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Chapter 5

Glasses and glass-ceramics for biomedical applications

Francesco Baino*, Carla Migneco, Elisa Fiume, Marta Miola, Sara Ferraris, Silvia Spriano, Monica Ferraris and Enrica Verné

Institute of Materials Physics and Engineering, Department of Applied Science and Technology, Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Torino, Italy
* francesco.baino@polito.it

Abstract
The invention of bioactive glasse has undoubtedly represented an important watershed in the history of biomedicine, innovatively revolutionizing the key concept of biomaterials.
Although 50 years have passed since the first bioactive glass (45S% Bioglass®), these materials still continue to inspire numerous generations of researchers, attracted by the promise of numerous possible fields of investigations given by the versatility of glass manufacturing and processing strategies. This allows obtaining final clinical products that are incredibly diverse in terms of chemical characteristics, shape and texture and, therefore, adaptable to different therapeutic needs.
The possibility to tune textural properties and degradation rates, perform high-temperature sintering processes without or minimally altering the original properties of the glass, as well as the facile introduction of therapeutically active ions within the composition and the easy surface functionalization led, over year, to the development of multiple pruducts to be used in various clinical fields, including the regeneration of both hard and soft tissues, bacterial/viral infection treatments and development of antitumoral strategies.
This chapter opens a wide window on the world of bioactive glasses, starting with the description of their peculiar chemical properties, discussed in relation to the most commonly used manufacturing processes to obtain glass monoliths or particles. Then, an overview on the most common applications of BG-based products will be provided, paying particular attention to porous scaffolds for bone tissue engineering, bioactive coatings, antibacterial glasses and surface functionalization. In conclusion, a comprehensive overview on clinical applications updated to the state of the art will be provided.

Keywords: Bioactive glass; Bioactivity; Tissue engineering; Scaffold; Antibacterial; Biomaterials.

1. Introduction

Given their inorganic nature, mechanical rigidity and physical characteristics relatively close to hard tissues, bioactive glasses and glass-ceramics have traditionally received much attention for use in bone substitution and repair. The adult human skeleton is made of 206 bones, which perform support actions and also exhibit protective functions to internal, delicate organs.

The mechanical properties of osseous tissue are given by the complex internal microstructure of bone, which is made of an organic phase, composed mainly by collagen, and a mineral phase constituted by carbonated apatite, plus other proteins that stimulate cellular functions.

Unlike soft tissues, most of bony fractures can heal without scar formation and the regenerated bone matches perfectly to the pre-existing tissue. In fact, bones exhibit an intrinsic capacity for self-repair and regeneration. Bone regeneration process occurs during normal fracture healing, but can also be associated to physiological load conditions, which produce micro-damages and lead to continuous remodelling, which is known as bone turnover [1].

Moreover, there are special clinical conditions that require enhancement of bone regeneration, including skeletal reconstruction of large bone defects due to congenital abnormalities, infections (osteomyelitis), trauma, tumour resections, age- and sex-related pathologies such as osteoporosis and avascular necrosis, osteopenia and several dental problems associated to periodontitis [1]. Bone defects may also carry important social and psychological implications to patients, with an obvious impact on their overall life quality [2]. Therefore, bone defects due to trauma and pathological bone resorption or loss are a major challenge and must be considered as a global health problem.

There are different clinical approaches aimed at enhancing bone regeneration when the physiological healing process is not sufficient or somehow compromised. They can be divided into invasive methods, such as bone grafting and induction of cement spacer (Masquelet technique), and non-invasive techniques, which reproduce biophysical stimulation by applying low-intensity pulsed ultrasound and pulsed electromagnetic fields [1].

In orthopaedic and maxillofacial applications, bone grafting is a common surgical procedure to improve bone regeneration and involves the use of transplant materials (mainly autologous or allogenic bone graft substitutes), combined or not with growth factors [3]. The “gold standard” option is indeed represented by autologous bone grafts, where the bone tissue is usually taken from anterior or posterior iliac crests of the patient’s pelvis. In this case, side effects due to immunoreactions and infections are greatly reduced. On the other hand, the bone harvesting process requires extra-surgery to patients, with possible second-site complications and substantial cost increase [4]. These limitations can be overcome by allografts, obtained from human cadavers (and stored in certified bone banks) or – seldom – from living donors. Unlike autografts, tissues coming from another source than own patient may involve immunogenicity and rejection reactions, possibility of infection transmission, additional costs and ethical or religious issues.

A versatile alternative to autologous or allogenic grafting is represented by man-made bone substitutes, which typically consist of injectable powders, pastes or rigid

three-dimensional porous structures (scaffolds) made of synthetic or natural biomaterials that stimulate the migration, proliferation and differentiation of bone cells while providing mechanical support for bone regeneration. These approaches are already used in clinical practice and show great promise even when regeneration of large bone injuries is required [5].
In these regard, biomedical glasses have been extensively studied with a growing interest by scientists all over the world due to their appealing technological characteristics and bio-functional properties that allow suitability in advanced regenerative medicine.

2. Brief story of bioactive glass invention and development

The origin of biomedical glasses dates back to the late 1960s with the discovery of 45S5 composition, later marketed as Bioglass®, by Professor Larry L. Hench who was beginning his studies about glass-ceramics at the University of Florida. His interest about materials able to regenerate human tissue was triggered by a fortuitous conversation with Colonel Klinker, as reported by Hench in the article "The story of Bioglass®" [6]. Colonel Klinker had just came back to USA from Vietnam where he was enlisted with the Army Medical Corps. Hench described to him his recent studies about polymeric and metal implants and the problem derived from their use. Moreover, he mentioned other experiments about gamma rays applied to vanadia-phosphate semiconductors. These studies caught the attention of the Colonel as they had proved that these new materials could survive to high dose of high-energy radiation. After listening to the description of these new materials and applications, Colonel Klinker formulated a question which will deeply inspire Hench and his future discoveries: "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?". After coming back home from Vietnam War, a growing number of people in the USA during those years needed to be treated because of amputated limbs or damaged tissue: thus, the availability of materials able to regenerate defects without being rejected was actually crucial.

In his report, Hench described how he and his co-workers based their research upon a simply hypothesis: "The human body rejects metallic and synthetic polymeric materials by forming scar tissue because living tissue are not composed of such materials. Bone contains a hydrated calcium phosphate component, hydroxyapatite (HA) and, therefore, if a material is able to form a HA layer in vivo, it may not be rejected by the body.". On the base of this hypothesis, Prof. Hench and his research group had the intuition to study and test different glass compositions based on the SiO_2-Na_2O-CaO-P_2O_5 quaternary system. Specifically, the formulation 45SiO_2-24.5Na_2O-24.5CaO-6P_2O_5 (wt.%), referred to as 45S5 and trademarked as Bioglass® by University of Florida, was selected as the most promising one because of its easiness of melting and its high CaO-to-P_2O_5 ratio which improves material surface ability to react into a physiological environment.

Experiments carried on 45S5 Bioglass® showed an excellent biocompatibility as well as osteoconduction and even osteoinduction abilities: this new material could play an active role in the process of bone tissue regeneration, becoming the first example of surface-active or "bioactive" glasses (BGs) [7]. A number of *in vitro* and *in vivo* tests were conducted on 45S5 glass to investigate its bioactivity and bone regen-

eration potential, proving its extraordinary ability to induce the formation of a nanocrystalline HA layer which forms a strong bone-implant interfacial bond and finally leads to complete restoration of bone tissue.

Since then, many other compositions and different BGs have been studied and developed by scientists all over the world, leading to the development of three main classes of BGs categorized according to the main former oxide, i.e. silicate, phosphate or borate BGs.

45S5 Bioglass® is a silica-based composition and it has been demonstrated that silicon plays a fundamental role in bone regeneration process by promoting the activation of several molecular pathways involved in osteogenesis [8]. In silicate glasses, the network is formed by basic units of SiO_4 tetrahedrons and its connectivity can widely vary into 1-, 2-, and 3-dimensional structures. Each oxygen anion is coordinated by two silicon cations (Si-O-Si), thus resulting in relatively open structures which can be easily broken once in contact with biological fluids.

In 1997, Brink proposed the first borosilicate glass for biomedical application [9]. In that composition, the amount of B_2O_3 was carefully tailored to achieve a pronounced bioactivity. Glasses based on B_2O_3 as network former oxide are very reactive and characterized by lower chemical durability, which allows them to create the surface layer of HA more rapidly than the silica-based ones.

P_2O_5 was used as former oxide in biomedical glasses for the first time by Andersson et al. in 1980 [10]. In nature, the phosphate group [PO_4] is present as tetrahedral structural unit, which is intrinsically asymmetric. P-O-P bonds are easily prone to hydration and, therefore, phosphate glasses are highly soluble in biological fluids according to kinetics ranging from hours to weeks, depending on the glass composition [11].

In general, flexibility of bioactive formulations is an appealing characteristic which has permitted the design and production of a huge number of BGs with different reaction rates in vitro and in vivo.

3. Bioactivity process

In 1987, the European Society for Biomaterials proposed the definition of bioactive material as *"a material which has been designed to induce specific biological activity"* [2]. This definition may be declined to different application fields in medicine. Focusing on bone regeneration, BGs are highly attractive bone substitutes due to their property of chemically bonding to living bone through the formation of a bone-like HA layer at the implant-bone interface [12].

As first suggested by Hench for silicate glasses (Fig. 1), the bioactivity process can be conceived as a special type of glass corrosion and is governed by complex glass-fluid interactions driven by inorganic chemical (stages 1-5) and biochemical (stages 6-12) mechanisms [13].

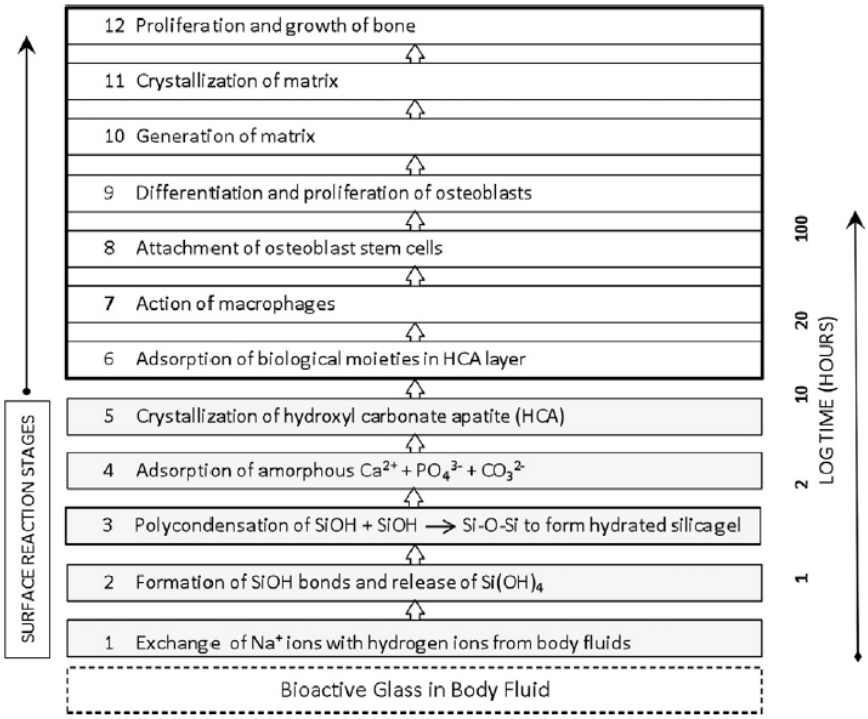


Fig. 1. Sequence of interfacial reactions between bone and a BG. Image reproduced from Hench et al. [14] with permission. Copyright © 2014 Elsevier B.V.

