help of bioglass and bioglass-ceramics
1973	Specification of the interaction mechanism at the bone-bioglass interface
1973	Binding of bone to active biovitroceram
1976	Measurement of the profiles of compositions in the bioglass-bone connection area
1976	Successful introduction of bioglass into the dental implant
1980	Comparative histology of variable bioactivity implants
1981	Ultrastructure analysis of biovitroceram and bone
1981	Toxicology and biocompatibility tests of biostycles and evidence of soft tissue binding
1981	Clinical use of vitroceram (Ceravital) in the middle ear prosthesis
1982	Comparison between the glass implant and other inert implants instead of the middle ear bone
1982	High mechanical strength vitroceram (apatite and wollastonite) for vertebral prostheses
1983	Mechanically machinable vitroceram based on apatite and fluoroflogopite
1984	The FDA approves the sale of bioglasses and prostheses for the middle ear
1986	Clinical trial of bioglasses for alveolar ridges
1993	PerioGlas approved by FDA (45S5 Bioglass® for bone and dental repair)
1998	Peripheral nerve repair
1999	Radioactive glasses approved by FDA (TheraSphere®) for cancer treatment
2000	Wound healing
2002	Medpor®-PlusTM approved by FDA (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 was 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

Table 1.
Stages of development of bioglass and glass-ceramics [4, 5, 15].

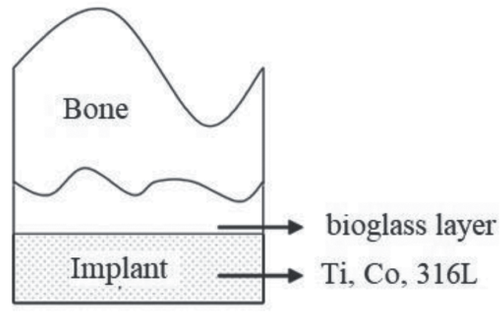


Figure 3.
Multilayer structure [9].

3. Relevant studies

Most of the commercial biomaterials (glass, ceramics, glass-ceramics and composites) are known that bind to bones, being called bioactive ceramics. Also other strictly specialized compositions of bioactive glasses bind to soft tissues. A common feature of bioactive glasses and ceramics is the change of the material surface after time-dependent implantation. On the surface it is formed a biologically active layer of hydroxycarbonate apatite (HCA), which provides the tissue-binding structure [4].

Many studies have shown bone-related bioactive implants with sufficient adhesion to the interface to withstand mechanical fracture. A failure never occurs at the interface, but either in the implant or in the bone.

Bone binding was initially demonstrated for some compositional domains of bioactive glasses, containing SiO_2, Na_2O, CaO and P_2O_5, in the proportions specified in **Table 2**.

During the years many types and variations of the composition were approved by FDA and named Bioglass.

When introducing a material into the living organism, a series of very complex interactions can appear, being able to identify four specific phenomena that are unitary in the so-called "concept of biocompatibility", namely:

1. initial processes that take place at the biomaterial interface ÷ living tissue and that are closely related to the physico - chemical processes that take place in the first minutes of the contact between the biomaterial and the living tissue;

2. the effect induced by presence of biomaterial as a foreign body in the living tissue surrounding the implant, which can be measured at any time, from a few minutes to years;

3. the effect that living tissue has on the biomaterial through the changes observed in the biomaterial, effect described in the form of corrosion or degradation;

4. consequences of the reaction at the interface that are systematically seen on the surface of the body or in certain specific areas, medically recognized as the development of specific allergies, the initiation of tumors or the appearance of infectious processes [5].

Chemical interactions that occur at the surface are:

- Rapid exchange of Na + and Ca2 + ions with H + and HO- ions in solution, leading to hydrolysis of silica groups, with the formation of silanol groups;

$$Si-O-Na^{+}+H^{+}+HO^{-}\rightarrow Si-OH+Na^{+}+HO^{-} \quad (2)$$

- The cation exchange increases the concentration of hydroxyl ions in the solution, which leads to the attack of the silica network;

- Condensation and repolymerization of a SiO_2-rich layer on the glass surface, depleted in alkaline and alkaline-earth cations;

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DOI: http://dx.doi.org/10.5772/intechopen.100567

