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Review Article

Bio-active glass coatings manufactured by thermal spray: a status report

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ABSTRACT

Superficial modification of implants *via* the incorporation of biocompatible coatings is an attractive option in biomedicine because of the positive attributes associated with bioactive materials. Bioactive glasses are an important subset of biomaterials that are known to stimulate bone regeneration; they are interesting materials that can be employed as bioactive coatings due to their unique response in physiological environments. Numerous clinical case histories and scientific studies have focused on successful examples of bioactive glasses being used *in-vitro* and *in-vivo*. However, unlike other biomaterials such as hydroxyapatite, bioactive glasses have not yet reached full potential as thermally sprayed coatings. The lack of fundamental research focused on establishing correlations between the available bioactive glass chemical compositions, the processing parameters selected for specific thermal spray processes, and the obtained coating performance has limited the use of bioactive glass compositions as reliable coatings. This paper reviews the current state of the art of thermally sprayed bioactive glass coatings; it looks at different studies dealing with thermally sprayed bioactive glass coatings in order to identify their strengths and weaknesses and provides key scientific points that could be explored in future investigations. This manuscript includes a brief introduction to bioactive glasses, an overview of thermal spraying techniques and current products, and a discussion of recent developments in this field.

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1. Introduction

In recent decades, the development of biomaterials and medical devices has grown substantially due to the large population of patients needing surgical interventions and government incentives in the healthcare sector [1,2]. The development of medical implants according to basic clinical guidelines aimed at favoring a good osseointegration and a short healing time is often a multidisciplinary task that requires materials capable of repairing bone tissues and/or substituting bones without any biological rejection [3,4].

Biomedical materials are employed for manufacturing medical devices in the healthcare sector. Biomaterials are classified according to their origin as synthetic (*e.g.*, ceramics, polymers, metals, and composites) and biological (*e.g.*, organic and non-organic compounds derived from human, animal or vegetable sources) (Fig. 1) [5]. Biomaterials that are available in the biomedical market include polymers such as polyurethanes, silicone hydrogels, ultra-high-molecular-weight polyethylene fibers, ceramics such as alumina (Al_2O_3), zirconia (3Y-TZP), hydroxyapatite, glass ceramic cements, and metals such as titanium alloys, cobalt–chrome alloys, and stainless steels.

Metallic materials are widely used in biomedical devices because of their mechanical and chemical properties. In particular, the capacity of metals for supporting tensile and shear stresses and fracture toughness is one of the primary reasons explaining their popularity in orthopedics. From the chemical point of view, biomedical alloys are considered to be bio-tolerant (*i.e.* they interact with the host environment releasing ions in non-toxic concentrations) and bio-inert (*i.e.* they exhibit minimal chemical interactions with the adjacent tissue, although a fibrous capsule may form around them, Fig. 2a). These alloys are conventionally used as bone fixators, in knee and hip prostheses, as orthodontic wires, as dental implants, and as external fixators [6,7]. Similarly, ceramic materials such as Al_2O_3 and zirconia (ZrO_2) are also bio-inert in biological environments. Some examples of the usage of bio-inert ceramics in the healthcare sector are femoral heads, dental implants, ventilation tubes, and drug-delivery devices [8,9].

In recent years, considerable efforts have been directed to develop bioactive materials that induce fixation with bone. According to Hench et al. [10,11], "bioactive" materials may present two types of response when they are implanted in the body. Type A bioactive materials, such as non-dense hydroxyapatite and bioglasses, may produce surface mineralization and the growth of tissue along the interface; they also promote the differentiation of osteoprogenitor cells into osteoblasts. These materials allow bone remodeling induced by osteoblasts cells (*i.e.* osteoinduction) and bone growth on its surface or down into pores or channels (*i.e.* osteoconduction), as a result of the chemical interaction between the implant and host tissue (Fig. 2b) [10,12]. The overall response of Type A bioactive materials is called surface mineralization with osteoconduction and osteoinduction. On the other hand, Type B bioactive materials, such as dense hydroxyapatite, titanium dioxide, and various bioactive polymers, only produce surface mineralization with osteoconduction along the implant/bone interface (*i.e.* they do not promote the differentiation of osteoprogenitor cells into osteoblasts).

Type A bioactive materials are very interesting for implant applications since they may favor interfacial bonding of an implant to tissue by the formation of a biologically active apatite layer early in the implantation period, which, thereafter, integrates with the bone matrix [13,14]. Bioactive fixation promoted by bioactive materials is regarded as an important phenomenon within the medical field since a bioactive bond forms at the implant/bone interface, leading to increase the bonding strength and to improve the early biological integration of the implant [14].

The application of bioactive coatings on metallic implants is an alternative proposed in the biomedical sector to achieve early biological fixation and to compensate for minor errors in placement of metallic prosthesis during surgical intervention [15,16]. A poor primary stability, which is defined as the biometric stability achieved immediately after implant insertion, is one of the major causes of metallic implant failure [17]. Clinical studies have shown that dental and hip implants coated with bioactive ceramics (hydroxyapatite and bioglass) results in enhanced primary stability and good interfacial bone-to-implant contact [18–20]. *In-vivo* studies in animals and humans have also shown that bioactive coatings present direct contact of bone to implant without a fibrous tissue interface in patients after successful total hip arthroplasties [21–23]. However, there are significant concerns when using pure bioceramic coatings on metallic implants due to their low durability, which has so far limited their use. For instance, fracture and interfacial adhesion (*i.e.* bonding at the coating/metallic implant interface) of hydroxyapatite coatings are questionable since *in-vivo* evidence has often shown the occurrence of this type of failures after several months or years of implantation [23–25]. The occurrence of dissolution and releasing of molecules containing calcium and phosphate to stimulate osteoblasts may lead to a decrease in the coating/implant bond strength, resulting in coating delamination and fracture. Although the main function of a bioactive coating is the promotion of early biological fixation of an implant in the first days after implantation, in recent times, several efforts have been focused to improve the quality of bioactive coatings to achieve a compromise between long durability and bioactivity. These efforts have been mainly focused on studying different deposition methods and proposing new coating compositions and architectures (composites, bilayers, graded)

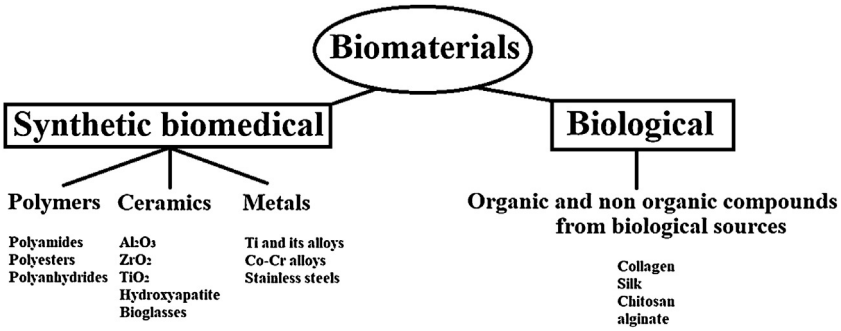

Fig. 1 – Classification of biomaterials.