In the first reaction, exchange of Na^+ ions from the glass with H^+ and H_3O^+ from body fluids rapidly occurs. The second step involves the breaking of Si-O-Si bonds and formation of Si-OH (silanols) at the interface between glass and bone tissue. In the third stage, condensation of silanols takes place yielding to formation of silica gel, followed by a migration of Ca^{2+} and PO_4^{3-} from the biological fluid to the surface; as a result, a layer rich of calcium oxide and phosphorus oxide is formed on top of the silica gel layer. Stage number five represents the progressive crystallization of amorphous calcium phosphate to HA (or better hydroxycarbonate apatite) by incorporation of OH^- and CO_3^{2-} anions from the solution.

While stages 1-5 may also occur in vitro in simulated body fluids, stages 6-12 take place in vivo only. Biochemical adsorption of growth factors has been observed on the newly formed nano-crystalline HA layer [14]. Macrophages do not recognize the HA as a foreign material due to its compositional and crystallographic similarity to the mineral phase of bone tissue. Furthermore, bone-like HA stimulates the attachment of stem cells that progressively differentiate into different cells of the bone tissue, allowing the generation of bone matrix. The crystallized matrix represents the final product of the bioactivity process, leading to bone regeneration [14].

This set of reactions is generally accepted for silicate BGs and, under proper adaptations, is valid for borate BGs as well (however, a borate-rich layer forms in stage 3

instead of silica gel). This is not the case of phosphate glasses, where solubility kinetics are typically faster than those of HA formation and re-precipitation.

The bioactivity mechanism can be simplified for some glass-ceramics, on the surface of which HA can form without the presence of silica gel [15]: for example, the apatite and wollastonite crystals in A/W glass-ceramics act as sites for direct nucleation of HA crystals [16] (Fig. 2).

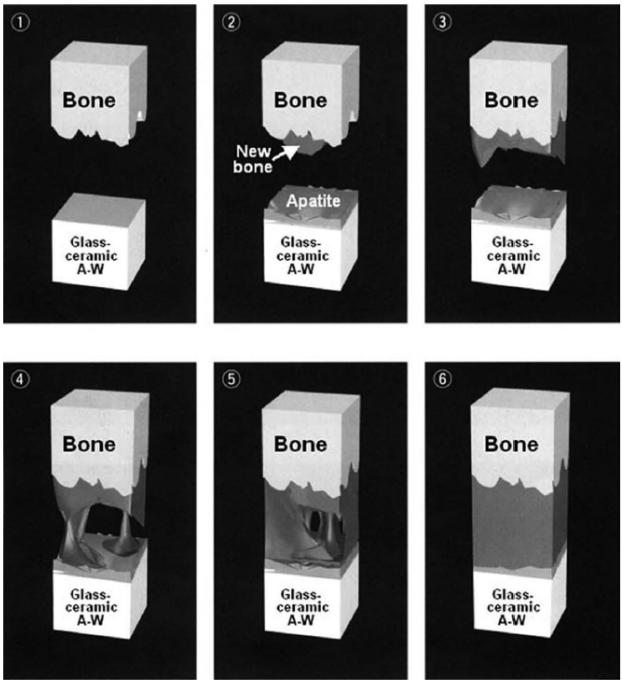


Fig. 2. Bioactivity process in A/W glass-ceramics. Image reproduced with permission from Ref. [17]. Copyright © 1969, John Wiley and Sons.

Some studies have convincingly shown that the ionic dissolution products released from BGs stimulate osteogenesis by regulating osteoblast proliferation, differentiation and also gene expression [18].

As illustrated in Fig. 3, BGs enhance bone cell gene expression depending on four main factors [19]:

a. Surface chemistry;
b. Surface topography;
c. Rate and type of dissolution ions released;
d. Mechanical properties of glass/bone interfaces.

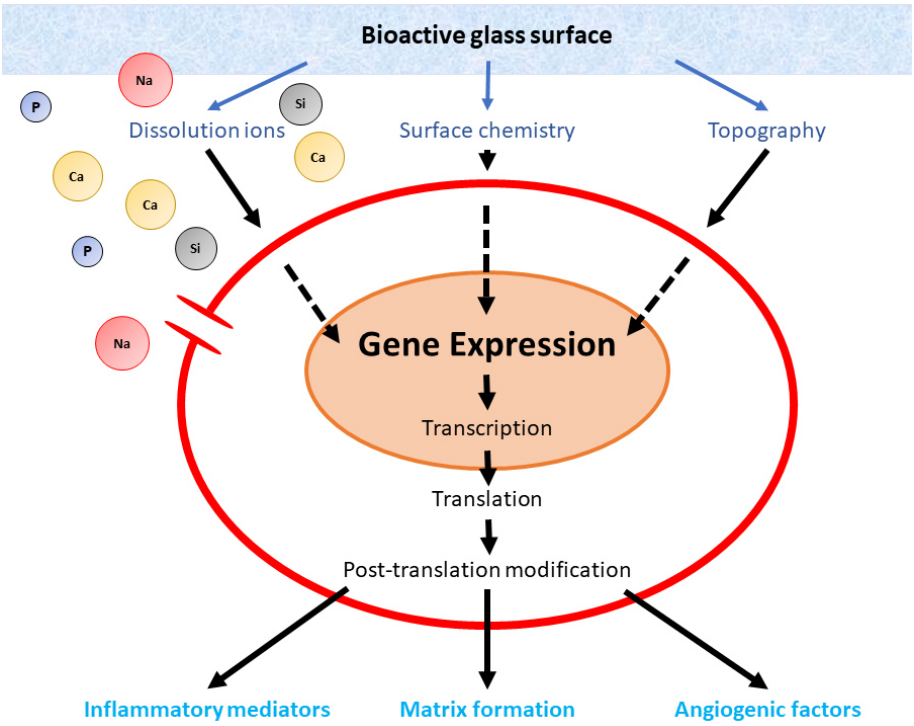


Fig. 3. Main mechanisms proposed to determine bone cell gene expression. Image adapted from Ref. [19] with permission. Copyright © 2006, Springer Science Business Media, LLC.

The bioactivity process can be evaluated through *in vitro* experiments by soaking the biomaterial into a Simulated Body Fluid (SBF) mimicking the composition of human plasma. The most commonly used SBF follows the Kokubo's formulation [20], which is also recommended in the relevant ISO standard [21]. Immersion studies in SBF allow evaluating the HA-forming kinetics of BGs (stages 1 to 5); however, in vitro bioactivity tests do not always represent a realistic prediction of the bone-bonding and bone-forming potential of the material in vivo, yielding to false positive or false negative results; further details on this issue and on how to properly adapt the tests in SBF according to the sample geometry (e.g. BG powders, tiles, porous scaffolds) can be found elsewhere [22]–[24].

4. Bioactive glass processing methods

Glass is a very attractive material for several applications from optoelectronics to biotechnologies and, for this reason, different processing techniques have been developed. The most common preparation methods of BGs are the melt-quenching and sol-gel techniques [25]. High-temperature post-synthesis treatments are often necessary to consolidate and/or sinter BGs, for example if processing of BG powders is required; in these cases, devitrification may take place, yielding to bioactive glass-ceramic final products [17] (Fig. 4).

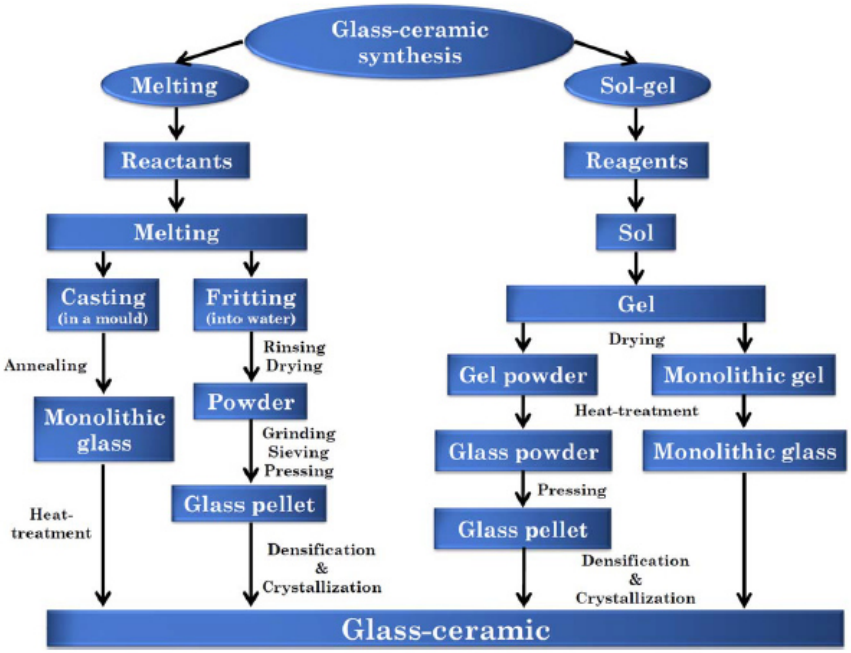


Fig. 4. Overall flowchart of bioactive glass and glass-ceramic production. Image reproduced from Ref. [17] with permission. Copyright © 1969, John Wiley and Sons.

4.1 Melt-quenching technique

The first BG with 45S5 composition was produced through melt-quench conventional technique [26]. This processing method is the most common way to obtain glasses by fusion of two or more components. Melting procedures begin from the mixing of raw precursors (usually powders of oxides, carbonates or inorganic salts) which should be highly pure to avoid unwanted contamination of the final products. Sometimes, after preliminary mixing of the precursors, the blend is introduced into a ball mill (with or without small amounts of acetone or ethanol) to break agglomerates and improve homogeneity. The resulting mixed powders are dried in air and melted in alumina or platinum crucibles at temperatures from 1200 to 1500 °C for silicate and borate BGs or around 1000-1200 °C for phosphate glasses [27]. Repeated melting procedures can also be applied to improve homogeneity, especially when high amount of glass is produced.

The molten product can be cast in air into graphite or metallic moulds (Fig. 5), thus obtaining a monolithic glass, or can be poured into water to obtain a glass “frit”, which is very useful for the production of glass powders being easily pulverisable.



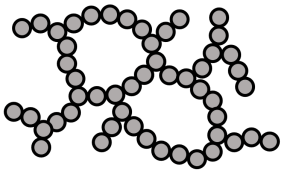
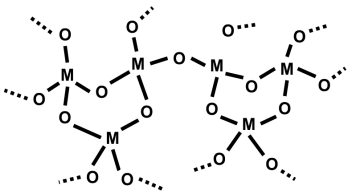
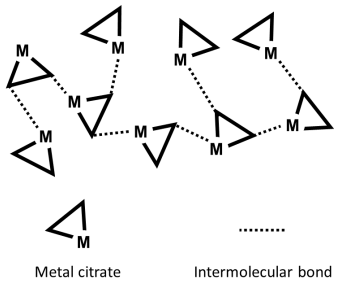
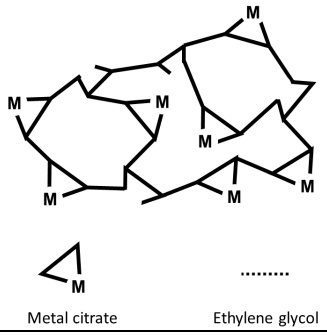
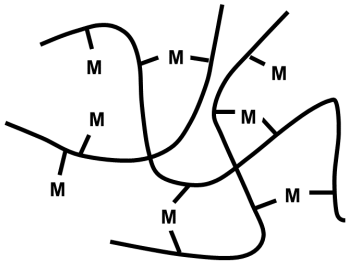
Fig. 5. Casting into a cylindrical mould during melt-quenching process (Glance Group's Lab, DISAT, Politecnico di Torino. Image courtesy of Elisa Fiume)

4.2 Sol-gel synthesis

In 1991, Li et al. first reported the synthesis of silicate BGs by sol-gel process [28]. This technique was first mentioned more than 150 years ago by Graham [29], who observed that the hydrolysis of tetraethyl orthosilicate (TEOS) could lead to the formation of SiO_2-based glasses.