Component	45S5 Bioglass®	45S54F Bioglass®	45B15S5 Bioglass®	52S4.6 Bioglass®	55S4.3 Bioglass®	KGC Ceravital®	KGS Ceravital®	KGy213 Ceravital®	A/W Glass–ceramic	MB Glass–ceramic	S45P7
SiO_2	45	45	30	52	55	46.2	46	38	34.2	19–52	45
P_2O_2	6	6	6	6	6				16.3	4–24	7
CaO	24.5	14.7	24.5	21	19.5	20.2	33	31	44.9	9–3	22
$Ca(PO_3)_2$						25.5	16	13.5			
CaF_2		9.8							0.5		
MgO						2.9			4.6	5–15	
MgF_2											
Na_2O	24.5	24.5	24.5	21	19.5	4.8	5	4		3–5	24
K_2O						0.4				3–5	
Al_2O_3								7		12–33	
B_2O_3			15								2
Ta_2O_5/ TiO_2								6.5			
Structure	Glass and glass–ceramic	Glass	Glass	Glass–ceramic	Glass–ceramic	Glass–ceramic	Glass–ceramic	Glass–ceramic	Glass–ceramic	Glass–ceramic	Glass–ceramic

Table 2.
Composition of bioactive glass and glass ceramics (% weight) [18].

- Migration of Ca^{2+} and PO_4^{3-} cations to the surface through the SiO_2-rich layer, forming above it an amorphous $CaO\text{-}P_2O_5$-rich film, which grows by incorporating calcium and phosphates from the solution;

- Crystallization of the amorphous film rich in $CaO\text{-}P_2O_5$ by incorporation from the solution of OH- and CO_3^{2-} anions, with the formation of a mixed layer containing carbonated hydroxyapatite (HCA).

The biomaterial versus tissue interface, which is established by implantation, is almost inevitably a blood ÷ material interface and the initial events are dominated by the absorption of blood proteins on the implant surface. At this contact it was established that a series of biological processes: Adsorption and desorption of biological growth factors, in the HCA layer, which determines the activation of stem cell differentiation; The action of macrophages, which phagocytose local residues, allowing cells to grow; Attachment to the bioactive surface of stem cells; Differentiation of stem cells with the formation of bone growth cells, called osteoblasts; Osteoblasts generates extracellular matrix with bone formation; Crystallization of the phosphate inorganic matrix by embedding bone cells in a living composite structure (**Figure 4**) [19].

The chemical and topological properties of the implant surface strongly influence the properties of the biolayer and this influence must be understood and controlled in order to optimize the biocompatibility of the material used. Relevant in the study of biocompatibility is the fact that proteins and cells have nano- and micrometer sizes, which requires extremely delicate approaches. Of equal importance are the properties of cells, for example, their ability to communicate via the extracellular matrix with signal molecules (molecules used in the process of living cell synthesis). During tissue healing, numerous bioactive signaling molecules control tissue formation, and some proteins have demonstrated the ability to stimulate healing near the implant. All these mechanisms contribute to the response of the tissues to the implant and can determine whether the body accepts the implant or not, whether it is biocompatible.

Japanese researchers have tested the effect of surface area on bone proliferation. Three types of biomaterials were compared: bioactive glass, dense hydroxyapatite and glass ceramics. Each material was implanted in a 6 mm diameter hole, which was drilled into the bone of an adult rabbit's leg. Bioactive glass has been found to produce