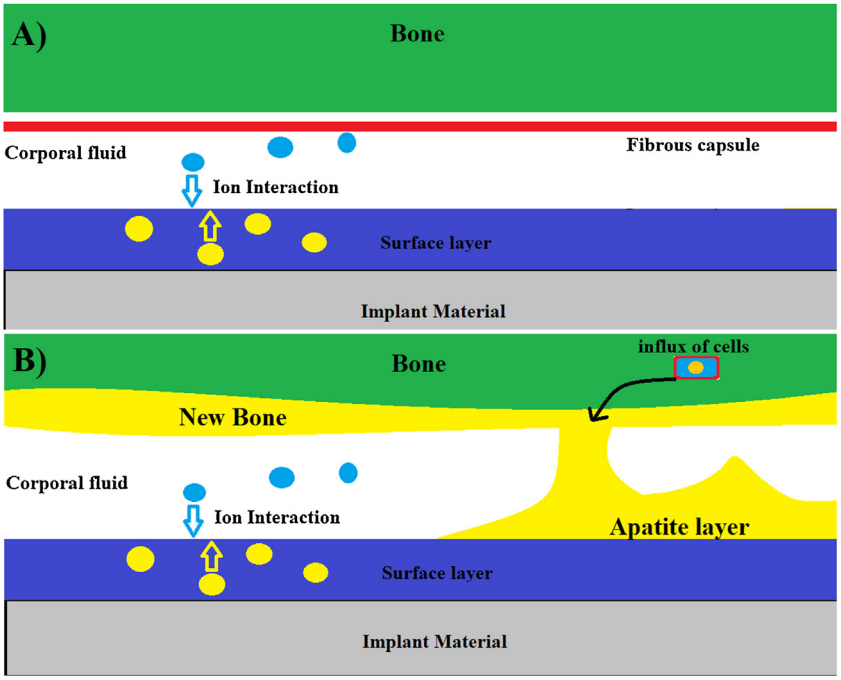

Fig. 2 – Schematic representation of the interaction of a bioactive material (a) and a bio-inert material (b) with corporal fluid and human bone.

that can provide good mechanical stability without compromising the biological activity [26–29].

Bioactive glasses are included among those inorganic non-metallic compounds that are interesting for practical medical applications; they have drawn a lot of attention as coating materials because they can be produced in varied chemical compositions, by adding secondary elements, in order to improve their chemical response in physiological environments [30]. Numerous investigations have been carried out to produce reliable bioactive glass coatings using different techniques including enameling, magnetron sputtering, laser cladding, and thermal spray processes [30,31]. Among various coating techniques, thermal spray processes represent a good option for the fabrication of bioactive glass coatings since the coatings obtained can be mechanically strong and can preserve the chemical properties of the feedstock material. Nevertheless, thermally sprayed bioactive glasses are not clinically used yet as there are still further research activities to be performed for improving their mechanical, chemical, and physical properties. This paper presents an overview of the current state of the art of bioactive glass coatings prepared by thermal spraying and discusses key research points that should be exploited in the future to produce reliable and functional bioactive glass coatings.

2. Bioactive glasses

Bioactive glasses are formed by a mixture of various oxides and, unlike conventional bioceramics, are characterized by a lack of a long-range crystalline structure. Bioactive glasses contain a glassy network promoted by the presence of elements called “formers” and other called “modifiers” which are responsible for creating or disrupting the atomic connectivity [32,33]. This glassy network can be partially dissolved by the physiological fluids, thus releasing calcium/phosphorus ions and silicon hydroxide groups, which are subsequently deposited at the surface of the glass. As a result, a thin hydroxyl-carbonyl-apatite film nucleates and grows, promot-

ing the adhesion of stem cells and development of new bone tissue attached to the bioactive glass surface [34]. An interesting property of most bioactive glasses is that they are osteoinductive and osteoconductive; that is, they stimulate osteogenic stem cells to colonize the implanted surface and provide a bioactive surface along bone can migrate [10].

The good biological response of bioactive glasses results from their atomic structure and composition. According to the main constituent, bioactive glasses can be classified as silicate-based, phosphate-based, and borate-based [35]. Silicate-based bioactive glasses are involved in many clinical studies and represent the main family of glasses presenting bioactive behavior. Both phosphate and borate-based glasses are known for their extremely high solubility rather than for their bioactivity; thus, they are interesting for healing applications [36].

Silicate-based glasses consist of a group of silica tetrahedra connected by oxygen–silicon bonds (–O–Si–O–), where silicon is the glass network forming atom, Fig. 3a. The main components in most silicate-based glasses are SiO_2, Na_2O, CaO and P_2O_5. In this manner, calcium and sodium oxides play the role of network modifiers having the task of disrupting the network by forming non-bridging oxygen bonds, Fig. 3b [32,33]. Bioactivity of silicate-based glasses is associated with the content of network modifiers and network formers. In fact, a simple way to predict bioactivity (osteoconduction) of a glass can be performed by calculating the average number of bridging oxygen bonds per silicon atoms, which is directly related to the amount of network modifiers and network formers [37,38].

$$N_c = 2 + \frac{Nbo - Nnbo}{Npb} \quad (1)$$

Eq. (1) estimates the network connectivity of glasses (N_c), where N_{bo} is the total number of bridging oxygen atoms, N_{nbo} is the number of non-bridging oxygen atoms, and N_{pb} is the total number of possible bridges. $N_{bo.}$ N_{nbo} and N_{pb} are molar percentage values. Structural units in silicate glasses with a low network connectivity are most likely of showing low molecular mass and are able to pass into solution. Therefore, as a rule, glass solubility increases when the network connectivity decreases. In this way, glass systems with low network connectivity are potentially bioactive. Overall, glasses that have N_c values greater than 2.6 are considered non-bioactive since they have high resistance to dissolution [37]. The *Nc* model considers that the bridging oxygen atoms are randomly distributed in the glass and the probability of one atomic unit bonding covalently *via* a bridging oxygen with another relies on their respective concentrations [37,39,40]. The distribution of bridging and non-bridging species directly influences glass properties, such as hydrolytic stability, bioactivity, and mechanical properties (fracture toughness, hardness) [40–42].