In order to better understand sol-gel procedure, it is necessary to introduce some definitions: the term "sol" refers to a colloidal suspension while the term "gel" generally identifies a more rigid and interconnected network in which pores and silicate chains are usually immersed into a liquid phase. More accurate classifications of gels have also been proposed. For example, Flory divided gels into four classes: ordered and lamellar gels, covalent polymer networks, networks of aggregated polymers and disordered particulate gels [30]. More recently, Kakihana [31] introduced a new gel classification based on five different classes and strictly relied upon the key features of sol-gel chemistry (Table 1).

Table 1. Classification of gels synthetized via sol-gel procedure. Table adapted from Ref. [32] under a Creative Commons Attribution 3.0 Unported Licence.

Type of gel	Bonding	Source	Gel schematic
Colloidal	Particles connected by Van der Waals or hydrogen bonding	Metal oxide or hydroxide sols	
Metal-oxane polymer	Inorganic polymers interconnected via covalent or intermolecular bonding	Hydrolysis and condensation of metal alcoxides, e.g. SiO_2 from tetramethyl orthosilicate	
Metal complex	Weakly interconnected metal complexes	Concentrated metal complex solution, e.g. aqueous metal citrate or ethanolic metal urea, often forms resins or glassy solids rather than gels	
Polymer complex I In situ polymerizable complex (Pechini method)	Organic polymers interconnected by covalent and coordinate bonding	Polyesterification between polyhydroxy alcohol (e.g. ethylene glycol) and carboxylic acid with methal complex (e.g. metal citrate)	
Polymer complex II Coordinating and crosslinking polymers	Organic polymers interconnected by coordinate and intermolecular bonding	Coordinating polymer (e.g.) alginate and metal salt solutions (typically aqueous)	

Depending on the modality of liquid removal, aerogels, xerogels and alcogels can be distinguished. In aerogels, the liquid phase is removed in the form of gas under hypercritical condition; xerogels are monoliths formed after liquid removal by thermal evaporation and, finally, alcogels are defined as gels in which the liquid phase is constituted by alcohols.

Adopting different synthesis parameters (e.g. temperature, pH) and applying different post-processing treatments on the gelled sol permit the formation of several different morphologies in the final glass product [33]. Therefore, sol-gel process is well recognized as a highly versatile approach to produce BGs.

Sol-gel products can be obtained through:

a. gelation of sol-derived colloidal powder
b. hydrolysis and poly-condensation of precursors, such as as alkoxides or nitrates, under hypercritical conditions
c. hydrolysis and poly-condensation of alkoxides in ambient atmosphere.

Three main phases can be defined in sol-gel processing method:

1. Sol preparation
2. Sol gelation
3. Solvent removal

BGs are usually produced through hydrolysis and poly-condensation process of alkoxide precursors in ambient atmosphere.

There are seven major reaction steps in the sol-gel process for biomedical glass production [34]:

1. Mixing of alkoxide or organometallic reagents at room temperature leads to the formation of the sol through covalent bonding between the elements. In this step, hydrolysis and poly-condensation reactions are concurrent and proceed simultaneously. A structure-directing agent (surfactant) may be optionally introduced in the sol for finely modulating the nanopore size distribution via self-organization of micelles, which will be thermally removed in the step no. 7.
2. Sol casting into a proper mould, if the beaker used for the synthesis is not appropriate or special geometries are required.
3. Gelation: the glass network is formed due to progressive increase of fluid viscosity. Gelation time depends on solvent concentration, oxides/elements involved in the synthesis and water amount; it can be accelerated by the use of a proper acid (e.g. HF, HNO_3) or basic (e.g. NH_4OH) catalyst, depending on the type of synthesis.
4. Aging: poly-condensation prevails over hydrolysis reaction causing a decrease in gel porosity and an increase of mechanical properties. This process usually occurs at 25-80 °C for several hours influencing also density, surface area and pore volume of the gel.
5. Drying (liquid phase removal): colloidal gels should be easily dried, but great capillary stress may be originated leading to cracking problems.
6. Dehydration (also known as chemical stabilization): silanol bonds are removed from the network reaching the final chemical stability of the glass.
7. Densification (also called calcination): this process occurs by thermal treatment in furnace at relatively high temperatures (about 500-700 °C, which

however are definitely lower than those required for melt-quenching technique).

TEOS is commonly used as precursor for silica while nitrates act as source for modifiers; metal chlorides can also be used to introduce additional cations (e.g. Fe^{2+}/Fe^{3+} or Cu^{2+}). A comprehensive picture of sol-gel processing and the role of precursors/reagents on the glass properties can be found elsewhere [33].

Different studies have shown the effects of H_2O/TEOS or ethanol/TEOS molar ratios and solvent concentrations on TEOS hydrolysis: increase of H_2O/TEOS ratio or decrease of EtOH/TEOS ratio improves solvent polarity and interfacial energy, with the formation of bigger primary particles of silica [35]. Hydrolysis and polycondensation are the key processes of sol-gel synthesis allowing the formation of the glass network through different bond recombination.

The two chemical reactions are represented below:

a. Hydrolysis is defined as a nucleophilic attack in which -OH group replaces -OR group (Eq.(1)):

$$\equiv Si - OR + H_2O \leftrightarrow \equiv Si - OH + ROH \quad (1)$$

b. Condensation yields water or alcohol as final products through the formation of silanol bonds (Eq.(2)):
   - Condensation with alcohol elimination:

$$\equiv Si - OR + OH - Si \equiv \leftrightarrow \equiv Si - OH - Si \equiv + ROH \quad (2)$$

   - Condensation with water elimination (Eq.(3)):

$$\equiv Si - OH + OH - Si \equiv \leftrightarrow \equiv Si - O - Si \equiv + H_2O \quad (3)$$

In these reactions, R indicates an alkyl functional group in the form C_xH_{2x+1}.

BGs produced by sol-gel technique have shown an enormous potential in tissue engineering applications compared to the traditional melt-derived materials [36]. Firstly, sol-gel is considered as a technologically appealing method due the lower temperatures required and the higher versatility of final products.

Others advantages of sol-gel BGs over melt-derived BGs include [37]:

1. High specific surface area (above 50 vs. less than 1 m^2/g), associated to higher solubility and higher reactivity (i.e., faster HA-forming kinetics) in biological environment;
2. Nanopore size which can be tailored by modifying the processing parameters;
3. Simpler compositions the avoid the addition of high amount of alkaline oxides to lower the melting temperature and facilitate the glass processing;
4. Possibility to adjust the composition during the synthesis;
5. Variety of products (e.g. monoliths, particles, hollow spheres etc.) that can be obtained by just modifying some processing parameters;
6. Bioactive properties in a wider compositional range (up to 90 mol.% of silica).

From a chemical perspective, the properties of sol-gel BGs can be further expanded by bonding functional groups on the glass surface due to the high presence of si-

lanol groups [38]. The grafting of functional groups usually occurs to enhance biocompatibility, binding affinity for proteins, adsorption of biomolecules and drug loading capacity.

However, sol-gel BGs have higher brittleness and lower mechanical properties than melt-derived glasses with the same composition due to their inherently porous structure comprising mesopores in the range of 2 to 50 nm [39]. Interestingly, mesopores are concurrently the strength (improvement of bioactivity, drug loading/release) and the weakness (poor mechanical properties) of such materials. Recently, additive manufacturing strategies have allowed overcoming – at least partially – these drawbacks [40].

5. Crystallization of bioactive glasses

The bioactivity mechanism of glasses relies upon the dissolution of the amorphous network when the material is in contact with biological fluids. However, during high-temperature post-processing treatments (e.g. sintering of glass powder compacts), BGs may undergo devitrification [17]. This involves the partial conversion of glass into crystalline domains, yielding the production of a glass-ceramic material. Development of crystalline phases reduces the volume of the glassy fraction and, therefore, has an obvious impact on bioactivity. The nature of the crystalline phases that may nucleate and grow are strongly dependent on glass composition. Heat-treated 45S5 Bioglass® and similar oxide systems typically form sodium-calcium-silicate phases: specifically, 45S5 and S53P4 ($53SiO_2$-$23Na_2O$-$20CaO$-$4P_2O_5$, wt.%) glasses tend to crystallize to combeite-like phases ($Na_2CaSi_2O_6$ [41], [42] and $Na_2Ca_2Si_3O_9$ [43], respectively) above 550-600°C. Glasses such as 1-98 ($5.9Na_2O$–$7.1K_2O$–$7.6MgO$–$23.9CaO$–$0.9B_2O_3$–$0.9P_2O_5$–$53.8SiO_2$, mol.%) crystallize as wollastonite ($CaSiO_3$) upon heating above 800 °C [27], [44]. It is also possible that some systems form diopside crystals ($CaMgSi_2O_6$) [45]–[47]. The presence of crystalline phases can significantly slower the formation rate of HA on the glass surface; however, even if 100% conversion is achieved, fully crystallized 45S5 Bioglass® was still reported to be weakly bioactive [48]. The HA-forming ability was also maintained to some extent in both partially and fully crystallized glasses having similar composition to 45S5 [49]. In general, the HA-forming kinetics are dictated by the amount of crystalline phase. If the crystalline fraction in the 45S5 system is below 60%, HA forms in less than 20 h on the glass surface; otherwise, it takes 25 h or more. For the sake of comparison, HA starts to form on fully amorphous melt-derived 45S5 glass by less than 10 h in SBF.

Both sodium-calcium-silicate and wollastonite crystals have been proved to dissolve in vitro when immersed into SBF, but the dissolution of wollastonite is much slower compared to the former phase [50]. On the contrary, wollastonite is significantly more reactive than diopside in SBF [51].

45S5 glass has a dramatically narrow sintering window, which means that glass powder compacts of this glass cannot be practically sintered without undergoing concurrent devitrification (i.e., sinter-crystallization occurs unavoidably). Some studies carried out over the last years have been addressed to developing BG compositions that can undergo high-temperature thermal treatments without devitrification, in order to obtain, for example, good sinterability while maintaining high bioactive properties. A successful example is represented by the 13-93 glass composition ($53SiO_2$–$20CaO$–

$5MgO–4P_2O_5–12K_2O–6Na_2O$, wt.%) [52], [53], which has received FDA approval in the USA and CE marking in Europe for clinical use.

Devitrification of BGs is also dependent on dimensional effects: the smaller the glass particle size, the lower the temperature for crystallization onset (in other words, crystallization is "anticipated" at lower temperatures) [54], [55]. This behaviour is generally common to all glasses and its details are described in the Chapter 4 of the present book.

Crystalline phases were also reported to nucleate and grow in a sol-gel multicomponent $47.5SiO_2–20CaO–10MgO–2.5P_2O_5–10K_2O–10Na_2O$ (mol.%) BG after calcination at different temperatures, without any significant impact in vitro bioactivity [56]. These gel-derived glass-ceramic materials, in spite of their partially crystalline nature, exhibited a faster HA-forming ability in SBF as compared to their melt-derived counterparts.

Bioactive glass-ceramics are highly appreciated in dental applications, as the crystalline phases play a role in improving the mechanical properties of parent BGs; for example, the toughening effect of crystals is key to withstand cyclic masticatory loads and extend implant lifetime [57].

The increase of mechanical properties in bioactive glass-ceramics as compared to the parent BGs is also beneficial in porous scaffolds, which are often produced by sinter-crystallization of glass powders.

6. Role of dopants

Incorporating different ions into the BG composition allows modulating some physico-chemical properties (e.g. solubility) while conferring specific therapeutic action [58].

Incorporation of special ions in the glass network is called doping process and has been widely employed for the production of BG-based multifunctional products for various clinical applications [59].

A doping element, by definition, is an additional incorporation in the main composition at a very low concentration as compared to the major components, ranging from a few ppm to a few percent units [58].