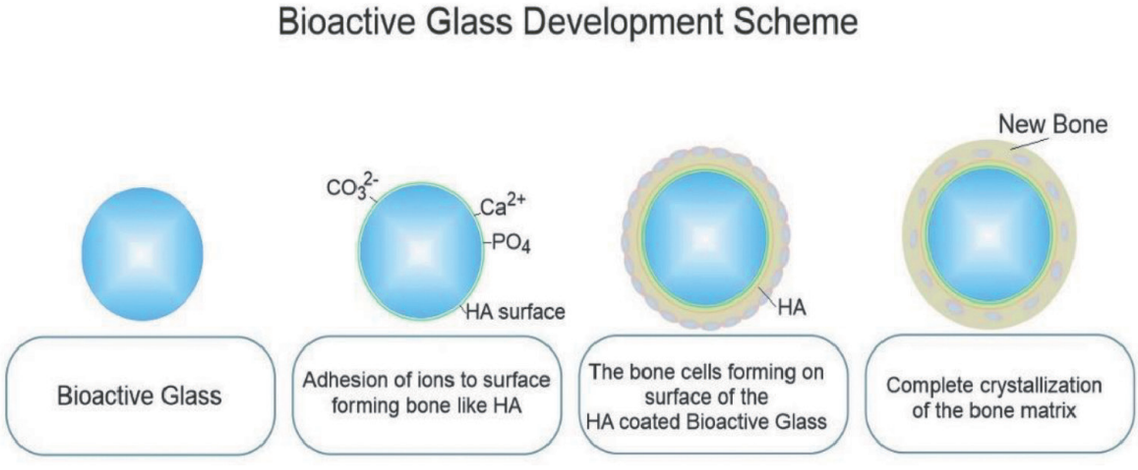


Figure 4.
Bioactive glass surface reaction [19, 20].

bone tissue and is subsequently resorbed much faster than the other two materials, both of which have a lower surface reactivity than glass.

The rate of bone growth around an implanted material depends in part on the rate of dissolution of the silica network and therefore it is very good to determine as accurately as possible the system in which the oxide composition of the bioglass.

Alkaline content plays an important role in the stability of bioglass. From this point of view, two categories are distinguished: bioglass with rich alkaline content and bioglass with poor alkaline content. The latter are characterized by a high degree of decomposition over time, during bone reconstruction. This type of bioglass has been used in maxillofacial applications and in the chaining of the inner ear bones.

Most determinations were made with glasses based on 6 oxides: SiO_2-Na_2O-K_2OCaO-MgO-P_2O_5, as it was found that the bone binds to materials with a wide range of compositions in this system. Soft tissue binding occurs for a much smaller range of compositions.

There are three basic compositional requirements for silico-chalco-sodium glasses to bind to hard tissue. These are: less than 60% SiO_2 (mol), high content of Na_2O and CaO, high CaO / P_2O_5 ratio. The level of bioactivity is strongly dependent on the relative concentrations of ions.

The most successful bioactive glass is the one that contains P_2O_5 between 6 and 15%.

In the diagram of the SiO_2-CaO-Na_2O ternary system (6% P_2O_5), some materials form a bond with the bone in 30 days. Other glasses bind to the soft tissue, some of the glasses are almost chemically inert and others are resorbable and dissolve in 10 to 30 days.

Bioglasses from another part of diagrams, from a technological point of view, are not forming glass and have not been tested as implant materials. Until now, it has been considered that in order to be bioactive, glasses and glass-ceramics must contain both CaO and P_2O_5, which are the component oxides of hydroxyapatite.

Ohura and collaborators have shown that glasses in the CaO-SiO_2 system without P_2O_5, as well as those containing very small amounts of P_2O_5, form a layer of hydroxyapatite on their surface when immersed in simulated body fluid (SBF). In contrast, under the same conditions, the glasses in the SiO_2-free CaO-P_2O_5 system do not form the hydroxyapatite layer. It follows that bioactive compositions can be obtained in the CaO-SiO_2 system rather than in the CaO-P_2O_5 system.

Bioactive glasses usually have weak strength and resilience properties, which is why they are reinforced with metal fibers made of stainless steel, titanium and Co-Cr alloys. As a result of the reinforcement with metal fibers, the volume of defects and the residual tensions decrease, and the microcracks produced are below the critical length and have rounded extremities.

4. Methods of obtaining

The most methods used for bioglass nanoparticles obtain are: quenching method, sol–gel, flame synthesis, microwave irradiation and microemulsion. Two main process that can synthesize the biomaterial are the melt quenching method and sol–gel.

4.1 Quenching method

The melt queching method can synthesize bioglass in a short time, by heating the initial precursors to high temperatures and following special rules. The preparation process proposed by Hench by melting is based on the following steps:

- Melting of the mixture of high purity raw materials, in Pt-10% Rh crucibles, covered, in order to prevent the volatilization of the components.
- The melt is loosened for at least 2 hours, without removing the lid.
- The glass is poured into graphite molds. If the sample diameter is larger than 1 cm then the mold is preheated to 300°C.
- The glass is annealed at different temperatures depending on the composition, for 4 hours (see **Table 3**)
- The glass is cooled slowly in the oven for 16 hours.

The role of annealing is to create the conditions for the formation of microcrystals, thus obtaining a bioactive glass–ceramic.