Fig. 4 shows a Na_2O–CaO–SiO_2 ternary phase diagram for a 6% wt. P_2O_5 addition, which has been a base for the development of a large series of bioactive glasses in recent decades. The research activities on this ternary diagram have allowed achieving a better understanding of the compositional dependence and effects of doping on the biological performance of bioactive glasses. For instance, silicate-based bioactive glasses prepared at the middle of the diagram (region A) form a bond with bone. However, silica glasses within region B are nearly inert materials and elicit a fibrous capsule at the implant-tissue interface. Alternatively, glasses designed within region C are resorbable in physiological fluid and dissolve completely within 10–30 days of implantation, while glasses within region D have low bioactivity because of its low glass forming ability [10,33]. One can observe that bioactivity of bioglasses is limited to a small range of compositions. Bioactivity of the Na_2O–CaO–SiO_2 glass system can be improved by the addition of P_2O_5 which allows to control the Ca/P ratio. Overall, glasses with Ca/P ratio lower than 5/1 do not show bone bonding [49]. Some authors have proposed the incorporation of oxides such as Al_2O_3, Ta_2O_5, TiO_2, and SrO as network modifiers, which have resulted in the improvement of mechanical properties at expenses of bioactivity (known as Ceravital glasses) [10,43–45]. Table 1 summarizes the main bioactive glass compositions developed so far.

The 45S5 bioglass® is the most known silicate-based bioactive glass system, which was first discovered by Hench et al. in 1969 [33,35]. Surprisingly, many bioactive glasses developed at present are based on this original bioglass composition. The 45S5 bioglass® composition is very close to a ternary eutectic, facilitating its melting and production [33,46]. The 45S5 bioglass® is currently commercially available in powder form and as void filler for bone regeneration [33]. Sintered bulk bioglasses (fully dense and porous) are often difficult to find in the market because some issues in their production are found such as crystallization of the glassy phase prior to significant densification, loss of bioactivity promoted by precipitation of crystalline phases during sintering, and intrinsic brittleness, all of them limiting their mechanical strength [47]. These facts have restricted their use only to small clinical applications where mechanical strength is not a crucial property [48,49].

The 45S5 bioglass® ceramic is a Type A bioactive material compositionally located at the middle of region A in the ternary diagram presented in Fig. 4. This bioglass composition is approved by the FDA for different tissue engineering applications. As a Type A bioactive glass, the 45S5 bioglass® is osteoconductive and osteoinductive and exhibits the highest *in-vitro* and *in-vivo* bone-like apatite formation rate. Also, is one of the main compositions currently investigated for the next generation of biomaterials designed to prevent tissue loss [50,51]. The overall mechanical properties of 45S5 bioglass® limit its use as a load-bearing material, in particular its low fracture toughness [52]. However, the mechanical properties of this material can be significantly improved by the formation of crystalline phases with higher mechanical strength such as the silica-rich combeite [53,54]. Although is well-known that the bioactivity level of bioactive glasses is diminished drastically upon crystallization, it has been demonstrated that the 45S5 bioglass® can keep its bioactivity when it contains combeite crystals ($Na_2Ca_2Si_3O_9$), with high levels of crystallinity (even up to 100%) [55]. Such high bioactivity is attributed to the large amount of specific glass modifiers (sodium and calcium) in its structure, making it easier to dissolve *in-vitro* and *in-vivo*. Karimi et al. [56] developed different heat treatment routes for producing various levels of combeite contents in a 45S5 bioglass®, from 5 to 95%. The formation of combeite happens by the occurrence of a spinodal transformation of the glassy phase in the 45S5 bioglass®

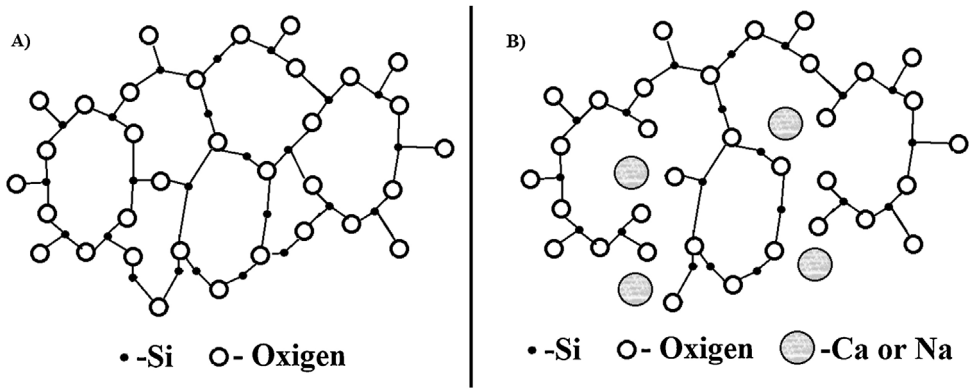

Fig. 3 – Schematic representation of a Si-based glass (a) and a bioglass (b).

Table 1 – Summary of most relevant bioglass systems [10].

Bioglass	Composition (wt.%)											
	SiO_2	P_2O_5	CaO	Na_2O	MgO	K_2O	$Ca(PO_3)_2$	Al_2O_3	Ta_2O_5	TiO_2	F	Cl
45S5®	45	6	24.5	24.5	–	–	–	–	–	–	–	–
Ceravital KG Cera®	46.2	–	20.0	4.8	2.9	0.4	25.5	–	–	–	–	–
Ceravital M8/1®	38	–	–	4	31	–	13.5	7	5.5	1	–	–
55S4.3®	55	6	19.5	19.5	–	–	–	–	–	–	–	–
52S4.6®	52	6	21	21	–	–	–	–	–	–	–	–
Biovert I®	29.5–50	8–18	13–28	–	6–28	5.5–9.5		0–19.5		Additions	2.5–7	0.01–0.6

material at 580 °C leading to the formation of two immiscible phases [57]. This glass-in-glass phase separation happens due to the coexistence of P^{5+} and Si^{4+} in the glass structure, as these ions prefer to concentrate separately because both have high valence numbers. As a result, the formation of two phases occurs, one rich in phosphorous and other in silicon; the latter forms a crystalline phase known as combeite. Many studies have reported the dominant formation of this phase when the 45S5 bioglass® is heat treated above 600 °C [50,55,58]. Depending on the amount of combeite formed, the bioactivity and stiffness of 45S5 bioglass® can be tailored to suitable levels for different applications such as bone scaffolds and glass ionomer cements [59,60]. However, fine-tuning of mechanical properties due to the formation of combeite in this kind of glasses is difficult as other secondary crystalline phases can be formed during heat treatments.