Recent studies have shown that the controlled introduction of dopants can lead to increased efficiency in performing a specific therapeutic action (e.g., antibacterial properties, angiogenesis) [60]. In other cases, doping may have an effect on glass dissolution kinetics, stability against crystallization, thermal and mechanical properties etc. [61]–[63].

At the beginning, the dopants were selected according to their similarity in valence with the elements already contained in the glass; later, the choice of the dopants was guided by a more "biological" criterion, depending on the essential trace elements required in the human body and their action on cell and tissue metabolism [64]. Many metal ions, acting as enzyme cofactors, can affect signaling pathways and promote tissue formation, and are thus considered highly-interesting doping materials in biomedicine (Table 2) [18].

Table 2. Biological role of the main BG elements and dopants in the human body.

Element	**Biological activity**

Si	• Stimulatory effect on formation of bone tissue • Intake of Si increases bone mineral density • HA precipitation • Helps to stimulate collagen I formation and osteoblast differentiation
Ca	• Favours osteoblast proliferation, differentiation and mineralisation • Activates Ca-sensing receptors in osteoblast cells
P	• Matrix gla protein (MGP) stimulation
Mg	• Helps to form new bone enhancing osteoblast activity • Increases bone-cell adhesion and stability
Zn	• Shows anti-inflammatory effect • Bone formation *in vitro* by activation of protein synthesis in osteoblasts • Increases ATP activity
Sr	• Beneficial effects on bone formation *in vivo* • Anti-resorption effect on bone (for osteoporosis)
Cu	• Stimulates proliferation of human endothelial cells and, in general, angiogenesis • Antibacterial properties
Ag	• Antimicrobial properties • Anti-inflammatory properties
Co	• Potent pro-angiogenic effect
Li	• Treatment of both bipolar and unipolar depressive disorder • Enhances immunological activities of monocytes and lymphocytes

7. Three-dimensional glass-based scaffolds for regenerative medicine

7.1 Properties and requirements

Before discussing about BG scaffolds, some concepts related to tissue engineering and its latest developments need to be introduced. Tissue Engineering and regenerative medicine are considered the new frontier of biomedicine for repairing and regenerating damaged biological tissues. These multidisciplinary fields of research concern the development of biocompatible tissue substitutes to be implanted in the injured site and able to stimulate the growth of functional tissue [65].

Fig. 6 schematically shows the regenerative process, highlighting the three main elements considered in the tissue-engineering approach:

- The cells relevant to the diseased tissue are the first element to consider before developing a tissue substitute. Cells are responsible of tissue synthesis and trigger regeneration mechanisms.
- Scaffolds are three-dimensional (3D) porous structures that provide support to cells allowing them to adhere, migrate, proliferate and differentiate.
- Biological, chemical or physico-mechanical signals influence cell pathways during each steps of cell proliferation and differentiation.

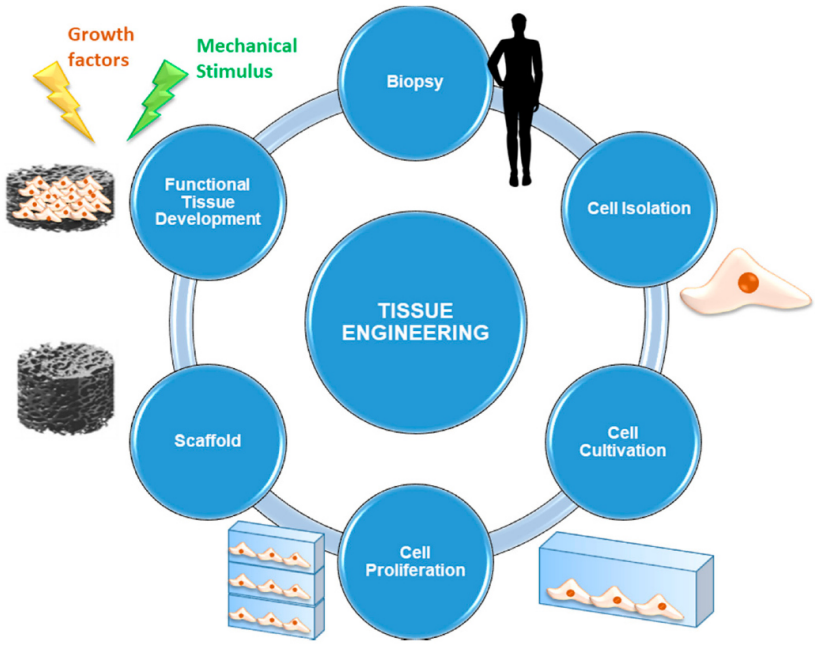


Fig. 6. Schematic illustration of tissue-engineering approach from patient biopsy to tissue substitute implantation. Image reproduced from Ref. [65] nder the terms and conditions of the Creative Commons Attribution (CC BY) license.

The term "scaffold" literally means "supporting framework" and was originally introduced in the field of Civil Engineering. In tissue engineering, scaffolds can be defined as (porous) materials that have been engineered to cause desirable cellular interactions contributing to the formation of new functional tissues for medical purposes.

In bone repair applications, scaffolds should mimic as much as possible the 3D trabecular architecture of healthy cancellous bone (Fig. 7) in order to optimize the integration with the host tissue and provide a suitable template for tissue regeneration. Given the broad variability in the structural and mechanical features of bones due to sex, age, activity and pathologies of patients, a "universal" scaffold does not exist but some design recommendations can be identified, regardless of the biomaterials used. The basic functions that a scaffold should primarily perform are [66], [67]:

1) Providing the correct anatomic geometry, matching the defect size and shape
2) Withstanding the mechanical loads typical of the interested site
3) Stimulating tissue regeneration.

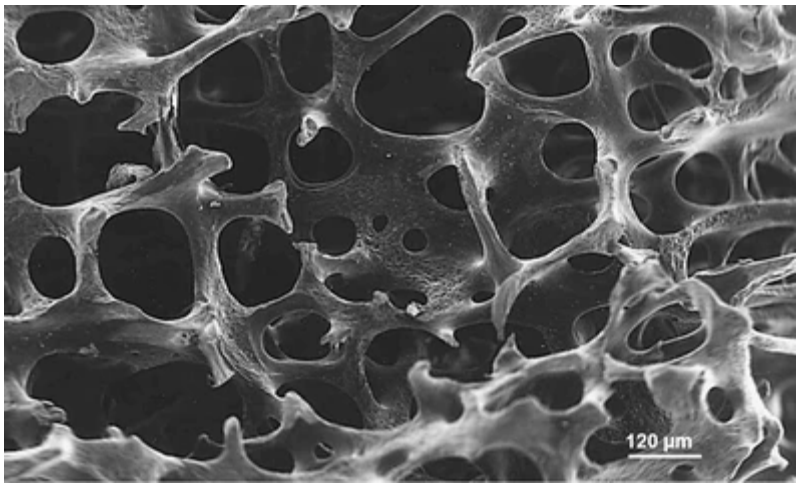


Fig. 7. SEM imaging of bone acquired in secondary electron mode shows the microarchitecture of trabecular bone. Image adapted with permission from Ref. [68]. Copyright © 2011, International Osteoporosis Foundation and National Osteoporosis Foundation.

According to the final application, scaffolds should match the structural and mechanical properties of host tissue and optimize the micro-environment of the defected site. Focusing on bone repair, the design and development of an "ideal" scaffold should account for different requirements (Fig. 8), including [69]–[71]:

1) Biocompatibility and bioactivity (i.e. HA-forming ability)
2) Capability to bond the host tissue without scar formation
3) Porous and interconnected structure
4) Mouldability in different shapes and sizes
5) Suitable degradation rate
6) Maintenance of mechanical properties
7) Easy fabrication with affordable cost
8) Sterilization without damage or deterioration.

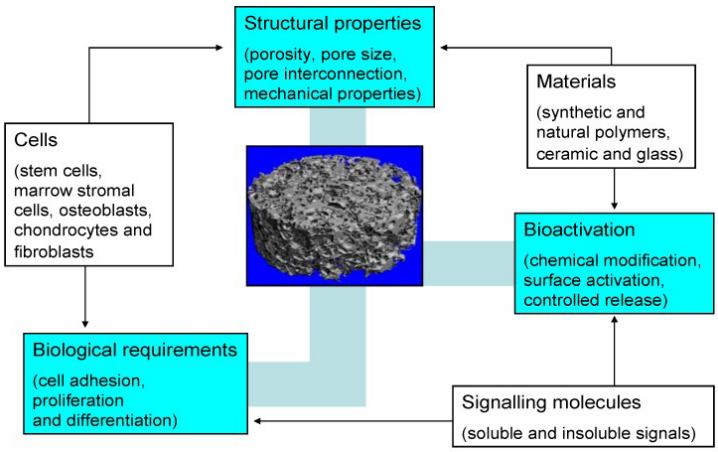


Fig. 8. Schematic diagram of the key factors involved in the design of optimal scaffolds for bone tissue engineering. Image reproduced from Ref. [69] under the terms and conditions of the Creative Commons Attribution License (CC BY-NC-SA 3.0).

The main properties required for bone tissue-engineering scaffolds are also collected and shortly discussed in Table 3.

Table 3. Overview of the key properties for a scaffolds aimed at regenerating bone [72].

Property	Effect/explanation
Ability to deliver cells	The material should not only be biocompatible but also foster cell attachment, differentiation and proliferation
Osteoconductivity	Osteoconductivity not only allows avoiding the formation of fibrous tissue around the implant (encapsulation) but also brings about a strong bone between scaffold and host bone
Biodegradability	The composition of the material, combined with the porous structure of the scaffold, should lead biodegradation/dissolution *in vivo* at rates appropriate to tissue regeneration
Mechanical properties	The mechanical strength of the scaffold, which is determined by both the properties of the biomaterial and the porous structure, should be sufficient to provide mechanical stability and withstand loads at the implant site prior to synthesis of the new extracellular matrix by cells
Porous structure	The scaffold should have an interconnected porous structure with porosity >50 vol.% and pores sizes between 300 and 500 μm for allowing cell penetration, tissue ingrowth and vascularization
Fabrication	The material should possess a certain technological versatility, for example, being readily produced into irregular shapes so that the scaffolds can match the defect geometry in the bone of individual patients
Commercialization potential	The synthesis of the basic material and the scaffold fabrication process should be reproducible and reliable. The scaffold should also be sterilisable without losing its properties and be marketable at an affordable cost

BGs, being also osteoinductive (i.e. able to stimulate osteogenesis via ionic dissolution products) [8], [73], are highly promising materials for making scaffolds.

The first BG-based macroporous scaffolds were fabricated in the early 2000s by applying foaming techniques to melt-derived 45S5 glass (H_2O_2-driven foaming) [74] or sol-gel glasses (surfactant-mediated foaming) [75]; the latter approach actually yielded achieving hierarchical systems with macro- (>100 μm) and meso-scale (2-50 nm) porosity [76].

Since then, a lot of experiments have been carried out to produce BG-based scaffolds in myriads of shapes and sizes in order to best fit into the damaged bone. With the evolution of manufacturing processes, major issues concerning the intrinsic brittleness of glass and glass-ceramic materials have been overcome – at least partially – and scaffolds with mechanical properties comparable to those of human bone have been produced [72].

The concurrent need for adequate mechanical properties and a highly-porous structure of interconnected macropores, which are key in tissue engineering applications, is a big challenge for BG-derived scaffolds. These two factors are intrinsically correlated as high porosity in glass-ceramic scaffolds results in low mechanical properties. A deep analysis carried out by Gerhard and Boccaccini [69] on many types of BG scaffolds has shown a negative linear relationship between scaffold porosity and compres-

sive strength, characterized by coefficients of determination R^2 between 0.80-0.99. This result means that the systematic impact of porosity on the variability of compressive strength is at least 80% (Fig. 9). A power-law relation was observed between elastic or shear modulus and total porosity in highly-porous (>50 vol.%) 45S5-based glass-ceramic foams, while the Poisson's ratio was a linear function of porosity [77]. The relation between tensile strength and porosity in foam-like silicate BG scaffolds was reported to obey more complex models based on quantized fracture mechanics [78].