The melt quenching method synthesis was also carried out by Shams et al. in 2018. Bioglass nanoparticles were prepared from analytical grade SiO_2, Na_2CO_3, $CaCO_3$, and P_2O_5 precursors. As an example from the literature [21]: the precursors were mixed in 53.0 SiO_2:23.0 Na_2CO_3:20.0 $CaCO_3$:4.0 P_2O_5 molar ratios followed by milling in an agate mortar [22]. The blend was mixed in a jar for several hours and then pressed into discs with 10 mm in diameter using a hydraulic press apparatus. Than the samples were placed in an alumina crucible and heat treated in the furnace [21].

In **Figure 5** we can see the thermal program: melting at 1400°C for 3 hours - resulting molten material, then quenched in distilled water to produce glass frit. The glass frit was than dried in an oven at 80°C for 5 hours. The dried glass frit was milled in a Retch PM400 milling machine using zirconia cups for 6 h to obtain the bioglass powder [21]. FESEM micrograph of bioglass nanoparticles, includes spherical particles with a wide size distribution from 100 to 800 nm [21].

Although the melt technique is a fast method, the resulting glass usually has a low specific surface area value. According to previous research, the specific surface area value is a key factor affecting bioglass bioactivity. Increasing the specific surface area can increase the surface reaction between the artificial material and the physiological environment, thereby increasing the formation of the HA layer.

4.2 Sol–gel method

One of the most common method - the sol–gel process is well known for obtaining synthetic materials, like silicate and oxide systems and respectively thin films, coatings, nanoparticles, and fibers. The sol–gel reactions takes place at low temperatures and involves the synthesis of a solution (sol), usually consisting of metal–organic and/or metal salt precursors followed by gelling by chemical reactions, or

Type	45S5	45B15S5	KLP1	KZS3020	45S5N	45S5-L	45S5-F
Tmelting [°C]	*1350*	*1150*	*1350*	*1500*	*1350*	*1350*	*1200*
T annealing [°C]	*500*	*375*	*550*	*700*	*550*	*550*	*350*

Table 3.
Heat treatment temperatures for Hench glasses.

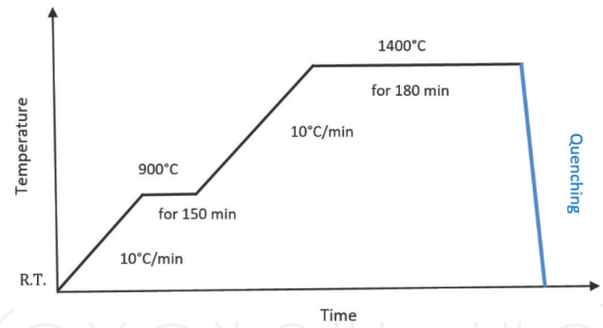


Figure 5.
The furnace temperature programming. Image adopted from [21].

aggregation, and finally thermal treatment for drying, removal of organic substances, and sometimes crystallization and cooling. Some ions (magnesium, zirconium, zinc, silver, titanium, boron) can be also added to the bioactive glass in order to enhance glass functionality and bioactivity. However, bioactive glass is difficult to synthesize on a nanoscale with the addition of ions [22].

The sol–gel method can synthesize bioglass at lower temperatures, has a porous structure, and a high specific surface area value which can increase the bioactivity of synthetic materials.

The raw materials used in the sol–gel method are alkoxide precursors or soluble inorganic salts derived from the oxide components of the glasses.

If a glass is prepared in the SiO_2-CaO-P_2O_5 ternary system, the precursors used may be:

- TEOS - tetraethylorthosilicate ($C_8H_{20}O_4Si$)
- Calcium nitrate (Ca $(NO_3)_2 \cdot 4H_2O$)
- PET - triethylphosphate ($C_6H_{15}O_4P$)

The following factors are considered: the raw materials are added dropwise, under continuous stirring; the pH is adjusted with nitric acid to 2–3 thus taking place an acid catalysis; the soil thus obtained is left to gel for a few hours in an oven at 60° C.

The advantages of the sol–gel method are:

- Low obtaining temperature;
- High purity;
- Improved homogeneity;
- Variation of the composition in order to maintain bioactivity;
- Modification of structural characteristics, by controlling hydrolysis and condensation reactions;
- Powders of nanometric dimensions;
- Nanostratified porous materials.