In the case of borate and phosphate-based glasses, the largest glass formers are boron and phosphorous, respectively, while their composition may contain a range of alkaline metals (Li, Na, K, *etc.*), alkaline earths (Mg, Ca, Sr, Ba), and transition metals (Fe, Cu, Zn, Ag, Au). Overall, bioactive glasses often form a calcium phosphate layer when they are immersed in a solution containing phosphates such as simulated biological fluid (SBF). Overtime, the calcium phosphate layer crystallizes into apatite. Some scientists have assumed that the soluble silica layer plays an important role in tissue repair and osteogenesis [61,62].

Borate-based glasses, unlike silicate glasses, form a bone-like apatite layer directly on the surface of the underlying unreacted glass rather than forming a boron-rich layer. This situation persists because boron, like phosphate glasses, is soluble in SBF. The glass degradation products can pass naturally through the body, predominantly through urine. The lack of a dissolution layer allows the borate glasses to react completely without a significant reduction in dissolution kinetics. The borate glass is totally converted into apatite by the dissolution of the glass (B_2O_3 and Na_2O are dissolved into the solution and the CaO reacts with the PO_4^{-3} present in the phosphate solution) and the silicate glasses are partially converted into apatite, leaving a depleted sodium core surrounded by a rich silica layer [61,63,64]. In addition, the presence of Na_2O and CaO in a system composed of borate-based bioactive glass remarkably reduces the effect of immediate dissolution caused by water because the triangular boron structures are

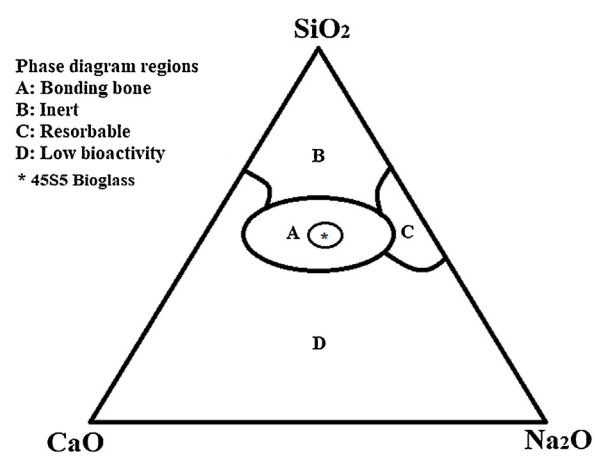

Fig. 4 – Schematic representation of a CaO-Na_2O-P_2O_3 ternary phase diagram.

lost and are transformed into tetrahedral structures. These structures are more compact because they are interconnected in four directions to adjacent oxygen atoms, thereby yielding greater chemical stability [62].

Borate-based glasses are a good option for achieving the degradation and bioactivity characteristics required for tissue engineering applications. Compared with silica-based glasses, borate glasses exhibit better degradation behavior and produce a faster bone-like apatite conversion rate in SBF. The degradation rate can be controlled by adjusting the boron content in the glass or by incorporating strontium (Sr), which also induces the adhesion of osteoblasts as sarcoma osteogenic cells (SaOS-2 cells), *i.e.* SaOS-2 cells are used as a permanent line of human osteoblasts-like cells and as a source of bone related molecules [62,65].

For borate-based glasses, the network connectivity calculation and the prediction of bioactivity by means of the N_c model (Eq. (1)) can be more complicated than for silicate-based glasses due to the formation of BO_3 or BO_4 units and linkages such as Si–O–B and P–O–B, which make more difficult the application of equation 1 for the prediction of properties. However, some studies have suggested that even in this type of glasses the formation of bridging and non-bridging oxygen atoms is a key factor influencing the bioactive properties of the glass (*i.e.* increased disruption of the glassy network improves bioactivity) [66–68]. It is also important to remark that the N_C model associates bioactivity with the ability to form apatite in bioactive glasses (*i.e.* only considers the osteoconduction ability of the glass). Osteoconduction is then correlated with the ability of the glass for rapid dissolution in a physiological environment. However, this fact can be considered as a limitation of this model. Although dissolution is established as a previous step for apatite formation, it is not always associated with bioactivity because the ions released may not contribute to super-saturation and apatite formation [33,37]. In addition, another limitation of this model for bioactivity prediction is the fact that bioactivity is associated with dissolution and apatite formation (*i.e.* osteoconduction only). Nevertheless, the osteoinductive part of bioactivity is even more complicated to predict with a simple model since it involves the ability of the material for promoting both intracellular and extracellular response at its surface. Despite these limitations, the N_C model has been widely applicable for free-boron compositions where *in-vivo* studies have shown that osseointegration and new bone formation around the implant improves as the network connectivity decreases [69,70]. In some borate glass systems, the N_C model has also been successfully applied as a method for predicting their bioactive response in physiological fluid [66].

3. Thermal spraying and its application in the biomedical industry

As noted previously, orthopedic prostheses and dental implants are often manufactured using metallic alloys. Orthopedic and dental implants are often designed to guide, support, and distribute stresses. The implant yield strength must be enough to support natural loads and possible distortion stresses that may cause failure. In particular, titanium alloys are the primary choice for the production of implants in load-bearing applications over other metallic alloys because of their mechanical strength, low density, and good corrosion resistance. They also have exceptional fracture toughness and dynamic loading properties. The fact that titanium alloys remain stable under cyclic loading is a deciding factor for their choice over other metallic systems [59,60,71]. However, the limited bioactivity of these alloys has led researchers to investigate other options to obtain materials with both high mechanical resistance and good bioactive properties. Three ways to obtain those properties are *via* the production of bulk composite materials, the application of pure bioactive coatings on metallic alloys, and the deposition of composite coating systems on metallic implants.