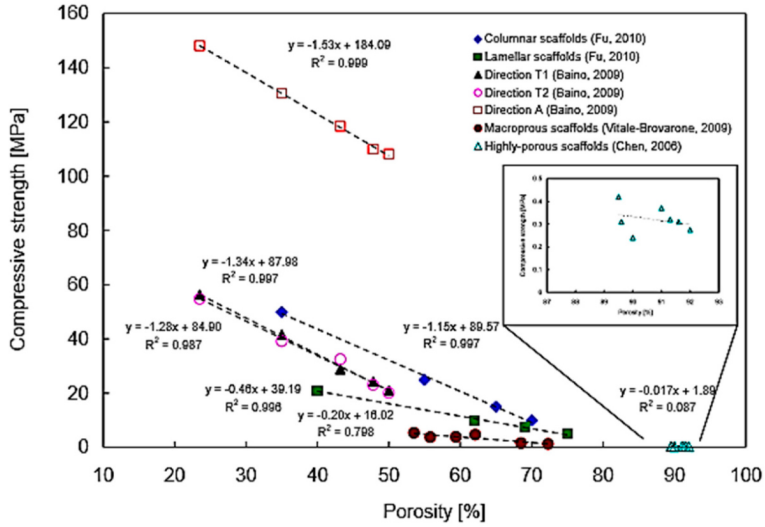


Fig. 9. Compressive strength vs. porosity curve for glass-ceramic scaffolds. The negative slope shows how increase in porosity percentage reduces mechanical compressive strength according to negative linear relationships. It can be noticed also that for very high values of porosity (≈ 85-95%) the relation does not fit a linear curve and the mechanical performances of the scaffold are dramatically poor (<0.4 MPa), being unsuitable for biomedical applications. Image reproduced from Ref. [69] under the terms and conditions of the Creative Commons Attribution License (CC BY-NC-SA 3.0).

In this scenario, one possible solution to solve the mechanical drawbacks of BG-derived scaffolds relies on the use of multifunctional composite structures, which are typically produced by (i) the integration of a biodegradable polymer matrix with BG particles as filler phase or (ii) a polymeric coating on BG surface [79]. In this way, the polymeric component strongly improves the mechanical properties of BGs (strength and toughness), acting as a "glue" in keeping glass particles together while the scaffold starts to fail [80], [81].

However, some recent studies have shown that composite BGs and polymeric coatings introduce significant side effects in scaffolds features. For example, the polymeric coating may negatively affect scaffold bioactivity performances due to its covering role. Furthermore, the introduction of the coating also influences environment conditions by its premature degradation which releases acidic products that strongly reduce pH. Finally, mechanical strength and properties do not remain constant after the scaffold implantation *in vivo*, but rapidly decrease because of the interaction between

polymeric coating and glass and the influence of reciprocal degradation mechanism [82].

7.2 Fabrication methods

Since the fabrication of the first BG scaffold in 2001 [74], a lot of researchers had focused their studies on the optimization of manufacturing processes in the attempt of obtaining an "ideal" scaffold [83]. In principle, manufacturing processes should be easily repeatable and should give the same outputs, guaranteeing constant characteristics of scaffolds and allowing potential mass production. The processing route should also be economically sustainable and safe for all workers involved in the process.

In the last two decades, different technologies have been developed to produce glass-based scaffolds. Manufacturing methods may be divided into two different major categories, known as conventional methods and additive manufacturing techniques (Table 4).

Table 4. Overview of the manufacturing techniques used for the production of glass-based scaffold in bone tissue engineering [72].

Manufacturing methods	Technological class	Specific methods
Conventional	Foaming techniques	Gel-casting foaming, sol-gel foaming, H_2O_2 foaming
	Thermal consolidation of particles	Organic phase burning-out: polymeric porogens, starch consolidation, rice husk method
	Porous polymer replication	Coating methods, foam replication
	Freeze-drying	Freeze-casting of suspensions, ice-segregation-induced self-assembly
	Thermally induced phase separation	
	Solvent casting and particulate leaching	
Additive manufacturing	Selective laser sintering	
	Stereolithography	
	Direct ink writing	3D printing, ink-jet printing, robocasting

Conventional methods are characterized by a top-down approach in which the realization of the desired form occurs by the progressive removal of material from a bigger bulk piece (e.g. sacrificial pore-forming agents). On the contrary, additive manufacturing technologies (AMTs) indicate those bottom-up approaches where 3D structures are fabricated by progressively adding materials in the form of thin layers to obtain the desired morphology. A very comprehensive picture of BG fabrication strategies can be found elsewhere [72].

Historically, foaming methods were the first routes used to produce glass-based 3D scaffolds. These techniques take their name from the use of a foaming agent in the manufacturing process. The foaming agent is generally introduced in a slurry to create air bubbles which are responsible of porosity in the final product. The use of these techniques may lead to some side effects, such as high brittleness of BG-derived scaf-

folds, low pore interconnectivity, and lack of pores in the outer layer due to formation of an external compact "skin". Gel-cast foaming, sol-gel foaming and H_2O_2 foaming belong to this family of manufacturing methods.

Gel casting employs an organic monomer that is polymerized to cause the in-situ gelation of a foamed aqueous slurry containing melt-derived glass particles [84].

Unlike gel-casting, where the glass has been previously prepared, sol-gel foaming involves the formation of the 3D network of macropores simultaneously to the glass synthesis. A surfactant is added to the sol and, upon vigorous stirring, gelation occurs along with incorporation of air bubbles; thermal treatment allow consolidation of solid skeleton/glass formation [75]. The development of this method was due to the initial difficulty of producing melt-derived BGs that could undergo another high-temperature thermal step without crystallizing, with a partial loss of bioactivity. Although most sol-gel BG compositions are relatively simple, being based on binary (SiO_2-CaO) [85] or ternary (SiO_2-CaO-P_2O_5) [86] systems, Ag-doped [87] and Fe-doped [88] scaffolds were also produced by this method to impart antibacterial and magnetic extra-functionalities, respectively.

H_2O_2 foaming process includes the use of a peroxide solution as foaming agent. It was observed that pore interconnectivity, pore size and total porosity of the final 3D scaffold increased with increasing H_2O_2 content, but controlling these increments was a difficult task [89].

Methods based on thermal consolidation of particles include all those processes which require the introduction of sacrificial porous templates or particles, usually polymeric, before the sintering procedure of the green body [72]. These techniques allow properly tailoring the porosity degree and characteristics by controlling process parameters and varying the type of templates (e.g. polyurethane sponge [90], marine sponge [91], stale bread [92]) or particles (e.g. starch [93], polyethylene [94]) used. In principle, both melt-derived and sol-gel glass particles can be used to produce the green. The process could also occur without the introduction of any sacrificial particles or template but just varying the sintering parameters; in this case the final porosity comes from inter-particle voids only [95]. A special variant of these methods involves concurrent foaming and glass particle sintering: for example, if dolomite fine powder is used as a foaming agent in the green compact bodies, the result is qualitatively similar to that obtained by sol-gel foaming but the scaffolds are mechanically stronger [96].

As an alternative to the use of organic particles/foams as porogen agents, freeze-drying methods have been developed in which the formation of ice crystals generates porosity in the final 3D scaffolds [97]. In these methods, the suspension containing glass particles is frozen and then the solvent crystals are removed, leaving a porous structure in the scaffold that will be thermally consolidated during the final processing step.

Another conventional method involves thermally induced phase separation, which relies on the change of solubility between different polymers depending on temperature variations. This process mainly produces polymeric scaffolds, but it can be also extended to the fabrication of polymer/glass porous composites [98]. The main step is addressed to polymer solution cooling which reveals phase separation; then, porous structures can be obtained by selective phase removal.

Unlike conventional methods, AMTs include all the techniques which involve the use of a CAD model or a computed tomography (CT) reconstruction as a template for the final product [99]. There are two main classes of AMTs to produce ceramic and glass materials, i.e. direct fabrication techniques, which produce sintered ceramic or glass parts without needing any further thermal treatments, and indirect fabrication techniques that involve layer-wise building of the scaffold (printing), thermal debinding and sintering.

Selective laser sintering belongs to the class of direct fabrication techniques because just one step is necessary to produce the 3D scaffold. In fact, the CAD model of the object is followed by a computer that controls a laser over a bed of glass powders, which can be locally melted or sintered to produce the desired path [100].

Stereolithography probably represents the most accurate AMT, reaching high resolution values up to 20 μm. In this process a UV-photocurable liquid polymer, a UV-laser and a movable platform are used to build layer-by-layer the 3D object [101]. The major limitation of this technique is the poor availability of UV-curable polymers with appropriate rheological characteristics.

Direct ink writing methods include many different AMTs, such as 3D printing, ink-jet printing and robocasting [102]. In all these techniques, a pattern-generating device (print head or nozzle) builds up a 3D object by following computer instructions from a script file or virtual CAD model. While in 3D printing the ink is formed by the binder and glass particles are in the building bed, in ink-jet printing the ink contains all the components. Both in 3D printing and ink-jet printing, the ink flow through the nozzle is generated by acoustic, electrical or piezoelectric systems (or their combinations). Generally speaking, the expression “3D printing” is often used to indicate any technique belonging to direct ink writing methods. Robocasting is probably the most common AMT and involves the extrusion of a continuous filament by pressurized air [53], [103]. Its main advantage is the possibility to change ink viscosity through chemical and physical processes in order to achieve strong 3D porous structures. Robocasting also allows printing polymer/BG filaments, thus obtaining composite scaffolds [104].

8. Bioactive glass coatings

The need for bioactive coatings is of particular interest when inert materials are implanted in the patient’s bone. In fact, after being implanted, nearly-inert ceramics (e.g. alumina) or metals are typically encapsulated within fibrous tissue without establishing a chemical bond with host bone. BG coatings have the potential to overcome this limitation as they can improve the stability of underlying implant by tightly bonding it to the host bone. Furthermore, if metallic implants are used, BGs protect the metal from corrosion and avoid the release of toxic metallic cations *in vivo* [105]. The glass composition, which dictates the bioactive behavior, should be carefully designed if the intended application is for coating: in fact, glasses with high bioactivity are also prove to quickly dissolve in the biological fluids, thereby causing instability of the implant lying underneath. This is probably the major reason why the use of BG coatings is still limited compared to other bioceramics, such as non-resorbable thermal-sprayed HA [106].

Another key point to consider is the mismatch between the thermal expansion coefficient (TEC) of BG and substrate. Ideally, the TEC of BG should be as close as pos-

sible to that of the substrate to prevent the glass pulling away from the implant upon thermal processing (e.g. sintering) [107]. However, the TECs of 45S5 Bioglass® (15×10^{-6} °C^{-1}) and of most of silicate BGs are significantly higher than that of titanium alloys (about 9×10^{-6} °C^{-1}), which are commonly used in orthopaedic and dental prosthetics. Therefore, a great challenge of the next few years will be the development of new BGs with more suitable TEC and dissolution rate for use as coating materials.

Conventional techniques for producing BG coatings include manual deposition or dipping followed by glass particle sintering (enameling and glazing) [108]–[114] and thermal spraying [115]–[117]. In the last years, new approaches (e.g. multilayer BG coatings to achieve a good compromise between adequate TEC, slow dissolution rate and bioactivity [118]) and fabrication methods (e.g. electrophoretic deposition [119], radio-frequency sputtering [120]) have been experimented to produce well-adherent and durable coatings on a variety of materials and implants, including scaffolds, suture wires, surgical screws and ocular implants. Composite coatings were also produced where the polymeric phase, acting as a glue, ensures a good adhesion of the coating to substrates of complex geometries [121], [122]; in this case, thermal post-processing must be avoided to preserve the organic phase. A comprehensive overview of BG coatings has been provided by Baino and Verné in 2017 [123]; in this regard, a special update of that work deserves to be reported here about antiviral coatings, the potential of which became so apparent from winter 2019 in the frame of the global battle against Coronavirus SARS-CoV-2.