Kumar et al. [23] synthesizing bioglass nanoparticles (SiO_2 (60%)-CaO (30%) -P_2O_5 (10%)) through the sol–gel method. The synthesis of bioglass nanoparticles was carried out by mixing TEOS (4.054 g) with ethanol using a magnetic stirrer for one hour at room temperature. In separate containers, calcium nitrate tetrahydrate (2.372 g) and phosphate pentoxide (0.267 g) were dissolved in distilled water and stirred each with a magnetic stirrer for 30 minutes at room temperature as well. After one hour, the solution containing calcium was added dropwise to the solution containing TEOS, as well as the solution containing the phosphate. After that, ammonia solution was added to the mixture to maintain pH 11. The mixture was then put in an incubator for 48 hours to obtain the gel. The obtained gel was placed in an oven at 100°C to dry [23]. The result of TEM analysis shows that the shape of the bioglass nanoparticles is irregular at the nano and micro scales due to the presence of agglomeration, the particle size varies from 200 to 500 nm, average surface area of the bioglass nanoparticles measured using BET with N2 was 10.4 m^2/g. The larger the particle size, the smaller the surface area.

Another study made by Durgalakshmi et al., by mixing tertraethyl orthosilicate (TEOS) and HNO_3 as an acid medium, then added alcohol to help the hydrolysis process. Gel formation occurred after 30 minutes of mixing. At 20 minute intervals, other reagents are added to the mixture such as phosphoric acid, calcium nitrate, and sodium hydroxide. The solution was mixed for 4 hours to obtain a homogeneous gel. After the hydrolysis process is complete, the sol is stored at 70°C for 24 hours, and then the dry white powder is taken at 600°C for 2 hours [24]. Scanning electron microscope analysis shows that the particles do not have a well-defined shape, having less than 100 nm in length [24]. The large particles of over 200 nm could be formed due to particle agglomeration during sintering [25].

5. Applications

From ancient times there has been an interest in repairing and replacing parts of the human body that present problems and this has been done using various materials more or less suitable depending on the information available at that time [26].

Due to the evolution of science and equipment today, the medical world is in a period of transition from the healing of existing organs to their replacement with synthetic materials obtained in high-performance laboratories [27].

Bone replacement is in the 2nd place as a tissue replacement procedure, in the first place being the blood transfusion. Yearly are done more than 2 million bone reconstructions in orthopedics, neurosurgery and dentistry.

A wide variety of biomaterials are used in restorative medicine. The choice of material for a practical application in medicine remains a key factor in the design and development of medical implants and devices. Currently, more than 50 biomaterials (BIOGLASS 45S5®, CERABONE A-W®, TheraSphere®, Corglaes®, NovaBone®, NovaMin® etc.) of synthetic or natural origin are used in medicine, covering a wide variety of applications. The tables below (**Tables 4** and **5**) show some of the applications of bioactive glass and glass ceramics due to their well-defined bioactive properties [28].

Figure 6 illustrate some examples of commercially glasses, available on the market. All research leads to a great potential of BGs in medicine but it is not fully exploited yet and the next years a rapid growth is expected.

Composition	Form	Application	Function
Bioglass 45S5	Solid body	Reconstruction of the alveolar margin	Filling the space and tying the tissue
	Solid body	Middle ear prosthesis	Reconstruction of the ear canal by replacing part of the bone chain
	Powder	Reconstruction of defects caused by periodontitis	Replacing lost bone and preventing gum retraction
	Powder	Fixation of hip implants	Replacement of lost bone due to a defective fixed implant

Table 4.
Applications for BIOGLASS 45S5.

Composition	Form	Application	Function
Cerabone A-W glass–ceramic	Solid body	Iliacal ridge prosthesis	Replacement of extracted bone for autograft
		Vertebral prosthesis	Replacement of a vertebra lost during surgical removal of a tumor
	Deposition	Fixing hip prostheses	Provides bioactive binding of the implant

Table 5.
Applications for CERABONE A-W.



Figure 6.
Examples of commercially produced glasses, available on the market [29–33].

6. Future trends

It is hard to say which is the most feasible bioglass. So the focus of the research is now on optimisation of the materials with deposition techniques, influenced by the parameters of the coatings and the composition of the bioglass, in order to obtain a multi-functional coatings, that will give long-term qualitative implants without side effects and ensuring regeneration.

Figure 7 shows the challenges and future trends for bioactive glasses (BGs)in medicine promoted by researchers which will lead to better implants. The properties of a biomaterial are decisive in ensuring the biocompatibility of an implant:

- from a chemical (compositional) point of view, a biomaterial must not contain elements that generate adverse and / or inflammatory reactions upon implantation. An important aspect is also related to the possible formation on the implant surface, in in vivo conditions, of new structures and compositions, dependent on the interactions that are manifested between the biomaterial and the environmental conditions specific to the implantation area. Their nature and physico - chemical characteristics can affects the long-term reliability of the implant.