In particular, the fabrication of bioactive coatings is regarded as a good option for providing bioactivity to metals and alloys. Bioactive coatings are normally applied prior to implantation of the prosthesis in the body. So far, several methods have been employed for the fabrication of bioactive coatings including sol–gel, electrophoretic deposition, dip coating followed by sintering, sputtering, flame spraying (FS), cold gas spraying (CGS), plasma spraying (PS), and high velocity oxy-fuel spraying (HVOF) [72–78]. Some of these processes produce coatings showing disadvantages such as poor bonding strength between coating and implant, the induction of phase transformations, changes in the properties of both the metallic implant and/or the bioactive coating due to the involved processing temperatures, and presence of impurities.

Among the various coating techniques, thermal spraying has a great acceptance in the biomedical industry since the coatings obtained by this family of processes can be successfully controlled (structurally and chemically), and can be deposited on various implant shapes [79–82]. Thermal spraying processes have been used industrially for more than 50 years for surface modification of metals [83]. They were initially employed for coating medical devices in the 1980s, primarily focused on the application of hydroxyapatite coatings [84]. Overall, thermal spraying processes use a source of energy (chemical, kinetic, or electric) to provide acceleration and high temperature to the feedstock material, usually in powder shape, which is molten, partially molten, or softened and deposited onto the surface of a metallic substrate (prosthetic device). The final properties of thermal spray coatings depend on the thermal and kinetic energy involved during the spraying process; that is, on the energy available at impact to heat and to deform the particles. Particularly, thermal energy is employed to melt and/or partially melt in-flight particles, while kinetic energy is converted in visco-plastic work at impact. Therefore, a good control of the processing conditions is crucial for the fabrication of reliable and optimized coatings. Usually, thicknesses of thermally sprayed coatings range from 50 μm to 2 mm. Fig. 5 summarizes the various thermal spraying processes that are currently available in the market [83,85].

The atmospheric plasma spraying process (APS) is one of the most accepted methods for the preparation of bioactive coatings in the scientific community, which is supported by successful cases of clinical experiences that have demonstrated improvement in the osseointegration of implant devices [81,84]. The APS process consists of a gun that is

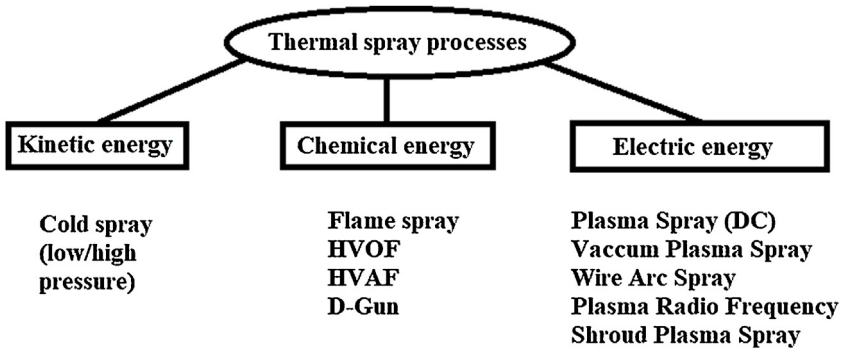

Fig. 5 – Summary of thermal spray processes.

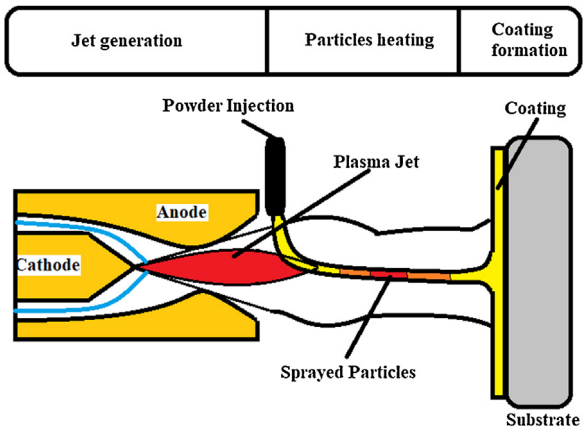

Fig. 6 – Schematic representation of the atmospheric plasma spray process (APS).

formed by a copper anode and a tungsten cathode. An electronically controlled power supply provides enough electrical energy to ionize a non-reactive gas (N_2, Ar, H_2, He) or a mixture of them as they pass through a high energy electrical arc formed inside the gun. Following gas ionization, energy is delivered when electrons drop to a lower energy state and ions recombine. Maximum plasma temperatures are between 10,000 °C and 25,000 °C depending on the gas mixture and electrical power, while particle velocities can range between 80 and 300 ms^{-1} [83]. Fig. 6 shows a schematic representation of the APS process. This process allows the preparation of large-scale coatings that exhibit good adhesion on substrates of complex shape. Currently, APS hydroxyapatite (HA) coatings are preferred over the use of poly-methyl-methacrylate (PMMA) based bone cements on implants, since the former can provide better long-term stability and do not cause adverse responses inside the body. APS-HA coatings have been used extensively as implant coating materials on bio-inert metals such as stainless steel (316L and 304L), Co–Cr alloy, and Ti–6Al–4V alloy [84].

Overall, plasma sprayed HA coatings have proven to be useful as bioactive coatings for improving fixation of implants in patients, especially during the first years after implantation. Medical studies have also demonstrated that the presence of multiple phases in plasma sprayed HA coatings is an issue that endangers long-term bone/implant bonding [84,86]. Currently, the stability of biomedical coatings is one of the most critical factors to ensure the success of this type of solution and involves numerous researches in this field.

4. Thermal sprayed bioactive glass coatings

Bioactive glasses are particularly interesting as biomedical coatings because they possess a high degree of bioactivity. The APS process has been widely used for producing bioactive glass coatings, which usually display good mechanical performance and bioactive behavior [87–89]. The APS process requires a large number of parameters to be optimized [83]. For instance, to maintain the typical amorphous phase of bioglasses, several spray parameters must be carefully adjusted to minimize the particle heat input. The primary APS operating parameters that have an effect on phase stability are the type and ratio of primary and secondary gases, the total plasma gas flow rate, and the plasma arc current. However, other parameters such as powder feed rate, spraying distance, raster speed, and substrate temperature can also play an important role in the formation of bioactive glass coatings. The amorphous nature of bioactive glasses is one of the main features that must be controlled while processing these materials by thermal spray. Total and partial crystallization of bioactive glasses could modify their mechanical and chemical behavior since new phases appear on the coatings [55,90,91]. Various studies have reported that substrate temperature and cooling are among the key parameters in the APS process that affect the stability of the amorphous phase in bioglass coatings [92–94]. For instance, Monsalve et al. [93] reported that fast cooling of bioglass coatings processed by APS can favor an increase in the amount of amorphous phase content in those systems. Similar results are also reported in the literature [94]. However, it is worth noting that partial crystallization of bioactive glasses processed by APS is also a function of the chemical composition of the bioactive glass system, as each single system has a specific glass forming ability (GFA). The GFA represents the capacity of a liquid material to form an amorphous phase upon cooling. In the APS process, the initial feedstock powder is totally or partially molten. Consequently, the degree of amorphous phases in the final coatings will depend on the GFA of bioactive glass particles. This phenomenon was observed by Monsalve et al. [93] using two different bioactive glass compositions.