During the pandemic of COVID-19 caused by the new Coronavirus SARS-CoV-2, the confinement measures slowed down the contagion but did not completely avoid the disease diffusion. The individual protection equipment (e.g. facial masks) as well as the filters for air conditioning systems and medical respiratory devices do not possess an intrinsic antimicrobial/antiviral action and, thus, are susceptible to microbial/viral colonization. An efficient antimicrobial/antiviral technology on air filtering media is crucial for maintaining a safe air environment and protecting people, in particular when lockdown is eased. In this regard, a silver nanocluster/silica composite coating deposited with a patented co-sputtering process [124]–[126] demonstrated its antibacterial, antifungal and antiviral behavior in different applications, such as biomedical implants [127], natural and technical textiles [128], [129], mobile phones [130], air filter [131] and aerospace structures [132]. Recently, this coating has proved to elicit an antiviral effect towards Coronavirus SARS-CoV-2 [133], [134]. In principle, this coating can be deposited on every kind of substrates (i.e. metallic, ceramic, polymeric and glass surfaces), including filtering devices and textiles. It can hence provide an effective contribution to safety of crowded areas like supermarkets, production sites, schools, hospitals etc., where surfaces are exposed to many contacts with body parts every day. This coating can also increase the working life of filtering masks and filtering media, thereby reducing the waste production related to their disposal. This thin antimicrobial/antiviral silver nanocluster/silica composite coating (less than 200 nm) deposited on a disposable facial FFP3 mask in non-woven fabric is shown in Fig. 10. The coating, made of silver nanoclusters well embedded in a silica glass matrix, exhibits the typical morphology displayed in Fig. 11, as already observed in several previous works [127], [131].

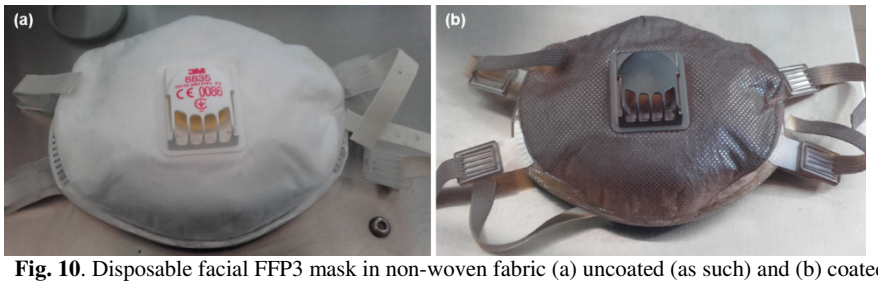


Fig. 10. Disposable facial FFP3 mask in non-woven fabric (a) uncoated (as such) and (b) coated by a co-sputtered antimicrobial/antiviral silver nanocluster/silica composite layer (original photos, courtesy of Monica Ferraris).

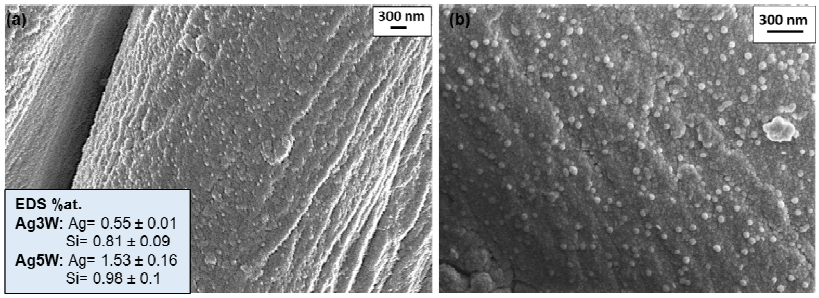


Fig. 11. Typical morphology (FESEM images) of a coated textile at lower (a) and higher (b) magnification: bright spots are silver nanoclusters embedded in the silica matrix (original SEM micrographs, courtesy of Monica Ferraris).

While most studies on coatings underline the need for obtaining pore-free layers, Verné et al. [135] innovatively applied the concept of "trabecular metal", which is already used in clinics for improving fixation of orthopaedic and dental devices, to the field of BG surface coatings. Specifically, they claimed the concept that a single-piece ceramic acetabular cup can be fixed to the patient's bone by means of a porous BG coating with trabecular structure. Fabrication of early prototypes of such an implant was a highly challenging task: specifically, dipping procedures combined with air-brush spraying of BG slurries were used to manufacture the non-porous interlayer on the curved surface of the cup [136], while the outer trabecular coating was produced by properly adapting the sponge replica method to the 3D radial geometry of the ceramic prosthesis [137], [138]. A second-generation prototype was produced by laser cladding of the BG particles directly on the outer surface of the cup [139].

9. Bioactive glasses as platforms for controlled drug release

Drugs and growth factors, being organic by nature, cannot be incorporated in the glass during the manufacturing process if the material is produced by melting due to thermal degradation of biomolecules. On the contrary, drugs can be mixed into the starting sol if the glass is synthesized by a low-temperature sol-gel process [140]; however, this approach suffers from the obvious impossibility of performing calcination, which would be required for the glass stabilization and the removal of organic by-products. Another approach involves the introduction of therapeutic molecules

into the organic phase of polymer/BG composites [141]; however, this approach may require complex procedures for drug incorporation.

Therefore, post-synthesis incorporation of biomolecules in the BG, once the material has been produced and no additional thermal treatment is required, seems to be the most feasible strategy. Silicate mesoporous materials, having an ordered arrangement of nanopores matching the size of many therapeutic molecules, have attracted great attention in the biomedical community due to their capacity of acting as efficient platforms for uptake and controlled release of drugs [142]. Mesoporous BGs (MBGs), which were first synthesized in 2004 [143]. are typically obtained by a modified sol-gel process relying on cooperative self-assembly of micelles (forming the mesopororores) and oligomeric silica species (forming the glass network). The surfactant and other by-products are removed by calcination, leaving behind an ordered arrangement of mesopores with channel diameter from 5 to 20 nm. The critical aspects of MBG synthesis have been recently discussed elsewhere in detail [144].

MBGs have faster HA-forming kinetics than conventional sol-gel BGs due to the high pore volume and surface area, which also allow achieving high loading efficiency of biomolecules into the mesopores as well as slow and controllable drug release kinetics [145]. The formation of a HA layer on the walls of mesopores implies a partial occlusion of the channels, which decreases the burst release effect and the overall release rate, thereby allowing a prolonged therapeutic effect to be obtained [146].

The uptake ability (and subsequent release) of biomolecules is affected by the composition, specific synthesis method and final form (e.g. spheres, fibres, coating…) of MBGs. It was observed that the increase of CaO content in the MBG formulation led to the enhancement of loading efficiency and decrease of drug release rate and burst effect [147]. The explanation was that the drug molecule (tetracycline in their study) was chelated with calcium on the pore wall, which made it difficult to be released. Xia and Chang [148] observed a similar trend after comparing the gentamicin loading/release kinetics of different MBG compositions.

Mesopore size and volume are strongly dependent on the type of surfactant used during the MBG synthesis. It was observed that Pluronic P123-templated MBG had higher pore volume and specific surface area compared to Pluronic F127-derived MBG, hence the former material exhibited a significantly higher drug (metoclopramide)-loading efficiency (47.3%) compared to the latter (16.6%) [149]. A similar trend was observed by Arcos et al. [150] in the case of triclosan-loaded P123- or F127-templated MBGs (loading efficiency: 9.7 vs. 9.1%); drug uptake could be further improved to 10.7% by using CTA-Br as a structure directing agent, leading to smaller pores that fit better with the size of the drug molecule.

The form in which the material is produced is a third factor influencing the drug release kinetics of MBG-based systems. In general, a sufficient drug uptake/release ability may always be obtained as well as an adequate therapeutic action, provided that the biomolecules may have access to the mesopores during the loading phase [151].

MBGs have been traditionally used as bifunctional biomaterials, combining bioactivity and drug release function; recently, they have also been proposed as trifunctional platforms for the additional controlled release of therapeutic ions able to promote, for example, pro-angiogenic or antibacterial effects [60], [152].

10. Antibacterial bioactive glasses

Even if the introduction of meticulous hygienic protocols and the systemic administration of antibiotics have remarkably reduced the risk of infection development, the bacterial contamination of implants still remains a serious complication in surgery, causing often re-operation, damage to patients and prolonged recovery. Synthetic materials possessing antibacterial properties have been intensively investigated over the last decades; among them, bioactive glasses have become increasingly attractive due to their specific properties, such as their compositional versatility, surface reactivity and tailorable degradability.

Bioactive glasses with different composition (silicate-, borate- or phosphate-based systems) and different architectures (e.g. macro- or mesoporous glasses) have been proposed and investigated for their antimicrobial properties for both hard and soft tissue applications, following different strategies schematized in Fig. 12.

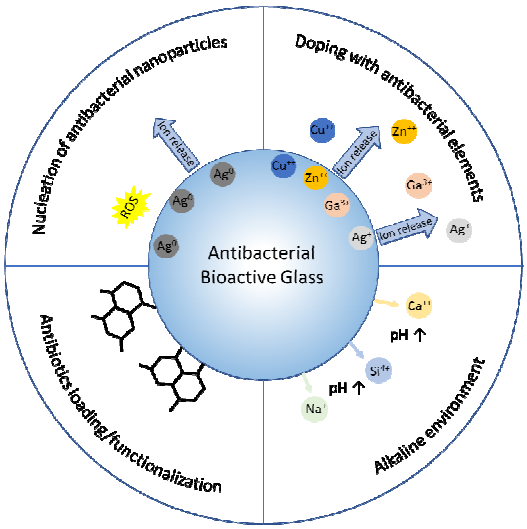


Fig. 12. Different strategies adopted to develop antibacterial bioactive glasses.

The most investigated approach to impart antimicrobial properties to a bioactive glass is the introduction in its composition of elements with antimicrobial properties, such as Ag, Cu, Zn or Ga. Doping elements can be introduced as reactants during the glass synthesis by melt-quenching process or via sol-gel technique [153]–[156]; otherwise, they can be incorporated [157]–[159] .

The most commonly-explored antibacterial elements are silver, copper and zinc [160]–[163]; however, other elements, such as Ga, F, Sr, Ce, Bi and recently Te have been investigated [164]–[167]. The extensive use of elements with antibacterial effect is due to their broad range of activity toward Gram-positive and Gram-negative strains and their poor aptitude to induce bacterial resistance. In particular, silver-doped glasses have been synthesized both by melt-quenching method and sol-gel technique, as well as by ion-exchange process. Several efforts have been focused on careful tailoring of the silver amount in order to avoid toxic effects while maintaining

unaltered the main properties of glass, especially the bioactivity[59], [168]. Due to the difficult control of the silver content and release, which were sometimes observed using the melt-quenching and sol-gel processes, the ion exchange technique looks very promising. This method allows preserving the structure of the pristine material (glass or glass-ceramic), maintaining the glass bioactivity and reaching a gradual and controlled release of silver ions [157], [159], [169], [170]. In general, the studies dealing with Ag-doped glasses revealed a good bacteriostatic or bactericidal behavior of the Ag-doped material towards both Gram-positive and Gram-negative bacteria (also biofilm producing) depending on the introduced silver amount, thus suggesting their potential application as base materials for a variety of bone substitution devices (e.g. bulk, coatings, macroporous scaffolds) [171], [172]. The high versatility of bioactive glasses doped with Ag ions allowed their investigation also as dispersed phase into polymeric bone cements [173]–[176].