- from a structural point of view, a biomaterial must have a density and a porosity corresponding to the structural function that the implant is to fulfill in the organism in which the implantation is made. Of particular importance is the microscopic nature of the implant surface.

- mechanical properties - a biomaterial, depending on the function that the implant must perform in the living organism, must have adequate mechanical strength, hardness and reliability.

- in the case of ocular, dermatological and dental applications, biomaterials must also have appropriate optical properties.

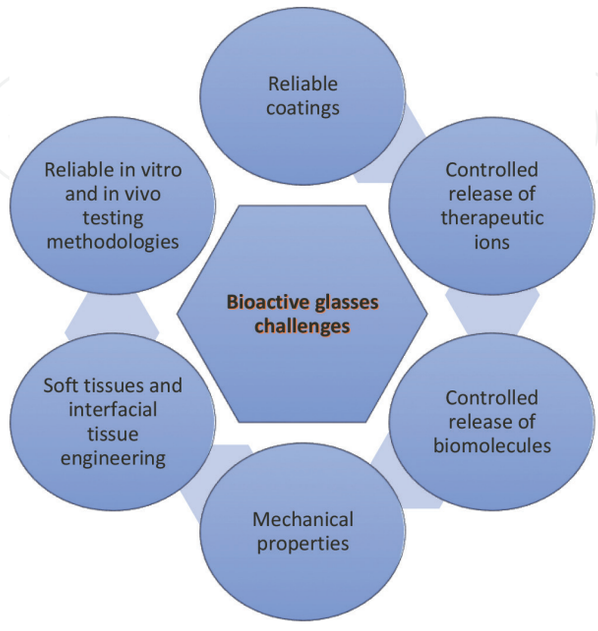


Figure 7.
Challenges and future trends for bioactive glasses (BGs)in medicine [34].

- another important aspect is related to the machinability of the biomaterial, this influencing the engineering of the implant itself.

Reliable Coatings with BGs on the mettalic implants are the oldest challenge but still researched. Thanks to their excellent mechanical properties and corrosion resistance, some metals are used as passive substitutes for the replacement of hard tissues (total hip and knee implants), as well as fracture implants (plates and rods), column fixing devices, and implantology. Dental. Other metal alloys have more active roles in implantology, such as vascular stents, catheter guidewires, orthodontic wires, and cochlear implants.

However, the biocompatibility of metal implants creates considerable concerns due to the fact that they can corrode in an in vivo environment [6]. Weakening of the implant by disintegrating its actual material, respectively the harmful effects of the resulting chemical compounds on neighboring tissues and organs are among the consequences of corrosion.

Pure metals are less commonly used, their alloys being used more often due to the fact that they improve some of their properties, such as corrosion resistance and hardness. Three groups of materials dominate the group of metallic biomaterials: 316 L stainless steels, cobalt and pure titanium alloys or titanium alloys.

Every material and class of materials works differently after the implantation, like some metals encapsulate fibrous tissue. The great advantage of the coatings on bioglass is that is not releasing toxic ions in the human body due to the potential to improve the implant stability by bonding it to the host bone and protect the implant from corrosion resistance.

The technologies involved for the surface modification of metallic implants with bioglass are: thermal spraying, sol–gel, chemical and electrochemical treatment. Unfortunately, not all technologies are suitable, some of them show many disadvantages like poor bonding strength between implants and coatings, the induction of phase transformation, modifications in the properties of coating or metallic implant, or both, and presence of impurities. **Table 6** present a synthesis of different glass coatings obtained through various methods [57].

Another perspective and future tendince of biomaterials is nanomedicine. Nanomedicine can be defined as an application of nanotechnology in the field of health in order to maintain and / or improve the health of the population using knowledge about the human body at the molecular level, as well as tools / nanoscale structures [22].

For this purpose, physical, chemical and biological properties of nanoscale materials are exploited, often new or improved properties, and the resulting nanostructures (nanoparticles or nanodevices), having the same size as biological entities, can interact more rapidly at the biomolecular level. on the surface as well as inside the cell [22].