The standoff distance and powder morphology are also two important parameters influencing the final properties of thermal spray coatings. In thermal spraying, the standoff distance is associated with the thermal and kinetic energy acquired by the particles before impact [83,85,95]. Helsen et al. [96] studied the effect of standoff distance on the formation of bioactive glass coatings; they reported that the standoff distance influences the degree of crystallinity of such coatings. The increase of crystallinity with the increase in the standoff distance was attributed to the excess of thermal energy in the particles due to the longer residence times in the plasma plume. In general, standoff distances reported in literature range from 60 to 140 mm for bioactive glass coatings prepared by APS [93,94,96,97].

On the other hand, powder morphology is a factor that influences the heat rate exchange, kinetic energy, and flowability of the raw materials employed in APS processing, and hence the final properties of coatings. For instance, Cañas et al. [89] studied the effect of powder morphology on the processing and microstructure of bioactive glass coatings prepared by APS. They employed powder fractions with different particle size and morphology. Interestingly, the particle size of the bioglass powder was directly related to the efficiency of the APS process. No coating formation was observed when the sprayed particles were either too big or too fine. Large bioglass particle fractions are not recommended for APS since they cannot be completely molten while they are traveling in the flame; this results in particle breaking and bounce-off when they reach the substrate due to the brittle nature of solid-state glasses. As commonly reported for many other thermally sprayed ceramics, bioactive glass particles with spherical morphology show better flowability than that observed in irregular counterparts. Irregular particle morphologies may result in better coating microstructures than spherical ones, mainly because the spherical particles are formed by agglomerates and have internal porosity. The spherical porous particles, consequently, may not be heated uniformly during the spraying process, resulting in porous coatings with low mechanical strength. However, if particle density and particle size distribution are properly designed, the APS process may lead to a uniform and dense bioactive glass coating. Hence, the particle size distribution and morphology of a bioactive glass powder are crucial factors influencing the quality of the coatings obtained. Extremely fine powders can show poor flowability since bioactive glasses have the tendency to absorb water and agglomerate, while coarse powders are heated at the surface and break at impact [97]. Ideally, the particle size distribution for a bioactive glass powder in the APS process should be in the range from 63 to 200 μm, while ideal morphology is often spherical, since flowability tends to improve with respect to that observed for irregular shape particles.

Bioactive glass coatings prepared by APS consist of molten and partially molten particles, pores, and both vertical and parallel cracks. Cracks are produced in the coating by residual stresses generated during spraying and cooling. Bonding strength of APS coatings arises from the combination of mixed adhesive and cohesive forces present at the coating/substrate and lamellae/lamellae interfaces. Various studies have reported that bioactive glass coatings prepared by APS present adhesion values in the range of 6– 41 MPa, according to the ASTM C-633 standard [88,94,96,98,99]. Goller et al. [88] proposed the application of a bond coat between a bioactive glass and a Ti substrate, the authors studied the effect of that layer on the bonding strength of bioactive glass coatings prepared by APS. Bioactive glass powders were plasma sprayed onto an Al_2O_3-TiO_2 (60/40) bond coat layer, previously sprayed on a Ti substrate. Interestingly, the results indicated that the bonding strength of bioactive glass coatings was remarkably improved using the bond coat. This fact was attributed to the improvement in the adhesive strength between the titanium substrate and the bond coat, favored by the reduction of the stress mismatch during cooling. Alternatively, other authors have proposed post-deposition heat treatments for the improvement of bonding strength in bioactive glass coatings. For instance, Canillo and Sola [92] carried out a post-deposition heat treatment on plasma sprayed bioactive glass coatings at 700 °C for 1 h. The results revealed that heat treatment is very helpful for coating consolidation; however, the post-deposition heat treatment can also induce precipitation of crystalline phases. The choice of a post-deposition heat treatment must be carefully taken, since the treatment temperature has to be properly selected bearing in mind the particular glass composition in order to induce sintering of the bioactive glass without damaging the substrate and/or modifying the phases present in the as-sprayed coating.

Alternatively, the Vacuum Plasma Spraying (VPS) process has been also employed to produce bioactive glass coatings. VPS has a similar operational principle than APS; however, the VPS process is conducted in a vacuum chamber. The vacuum chamber is evacuated by a pump system and then filled with an inert gas at a low pressure ($\tilde{1}$00 mbar) before the process starts. This ensures that residual oxygen and/or water vapor adhered to the chamber walls have no influence on the high-purity gas atmosphere. This results in the deposition of high-quality coatings with good adherence and with very little or even no oxidation, as the interaction of the row materials with oxygen is limited [83]. Bioactive glasses have been successfully deposited by VPS on Ti-6Al-4V substrates, presenting good adherence and homogeneity, without any modification of the initial bioactive glass composition. In terms of bioactivity, VPS-sprayed bioactive glasses have presented ionic interaction with corporal fluids preserving the bioactivity of the starting powder [100].

The suspension plasma spraying process (SPS) has been used as an alternative thermal spray method for the production of bioactive glass coatings. In SPS, an aqueous precursor containing the feedstock powder is injected into the plasma jet *via* an atomizer or by means of direct injection. The evaporation of the solvent occurs within the plasma jet allowing the particles to be heated and molten. The molten and partially molten particles reach the substrate and build up the coating as it happens in the conventional APS process. The advantage of the SPS process, over traditional options employing gas-driven feeders, is that flowability of fine powders is guaranteed, allowing the production of thinner coatings than those obtained by APS. Nanostructured, graded, and bilayer bioactive glass coatings have been prepared using the SPS process [99,101,102]. Usually, SPS coatings exhibit the co-existence of flattened lamellae together with regions composed of sintered and un-molten particles. Unlike APS coatings, SPS ones typi-

cally contain numerous, rounded, and sub-micrometric pores. In APS coatings, pores are large, elongated, and in the micrometric scale. Microstructural features in the SPS coatings are sensitive to the properties of the suspension, *i.e.* selection of the dispersant, particle size distribution, viscosity, and sedimentation rate [89]. In the case of bioactive glass coatings, the suspension plasma spray process results in highly porous coatings [102,103]. This fact makes bioactive glass coatings by SPS more reactive in SBF than their counterparts sprayed by APS.