However, the widespread use of silver-containing devices and the recent discovery of bacterial resistance to silver [177] is pushing researchers to investigate the antibacterial properties of other glass compositions. Therefore, copper or zinc-containing bioactive glasses have also been deeply investigated. In this case, the introduced amount of Cu or Zn must be carefully tailored in order to not compromise the glass bioactivity [59], [178]. Cu-containing bioactive glasses have been mainly obtained by sol-gel process (silica-based glasses) by introducing up to 10 mol% of copper [179], [180]. The traditional melt-quenching process was also adopted for silica-based, phosphate and borate bioactive glasses [156], [162], [181] evidencing that the release of copper ions significantly reduced the bacterial adhesion and proliferation. Recently, the ion-exchange process in aqueous solution has also been proposed to introduce copper in the surface of bioactive glass powders [158], demonstrating the ability of Cu-doped bioactive glasses to limit the *S. aureus* adhesion and proliferation, without affecting the bioactive properties. Furthermore, as for Ag-doped ones, Cu-doped bioactive glasses have been successfully investigated as dispersed phase in composite bone cements [182].

Zn-doped bioactive glasses with antibacterial properties have been investigated [163], [183] showing also in this case a dose-dependent antimicrobial effect. However, the performed studies evidenced an important influence of the ZnO amount in the leaching properties and reactivity of the glasses [184]. Finally, a comparison between the antimicrobial performances of Ag, Cu or Zn-doped glasses demonstrated that silver-containing bioactive glasses have better antibacterial effect than Cu- or Zn-doped glasses [156], [185].

Aiming to better understand the “killing” mechanism of antibacterial elements and to assess the differences among ion release and “contact-killing” mechanism, bioactive glasses containing nanoparticles with antibacterial properties have been recently developed. The formation of antimicrobial nanoparticles can be obtained during the glass synthesis [186][187] or their nucleation can be promoted directly on glasses surfaces after the material synthesis [188], [189]. Even if the antibacterial action of nanoparticles is not yet fully understood and the efficacy of nanoparticles versus ions is still debated [190], the performed studies revealed a significant *in vitro* antibacterial activity against the most common bacterial strains.

Another approach to confer antibacterial properties to bioactive glasses is to functionalize or load them with antibiotics, as reported also in Section 11. The glass sur-

face can be activated to exhibit many hydroxyl groups useful for the grafting of several drugs; moreover, the reactivity of the glass in aqueous solution, as well as in SBF, can be exploited to incorporate antibiotics. For example, Miola et al. explored the possibility to graft an antibiotic (carbenicillin) on a bioactive glass surface by taking advantages of the bioactivity process, which occurs by dipping the glass in SBF [191]. The authors confirmed that carbenicillin can be easily incorporated and released with different kinetics on a self-formed silanols/silica gel layer by overworking the bioactivity process.

Mesoporous bioactive glasses, as reported in Section 9, have also been explored as smart drug delivery systems. They are characterized by highly ordered mesoporous channels useful to confine antibiotics and release them in a controlled manner. Different antibiotics, such as gentamicin, tetracycline hydrochloride, vancomycin, ceftriaxone and sulbactam sodium have been incorporated into mesoporous glasses. It has been demonstrated that the drug incorporation and release, and as a consequence the antimicrobial activity, are influenced by the use of different surfactants, which in turn impact on the pore dimension and the surface area [192]–[196]. Although the effectiveness of antibiotic-loaded bioactive glasses has been demonstrated both *in vitro* and *in vivo,* the prevalence of antibiotic-resistant bacterial strains still remains a major problem.

The last strategy exploited to limit bacterial contamination relies on the release of ionic compounds once bioactive glasses are immersed in aqueous-based solutions. It has been shown that bioactive glasses are able to increase the local pH due to the ion-exchange mechanism that occurs with protons in simulated (*in vitro*) or body fluids (*in vivo*). Specifically, it was proved that the alkaline microenvironment caused by the ion leaching limits the bacteria growth by altering their morphology and changing the expression pattern of numerous genes and proteins. Moreover, the release of ions that characterize a bioactive glass, such as silicon, sodium, calcium and phosphate ions, increases the salt concentration and enhances osmotic pressure, thus affecting bacterial proliferation [197], [198] section. The antimicrobial effect of bioactive glasses due to the release of ionic compounds has been reported by several authors *in vitro* [199], [200], also towards multi-drug resistant bacterial strains able to form biofilm [201]. However, the *in vivo* efficacy of the proposed mechanisms still has to be confirmed, since different works demonstrated that some bioactive glass compositions did not show antimicrobial efficacy *in vivo* due to the buffering of the biological environment [202], [203].

In conclusion, the results obtained by the different strategies highlight the promising features of bioactive glasses in reducing bacterial contamination. However, further investigations are needed to deepen the knowledge of the mechanisms involved in the different approaches, enhancing the efficacy of bioactive glasses in eradicating the biofilm and limit the infection development.

11. Functionalization of bioactive glasses

Bioactive glasses easily expose hydroxyl (-OH) groups upon contact with water-based media [14], [204], [205]. This is the first step of their bioactivity mechanism, but it can be also exploited for the effective grafting of specific moieties to their sur-

face [204], [206]. Surface functionalization of bioactive glasses, which at the beginning was less explored than the one of metals and polymers, is gaining increasing interest in the scientific community, as demonstrated by some recent reviews [207], [208]. Surface functionalization represents an interesting and versatile strategy to combine well known properties of bioactive glasses (e.g., bioactivity as the ability to induce apatite precipitation in contact with physiological fluids and bone-bonding ability, as well as specific ion release) with specific properties of the grafted moieties designed for selected applications. In fact, it has been widely reported that surface grafting of active molecules does not inhibit the glass bioactivity [209]–[211].

Functionalization can be achieved through addition of surface functional reactive groups with a specific biological response or acting as linkers for a further step of grafting. Active biomolecules can be grafted directly to the glass surface or by means of proper spacers, as schematized in Fig. 13.

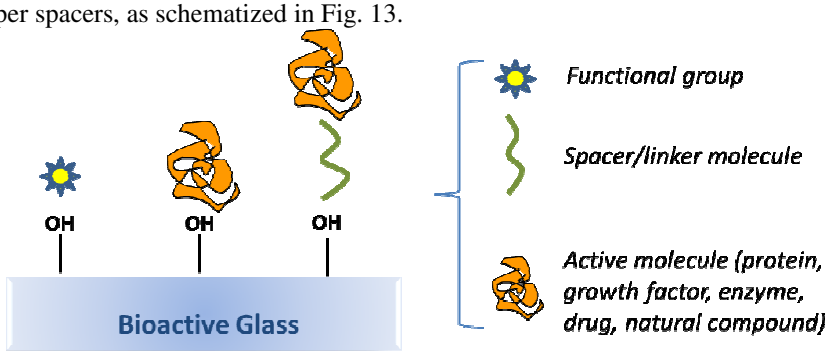


Fig. 13. Scheme of the surface functionalization strategies on bioactive glasses.

As far as reactive groups are concerned, the most widely explored ones are amino groups (-NH_2) introduced on the glass surface by means of silanization, mainly with 3-aminopropyltriethoxysilane (APTES) [204], [212].

Silanization can be performed to exploit the peculiar properties of the amino group itself, such as regulation of bioactivity [209], [213], enhanced protein absorption [214], [215], and cytocompatibility [216], or for covalent grafting of active molecules [206], [210], [211], [217]. Most of the literature is focused on the silanization of silica-based bioactive glasses; however, APTES grafting on borate and phosphate glasses has also been reported [218], [219]. It was found that, even upon optimization of surface modification, the level of APTES grafting in the last case was lower than in typical silica-based glasses, most likely due to the lower content of –OH group on the surface and congruent dissolution of phosphate glasses.

Silanization induces a switch of zeta potential toward positive values because of the presence of the amino group and a strong beneficial effect on the fibronectin adsorption capacity, which is the highest for the NH_2 groups than for all functional groups (such as CH_3, COOH, OH) [220]. The hydrophilic-hydrophobic balance of the silanized surface, with respect to a simple hydrophilic glass surface, can be beneficial for protein adsorption.

Concerning protein adsorption, it must be underlined that 45S5 Bioglass® and bioactive silicate glasses adsorb a larger amount of bovine serum albumin () than bioinert

glasses in a wide range of pH. The BSA adsorption on 45S5 Bioglass® is pH-dependent, with a larger amount of adsorbed BSA at lower pH such as in fractured or injured bone tissues (pH = 5). This could be beneficial to reduce the inflammatory response, but several attempts are reported to promote it further or to selectively enhance adsorption of adhesive proteins such as fibronectin. In contrast to bioinert glasses, the surface properties of BGs are time-dependent and change upon contact with the biological fluids due to ion exchange and bioactivity mechanism. After preconditioning in SBF, BSA adsorption is significantly enhanced. However, the trend of pH-dependent adsorption is attenuated without a smart effect in an inflammatory chemical environment [221]. It has been found that increasing the negative zeta potential of 45S5 Bioglass® could cause a significant decrease in the amount of adsorbed serum proteins while surface crystallization of 45S5 Bioglass® could inhibit protein adsorption.

Peptides can be grafted to bioactive glasses using dopamine as a coupling agent, to get antifouling surfaces [222]. On stable glasses, this strategy is often coupled to an antifouling micro- and/or nano-topography (through lithography or laser surface structuring), but in the case of bioactive glasses this is usually ineffective because of the fast growth of a hydroxyapatite layer on the surface. The use of single-molecule force spectroscopy (SMFS) based on atomic force microscopy can be of great interest to directly measure the adhesion force between a silica-binding peptide and glass surface at single molecule level [223]. The peptide-surface interactions can be due to Van der Waals force, hydrogen bond, electrostatic attraction, hydrophobic effect, etc. The measurement of the adhesion force can be of interest to discriminate among these different types of bonding.

Considering that blood compatibility of glasses should usually be further improved, silanization and grafting with zwitterionic polymers can be useful to significantly inhibit platelet adhesion and whole blood cell attachment, when it is required [224] this is not usually the case of bioactive glasses, but it could be further explored.

Plasma modification can be applied to produce polar functional groups (amine, carbonyl or carboxylate) changing surface free energy, with elimination of organic impurities and formation of cross-linking. Plasma modification generally induces an increment of wettability, but hydrophobic glass surfaces can be achieved by using helium [225].

The first attempts of surface functionalization of bioactive glasses were focused on the grafting of proteins, enzymes, and growth factors, such as Bovine Serum Albumin [226], [227], Bone Morphogenetic Proteins [206], [217], collagen[228] or alkaline phosphatase [210], [211] to cite some examples. These compounds are mainly intended for the achievement of a fast bone integration and regeneration.

More recently, the interest moved through natural compounds of vegetal origin [208], such as simple model polyphenols (gallic acid) [229]–[231], polyphenols from grapes and tea [232]–[234], sage [235], algae [236], bud extracts [237] or curcumin [238] to cite some examples. Since this kind of molecules show a variety of additional properties, such as antioxidant, antibacterial, anti-inflammatory, anticancer and even osteo-stimulatory properties, great effort has been done to optimize the grafting conditions in order to assure their effective immobilization while preserving their therapeutic activity. Compared to the above-described strategies based on proteins and growth factors, the use of natural compounds is more focused on the modulation of

the biological response (considering also inflammation control) rather than to the achievement of fast bone growth. For example, it was assessed that grafting of gallic acid on the surface of an iron oxide-containing bioactive glass-ceramic may influence the bioactivity of the pristine material, while an evident effect was observed on the redox activity, as the ability of the glass-ceramic to catalyze HO• radical release in the presence of H_2O_2 was significantly increased by gallic acid grafting. Moreover, grafting gallic acid acts as a pro-oxidant, probably reducing Fe^{3+} to Fe^{2+}. Furthermore, it has been reported that green tea extracts grafted on the surface of a bioactive glass show a selective cytotoxic action against bone cancer cells and that this action can be related to the production of reactive species in the cancerous cells causing selective DNA damage, while evidencing an anti-inflammatory action on healthy osteoblast cells.