So, in the near future, nanomedicine will seek to provide the tools and devices for research and practice, useful in the medical clinic, which could revolutionize the current way of thinking (prevention and diagnosis) and action (applied therapies) in the medical field.

By using nanoengineering, artificial tissues can be obtained and used to replace affected organs (kidneys, liver) or to regenerate nerves or produce implants that restore lost senses, such as sight or hearing. A major contribution is expected to nanomedicine could be brought about in areas such as: the definition and classification of diseases, their diagnosis and treatment, and the improvement of the structure and functioning of the human body [22].

Coating material	Substrate	Technique	Coatings' characteristics	Ref.
Biovetro®	Ti6Al4V	Atmospheric plasma spraying (APS)	Surface with wide superficial area of microcavities with round grains	[35]
45S5	Pure Titanium	APS	Bonding strength of BG + bond coat average 27.18 ± 2.24 MPa, and of BG average 8.56 ± 0.57 MPa.	[36]
P1, P2	AISI 316 L	APS	Microhardness of the coating 4.7–5.2 GPa; thickness of M1 389.8 ± 5.4 μm, M2 91.2 ± 8.2 μm, M3 262.6 ± 5.4 μm, and M4 80.8 ± 6.5 μm; adhesion strength of M1 2.7 ± 0.5 MPa, M2 3.7 ± 0.2 MPa, M3 3 ± 0.007 MPa, M4 4.4 ± 0.1 MPa	[37]
P0, P2	AISI 316 L & Ti6Al4V	Flame spraying (FS)	Microstructure consists of melted particles, pores and both vertical and parallel cracks. Thickness 126–275 μm; fracture toughness 5–7 MPa/$m^{1/2}$; Vickers hardness 4–5 HV	[38]
45S5	AISI 304	Solution precursor plasma spraying (SPPS)	Uniform coating average thickness 35 μm	[39]
Bio-K	Titanium	High velocity suspension flame spraying HVSFS	Coatings are entirely glassy. Tensile adhesion strength without bond coat: BioK-1 7 N/mm^2, BioK-2 3.8 N/mm^2, BioK-3 5 N/mm^2, BioK-4 9.8 N/mm^2 BioK-5 8 N/mm^2. With bond coat BioK-1 4 N/mm^2, BioK-2 5 N/mm^2, BioK-3 3 N/mm^2, BioK-4 9.8 N/mm^2 BioK-516 N/mm^2	[40]
BG-Ca/Mix	Grade 2 Titanium	HVSFS and suspension plasma spraying (SPS)	HVSFS coating very dense and thin. Hardness 396–516 HV; elastic modulus 61–95 GPa. Thickness 20–50 μm. SPS coatings thickness 50 μm	[41]
BG_Ca/HA	316 L Stainless Stell	SPS	Coatings compact and with continuous thickness with limited presence of pore	[42]
BG_Ca glass	Ti6Al4V	SPS	Coatings continuous and homogeneous thickness 31–40 μm; hardness 34–98 HV; elastic modulus 16–23 GPa and critical load 18–21 N	[43]
45S5, Bio K	Alumina	Enameling technique	Bio K completely amorphous, 45S5 some crystalline phases; both compact coatings. Vickers hardness 157 ± 39 HV, 146 ± 28 HV 45S5	[44]
RKKP, AP40	Zirconia	Enameling technique	Coatings with good mechanical properties and improved biocompatibility. ALP activity 1d 3.91 ± 1.15 μm AP40, 4.69 ± 2.10 μm RKKP. 9.98 ± 0.80 μm AP40 and 9.94 ± 2.90 μm RKKP at 5 and 10 days	[45]