Another suspension thermal spray technique, namely High Velocity Suspension Flame Spraying (HVSFS), has been proposed for the fabrication of bioglass coatings [104]. The HVSFS process is derived from the High Velocity Oxygen Fuel (HVOF) thermal spraying process. HVSFS involves a pre-ignited mixture of oxygen and fuel into a combustion chamber. The fuel gases can include propylene, propane, natural gas, hydrogen, acetylene, and kerosene. This process involves the free expansion of a compressed flame *via* a converging/diverging nozzle at the end of the gun, which generates a supersonic jet. Oxygen and the fuel gas create a high-pressure flame that is able to melt or partly melt the feedstock material. In HVSFS, a liquid suspension is axially injected into the flame. The advantage of HVSFS over SPS is the low flame temperature and high velocity of the particles obtained in the former, which ensure a good heat and momentum transfer to the particles [83,105] resulting in bioactive glass coatings with less porosity, and lower roughness, than those obtained by SPS [103,104,106].

A novel thermal spraying technique for producing bioactive glass coatings is known as solution precursor plasma spraying (SPPS). By employing this technique, nanostructured and thinner coatings with high density and homogeneous microstructures can be prepared [107]. The use of precursor solutions yields to high purity feedstocks avoiding traditional processing steps such as melting, quenching, grinding, sieving, *etc.*, which can introduce contaminants in the final feedstock. Successful bioactive glass compositions, such as 45S5 bioglass®, have been produced as coatings by employing SPPS. Cañas et al. [108] processed a fully amorphous 45S5 bioglass® by this technique employing different chemical precursors for obtaining a desired chemical composition (SiO_2 45%, Na_2O 24.5%, CaO 24.5%, P_2O_5 6% wt). The authors produced coatings with and without using nitric acid as catalyst; they found that HNO_3 additions to the solution feedstock resulted in dense coatings when compared to coatings produced without catalyst additions, which showed very poor adherence. This shows that without adding HNO_3 to the precursor solution, the sol–gel process and therefore the formation of a glass network does not occur in the plasma torch. The SPPS 45S5 coatings were also exposed to SBF by different soaking times resulting in the formation of hydroxycarbonate apatite (HCA), identified by EDX and XRD analyses. This study showed that the production of a sound 45S5 bioglass® coatings by SPPS is possible when employing a catalyst; it also shows the benefits of using SPPS *versus* conventional suspension plasma spraying (SPS), as the latter requires a large number of processing steps for producing a feedstock. Also, by employing the SPPS process for producing bioactive glasses the addition of different doping elements to the feedstock composition can be performed easily in order to obtain coatings with enhanced properties.

Bioglass coatings have also been prepared by Flame Spraying (FS), which is a simple and economic thermal spray process compared to APS and SPS. The FS process consists in the combustion of an oxygen fuel flame (oxy-acetylene, oxy-hydrogen or oxy-propane) to melt the feedstock powder. The maximum achievable combustion flame temperature depends on the selected fuel gas and oxygen/fuel ratios, while particle velocities are well below those reached in the HVOF/HVSFS processes [83,95]. The FS process cannot be only selected for economic reasons, but also because of its versatility that allows the preparation of porous coatings and composite coatings. A first attempt in the production of flame sprayed bioglass coatings resulted in poor bonding of the particles in the process [109], mainly due to the inefficient heating of them while flying in the flame, which is typical of this process. In order to solve this issue, the incorporation of a second ductile phase into the bioglass system was a proposed solution. As a result, Ti/bioactive glass composite coatings were successfully deposited using FS [109]. However, in recent years, Monsalve et al. [110] successfully prepared pure bioactive glass coatings using FS onto stainless steel (316L) and Ti64 titanium alloy.

Table 2 summarizes the results of relevant publications dealing with bioactive glass coatings deposited by thermal spraying. For each contribution, the composition of the coating and substrate, architecture, thickness, and bond strength are reported.

5. Biological activity of bioactive glasses and *in-vitro* studies on thermal sprayed bioactive glass coatings

Generally speaking, bioactive glasses are able to bond with bone, whereas some compositions of glasses bond with soft tissues. The activity of bioactive glasses results from the formation of a bone-like apatite layer that grows on their surface after they are immersed in a biological fluid [10,46]. A positive simulated body fluid test (forming a bone-like apatite layer) in a bioactive glass is a preliminary indicator that a bioglass composition can be *in-vivo* osteoconductive. Although the presence of a mineral layer in bioactive glasses does not guarantee *in-vivo* bioactivity [112], previous studies have shown that the formation of a bone-like apatite layer on the bioactive glass surface is a phenomenon preceding both *in-vitro* and *in-vivo* bioactivity [69,113–116]] In fact, Hench et al. [33] proposed various steps to describe the interfacial interaction between bioglasses and biological fluid. Such steps involve ionic reactions at the glass surface with a subsequent attachment and proliferation of cells. Glass dissolution is the first step in the active response of bioactive glasses in biological fluid. Both the chemical composition and the pH of the solution change due to the accumulation of dissolution products, yielding surface sites and a favorable pH for apatite nucleation. Bone-like apatite formation in either human body fluid (*in-vivo*) or simulated body fluid (*in-vitro*) is the result of the following stages: (i) creation of silanol bonds (Si–OH) on the glass surface, (ii) increase in the solution's pH promoting the formation of a silica-rich region close to the glass surface, (iii)

Table 2 – Summary of most relevant bioactive glass coatings obtained by means of thermal spray.