In addition to their peculiar features, these molecules, due to their chemical reactivity as reducing agents, can be effectively used to obtain an in situ green formation of antibacterial metal nanoparticles (e.g. Ag nanoparticles) directly on the glass surfaces [188], [189], [236]. This step can be considered to increase the antibacterial activity of the surface and to combine multifunctional actions on the surface.

Finally, surface functionalization with drugs can be mentioned. As far as mesoporous bioactive glasses are concerned, their use as substrates for drug release has already been discussed in Section 9 of the present chapter. In addition, the direct grafting of antibiotics [191] (Section 10) and chemotherapeutics [239]–[241] to the surface of non-porous bioactive glasses should be cited, as well as the glass covalent functionalization with model molecules (cysteamine and 5-aminofluorescein) by means of a covalent reaction with pH-sensitive organic molecules, in order to induce a triggered stimuli-responsive drug release [242]. The rationale and the experimental strategies are analogous to the grafting of the previously discussed active molecules, with the final aim to obtain localized antibacterial or anticancer properties, and - generally speaking – the specific delivery of drugs for treating bone diseases. Compared to a systemic administration of the same active principles, the local delivery through the implant surface can reduce the dose necessary to reach a therapeutic effect and, consequently, the potential toxicity.

Surface functionalization of bioactive glasses, as well as of other biomaterials, has to face the regulatory procedures (e.g. certification and sterilization) in order to be suitable to be applied onto real biomedical implants. As far as certification is concerned, the presence of active principles, which can be released upon contact with physiological fluids, can change the device class with a consequent increase in the certification times and costs. This point should be considered in the development of innovative surfaces and, in many cases, becomes a barrier for the lab to market transfer. Moreover, the presence of organic molecules, which are often sensitive to heat, radiation and chemicals, can make difficult the sterilization of functionalized surfaces by using conventional techniques. The possibility to sterilize the functionalized materials by a standard procedure is actually poorly explored, but it should be evaluated for the development of biomaterials intended for implantation. Despite some uncertainness, early evidence of the possibility to apply the conventional sterilization techniques to functionalized bioactive glasses has been reported [243].

12. Clinical applications of bioactive glasses

Recent estimates have shown that, since FDA approval in 1985, Hench's 45S5 Bioglass® was implanted in more than 1.5 million patients worldwide to mainly repair bone and dental defects [244]

The first 45S5 Bioglass® implant approved for clinical use in the USA had the purpose of substituting the small bones of the middle ear in order to treat conductive hearing losses [245]. This glass, being able to bond both to bone and to the collagen fibres of tympanic membrane, allowed sound conduction from the eardrum to the internal structures of the ear. After FDA approval in 1985, this device was marketed under the name of "Bioglass® Ossicular Reconstruction Prosthesis" or "Middle Ear Prosthesis" MEP®. Although exhibiting good performance in the short and mid-term, this 45S5 glass implant underwent dissolution and fragmentation in the long-term [246]. Therefore, this device was taken off the US market in 2000.

45S5 Bioglass® was also used to fix cochlear implants to the temporal bone of profoundly deaf patients suffering from irreversible damage to the cochlea. This device was commercialized as Bioglass®-EPI (Extracochlear Percutaneous Implant) in the late 1980s but was then taken off the market due to the same drawbacks already reported for MEP® prosthesis [247].

In 1988, 45S5-based Endosseous Ridge Maintenance Implant (ERMI®) was launched on the market and, still today, it is applied in periodontal surgery. This implant consists of a glass cone to be inserted into fresh tooth extraction area, thereby replacing the tooth root and giving an adequate support to dentures [248].

In 1993, 45S5 Bioglass® particulate (90-710 μm) was approved by the FDA for repairing jaw bone defects associated to periodontal diseases; this product is known under the tradename of PerioGlas® [249]. A similar type of 45S5 particulate, commercialized as NovaBone® (NovaBone Products LLC), is used to repair bone defects in maxillofacial or orthopaedic non-load-bearing sites [249]. Furthermore, 45S5 Bioglass® is also commercialized as porous glass-ceramic sintered blocks. In fact, the sinterability window of 45S5 Bioglass® is so narrow that it cannot be sintered without undergoing devitrification [250].

Recently, 45S5 Bioglass® has also been used to make oral hygiene products. In 2004 NovaMin®, a 45S5 Bioglass® fine particulate (average size 18 μm) was added to a toothpaste in order to treat dental hypersensitivity, which nowadays affects about one-third of world population [251]. The aim of NovaMin® is to occlude dentinal tubules and remineralize the tooth surface, thus eliminating the cause of the disease [252]. This device was also employed for tooth whitening treatments [253].

In addition to 45S5 Bioglass®, other FDA-approved or CE-marked BGs are available on the market, too. Most of commercial BGs are characterized by a SiO_2-based composition, containing some additional modifiers which increase the bioactivity or confer special characteristics/therapeutic effects to the BG. For example, 13-93 BG ($53SiO_2$–$6Na_2O$–$12K_2O$–$5MgO$–$20CaO$–$4P_2O_5$ wt.%) has a larger sinterability window than 45S5 composition, which allows obtaining fully amorphous products from it (e.g. porous scaffolds) with excellent bioactivity and mechanical properties even comparable to cortical bone [53].

A wide range of commercial glass-ceramics are in current use in dentistry for both dental root/alveolar bone surgery (if bioactive) and restorative/aesthetic applications (if inert) [57] .

Interest in BGs further increased over the last 15 years since it was found that ionic dissolution products released from glasses can stimulate angiogenesis, which plays a pivotal role in major healing processes in the body [254]. Currently, there are only two BG-based commercial products with a specific pro-angiogenic function. One is addressed to skin regeneration and is trade-named as DermaFuse™/Mirragen™. It consists of borate BG nanofibers (13-93B3 glass, $53B_2O_3$–$6Na_2O$–$12K_2O$–5MgO–$20CaO$–$4P_2O_5$ wt%) that aim at accelerating wound healing by imitating the microstructure of a fibrin clot [255]. This product is also used under the tradename of "RediHeal" in veterinarian medicine. Interestingly, this BG is effective also in the treatment of choric diabetic ulcers on the skin which are irresponsive to pharmacological therapy. The second device is a composite orbital implant that was approved by FDA in 2002: it comprises a porous polyethylene sphere coated with NovaBone® particles having a stimulatory effect on fibrovascularization (Medpor®-Plus™) [256].

In addition to DermaFuse™/Mirragen™, other BG-based commercial products for wound healing applications include resorbable Ag-doped phosphate glasses combined with a polymeric adhesive for wound care film dressing (Antimicrobial Arglaes®) or with alginate for topical powders (Arglaes® powder). In both cases, they control infection by constantly releasing silver, which has a potent antibacterial effect.

Bioactive and magnetic glass-ceramics have been emerging in the research scenario since several years, and are gaining increasing interest for the treatment of bone cancer by magnetic induction of hyperthermia [257]–[259]. Specifically, magnetite-containing bioactive glass-ceramics have been developed both as bulk materials and as dispersed phase into acrylic bone cements, revealing bioactive properties, negligible iron release, cytocompatibility and pro-osteogenic activity, with a synergistic effect between the bioactivity of the materials and cell mineralization in the formation of apatite crystals on their surface. Furthermore, these glass-ceramics revealed the capacity of generating heat under exposure to alternating magnetic fields and, in turn, of inducing *in vitro* cellular heating, thus causing tumour cell death by apoptosis while preserving the viability of normal cells [260]–[268].

Although not being "bioactive" according to the Hench's definition, radioactive glasses for cancer treatment deserve to be mentioned as well [269]. Insoluble Y_2O_3–Al_2O_3–SiO_2, glass microspheres (diameter around 25 μm, trade-named as TheraSphere® or TheraGlass®) were approved by the FDA in 1999 for radioembolization of hepatocellular carcinoma and metastatic liver cancer. Before arterial infusion, the glass beads are exposed to neutrons to create ^{90}Y, a radioisotope that has a short half-life (64 h) and decays to stable ^{90}Zr through emitting β-rays. As a result, a localized dosage of up to 15,000 rad can be locally delivered to kill cancer cells, with high benefits to the patient (3,000 rad is the maximum dosage allowed under external radiotherapy).

Besides the uses described above, there is a number of emerging applications in contact with non-calcified tissues and soft organs which have not reached yet clearance for clinical use, including cardiac tissue regeneration, artificial lungs, epithelial restitution in gastric mucosa and intestine, peripheral nerve regeneration and corneal repair [270]–[272]; the overall timeline of BG applications is reported in Table 5. These novel experimental studies are contributing to further expand the use of BGs in medicine and stimulate unconventional research, which could have a great impact on human life and health in the near future.

Table 5. Chronological overview of the key commercial/clinically-approved applications of BGs in medicine.

Year	Achievement/Application
1969	Invention of the 45S5 glass composition (45S5 Bioglass®)
1977	Replacing of middle ear small bones using Ceravital® glass-ceramics
1978	Ocular implant (biocompatibility with corneal tissue)
1985	Approval by FDA of the first 45S5 Bioglass® implant
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 PerioGlas (45S5 Bioglass® particulate used for bone and 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™ (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
2012	Embolization of uterine fibroids
2012	Spinal cord repair
2018	Use of radioactive glasses (TeraSphere®) in patients with metastatic colorectal carcinoma of the liver

13. A forecast for the future

The medical industry is constantly searching for new, better, and more cost-effective solutions; thus, advancements in the medical industry are progressing faster than just a few years ago due to the introduction of advanced materials.

In this scenario, BGs integrate with the human body in diverse ways to support human health. As aging populations and evolving healthcare approaches shift the medical landscape, increasing opportunities for both established and innovative technologies about biomedical glasses can be forecast. According to a report published by the American Ceramic Society in December 2020 [273], the global market for implantable biomaterials was estimated to be around $110 billion in 2019. In terms of the future of healthcare, regenerative medicine is a big business. The global market for tissue engineering and regeneration was valued at $25 billion in 2018 and is forecast to reach $109.9 billion by 2023 – very close to the global estimate for the whole biomaterials market in 2019! -, representing an impressive growth rate. While bone is indeed a significant focus of the BG and bioceramic market, the attention is moving to soft tissues as well, including strategies to repair injured cardiac, muscle, neural, and

skin tissues. There is potential for many different types of materials in this broad field which can be combined with BGs. In fact, in the field of regenerative medicine and tissue engineering, there is no one material that is going to tackle all the challenges. Many of the glass-based strategies to heal tissues actually combine BGs with organic materials, for example in polymer-matrix composites or hydrogels.

An increasing collaboration between materials scientists, biologists and clinicians is key to allow bioactive glass research to really progress. In this regard, understanding the genetic mechanisms and pathways activated by ionic stimuli released from BGs offers the possibility of developing patient-specific therapies, which is a huge challenge for the aging population. Furthermore, therapeutic ions released from BGs open new horizons in the field of implantable or non-implantable antibacterial and antiviral surfaces.

Given the complexity of biological systems, the future of regenerative medicine seems to be addressed to develop biomaterials and technologies able to treat multiple different tissues simultaneously. Although an isolated tissue-specific approach often guides biomaterials developments, components of the human body are known to operate together on several different scales. Therefore, in the attempt to somehow replicate Nature, researchers from academia and industry should focus on manufacturing different material types together to match the really different material types in the body. In this regard, additive manufacturing technologies combined with biofabrication, involving manipulation and printing of BGs along with other biomaterials, biomolecules and even cells, will be an exceptional resource.

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