Coating material	Substrate	Technique	Coatings' characteristics	Ref.
BG_Ca, BG_Ca/Mix BG_Ca_K	Ti6Al4V	Enameling technique	Uniform and well distributed coatings. Thickness BG_Ca 108 μm, BG_Ca/Mix 113 μm, BG_Ca_K 121 μm; Vickers hardness BG_Ca 232.1 ± 76.8 HV, BG_Ca/Mix 329.0 ± 81.0 HV, BG_Ca_K 317.9 ± 48.8 HV	[46]
LY-B0, LY-B1, LY-B2, LY-B3, LY-B4, LY-B5	Ti6Al4V	Enameling technique	Thickness 90–100 μm; critical strain energy release 6.56–14.61 J/m^2	[47]
6P61, 6P55	Ti6Al4V	Enameling technique	Some small pores. Thickness 86.0 ± 11.5 μm	[48]
Bioglass©, 6P44-a, 6P44-b, 6P44-c, 6P53-a, 6P53-b, 6P55, 6P57, 6P61, 6P68	Titanium, Ti6Al4V, Vitallium ©, Co-Cr alloy	Sol–gel method	Coatings without cracks or delamination. Hardness 5.3–6.3 GPa; density 2.5–2.7 g/cm^3	[49]
57.44CaO-35.42SiO_2-7.15P_2O_5 (mol.%)	CrCoMo alloy, Ti6Al4V, AISI 316 L	Sol–gel method	Glassy matrix with some defects and cracks. Thickness 1.5–3 _μm	[50]
45S5 BCG	AZ31 magnesium alloy	Sol–gel method	Integrated coatings with some asperities. Thickness 1.1 μm	[51]
Ag-BG	Titanium	Sol–gel method	Homogeneous and without macro and micro cracks	[52]
45S5	Ti6Al4V	Electrophoretic deposition (EPD)	Coatings with good adhesion without cracks. Rough surface in which the initial powder particles are still visible. Thickness 50–250 μm	[53]
Bioglass®	NiTi Alloy	EPD	Homogeneous microstructure without cracks or pores with uniform topography. Thickness 5–15 μm	[54]
45S5	Ti6Al4V	Pulsed laser deposition (PLD)	Coatings uniform without microcracks and pores. Thickness 1 μm; surface roughness 6 nm	[55]
T1, T2, T3, T4, T5, T6	Titanium	Radio-frequency magnetron sputtering (RF-MS)	Amorphous coatings with some crystalline phases. Thickness 1.8–2.4 μm	[56]

Table 6.
Summary of bioactive glass coatings on different metallic substrate.

In recent years, nanotechnology has found countless applications in the medical field, in the fields of: pharmaceutical (in targeted drug therapy), regenerative medicine (making nano-robots and devices used in cell regeneration), disease prevention, diagnosis (including by methods high-performance imaging) and nano-technology-based therapy.

The future of the field stays in the nanotechnology, being the most effective on cell and tissue level, mainly on the integration and regeneration, but also the identification of effective ways to trigger and control the regenerative process. The "nanobiomimetic" strategy depends on the following elements: intelligent biomaterials, bioactive signaling molecules and cells. Biomaterials are designed to react positively to changes in the proximity environment, stimulating specific regenerative events at the molecular level, directing cell proliferation and then differentiation, as well as the production and organization of the extracellular matrix.

A huge impact will also have the ability to implant cells, intelligent bioactive materials, which trigger the process of self-healing through the patient's own stem cells [22].

The field of nanotechnologies has established itself in recent years as one of the most topical fields, with a sustained pace of development and application and a revolutionary impact on industry and society. The global emergence of government investment programs in the field of nanotechnology is clear evidence of global interest in this field.

The potential evolutions of the research - development in the field of nanotechnologies, in the following years, are the following:

- half of the new materials that will appear will be obtained with the help of nanotechnologies, in sectors such as: electronics, chemical industry, heavy industry, pharmaceutical industry and aeronautical industry;

- the development of nanobiosystems science and engineering will allow a better understanding of living systems, the development of new solutions in health care and better biocompatible materials, the understanding of processes inside the cell or nervous system;

- application and integration of nanotechnology in fields of activity such as biology, electronics, medicine, etc., fields that include artificial organs, prolonging life, creating

- new systems by using biological principles, the laws of physics and the properties of different materials;

- tracking biocompatibility when creating new products;

- learning and education, based on nanoscale [22].

- In the future, the rapid development of nanomedicine could also be stimulated by better multidisciplinary collaboration between sectors of activity, such as industry, scientific research in general and medical research in particular.

7. Conclusions

In conclusion, bioglass is a chemical compound that belongs to a compositional family known to have the best bioactivity properties, as demonstrated by the connection with living tissues in a short time to only a few hours.

It is also known that the generation of artificial bone tissue would be very useful in cases of massive fractures. Based on bioactive glass, three-dimensional bioactive

matrices have also been developed for tissue regeneration using the deposition of human osteoblasts on the 3D matrix for tissue creation in vitro.

The results obtained so far qualify the bioglasses for widespread use in medical interventions and the ongoing research currently underway increases the hope of success of the intervention and also increases confidence in this material.

Conflict of interest

"The authors declare no conflict of interest."

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