Coating composition	Substrate	Technique	Thickness (μm)	Architecture	Adhesion strenght (according to the ASTM C633 standard) (MPa)	Ref.
Glass (wt.%: $52SiO_2$–$30.5CaO$–$9.8Na_2O$–$6.2P_2O_5$–$1.5CaF_2$)	Pure Ti	APS	150	Monolayer	>35	[91]
Glass (wt.%: $44.3SiO_2$–$43CaO$–$4.6Na_2O$–$0.2K_2O$–$2.8MgO$–$5CaF_2$)	Ti-6Al-4V	VPS	150	Monolayer	21–22	[100]
Glass (wt.%: $50SiO_2$–$16CaO$–$20Na_2O$–$6P_2O_5$–$1MgO$– $2Al_2O_3$–$5K_2O$)	Ti-6Al-4V	APS	50–100	Monolayer	–	[111]
Glass (wt.%: $46.87SiO_2$–$32.30CaO$–$16.01Na_2O$–$5.50P_2O_5$–)	Pure Ti	APS	80	Bilayer:bond coat (alumina–titania)/top coat (bioglass)	27.18	[88]
Glass (wt.%: $46.87SiO_2$–$32.30CaO$–$16.01Na_2O$–$5.50P_2O_5$)	Pure Ti	APS	80	Monolayer	8.56	[88]
Glass 45s5 (wt.%: $46.1SiO_2$–$26.8CaO$–$24.4Na_2O$–$2.6P_2O_5$)	Pure Ti	APS	–	Monolayer	–	[92]
Glass (wt.%: $49.13SiO_2$–$43.19CaO$– $7.68MgO$)	Ti-6Al-4V	APS	100	Monolayer	35.43	[94]
Glass 45s5 (wt.%: $46.1SiO_2$–$26.8CaO$–$24.4Na_2O$–$2.6P_2O_5$)	Pure Ti	HVSFS	40–80	Monolayer	–	[106]
Glass (wt.%: $45SiO_2$–$24.5CaO$–$24.5Na_2O$–$6P_2O_5$)	Pure Ti	SPS	100	Monolayer	17.7	[101]
Glass (wt.%: $46.9SiO_2$–$42.3CaO$–$4.7Na_2O$–$6.1P_2O_5$)	SS316L	SPS	150	Monolayer	–	[97]
Glass (wt.%: $46.9SiO_2$–$42.3CaO$–$4.7Na_2O$–$6.1P_2O_5$)	SS316L	SPS	–	Bilayer:bond coat (HA)/top coat (bioglass)	–	[97]
Glass (wt.%: $31SiO_2$ $57CaO$– $11P_2O_5$–$1MgO$)	SS316L Ti-6Al-4V	FS	100–200	Monolayer	–	[110]
Glass (wt.%: $47SiO_2$ $42.3CaO$– $6P_2O_5$–$4.7Na_2O$)	SS316L	SPS	50–60	Graded	–	[112]
45S5 bioglass®	SS304	SPPS	35	Bilayer:bond coat TiO_2/top coat bioglass	–	[108]

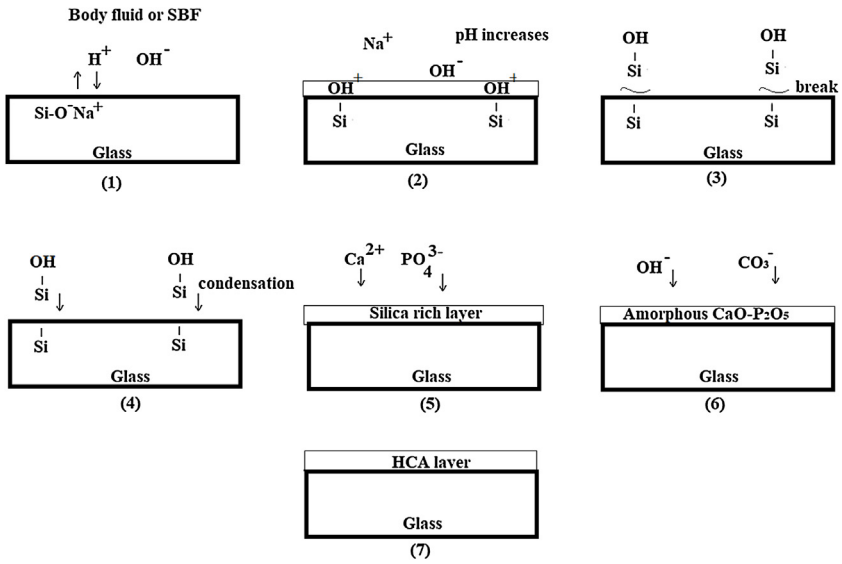

Fig. 7 – Schematic representation of the formation of hydroxycarbonate apatite (HCA) on the surface of bioactive glasses.

breaking down of silica bonds, (iv) further formation of silanol at the glass–solution interface, (v) precipitation of a silica-rich layer, (vi) formation of an amorphous CaO–P_2O_5 layer on the previously formed silica-rich layer, and vii) crystallization of the amorphous CaO–P_2O_5 layer to apatite [35,55], as shown in Fig. 7.

The formation of the apatite layer and bone growth around the implant are a function of the bioactive glass composition.

Overall, low silica content in the bioactive glass composition is related to a less connected network. This favors bioactive glass dissolution and at the same time increases the apatite formation rate. Bioactivity is often related to the activation energy of silica dissolution in the glass. However, the silica content is not the only factor influencing bioactivity of glasses. It depends also on the connectivity of the glassy-network. Herein, the presence of other cations to modify the glassy-network is important. The addition of multivalent ions such as Al^{3+} or Ti^{4+} reduces bioactivity since it reduces solubility [117]. Other cations such as sodium and calcium increases the dissolution rate and bioactivity [118]. In general, glasses with high silica contents result in a highly connected network containing a large proportion of bridging oxygen bonds, resulting in glasses with low dissolution rates and therefore low bioactivity. Consequently, network modifiers that can disrupt the glass network are important for dissolution and bioactivity.

Borate-based and phosphate-based bioactive glasses show the same mechanism of bone-like apatite layer formation as that described for silicate-based glasses except for the formation of a silica-rich layer. The fast deposition of the bone-like apatite layer in borate and phosphate-based bioactive glasses is attributed to their faster dissolution rate when compared to that showed by the silicate-based bioactive glasses [119,120]. The difference in apatite layer formation mechanisms between borate and phosphate-based bioactive glasses with respect to silicate-based glasses is illustrated in Fig. 8. When borate and/or phosphate-based bioactive glasses are immersed in SBF, dissolution of Na^+ and BO_3^{3-} or PO_4^{3-} ions from the glass structure occurs at a first stage. Subsequently, PO_4^{3-} ions from the solution react with Ca^{2+} ions favoring the nucleation and growth of the bone-like apatite layer [120]. Dissolution of the main constituents of the borate and phosphate-based bioactive glasses continues until the bioactive glass transforms completely into apatite. As for the silicate-based bioactive glasses, the solubility of phosphate and borate-based bioactive glasses can also be tailored. For instance, some previous reports have shown the possibility of changing the phosphate-based glasses dissolution rate by increasing the glass CaO content. The addition of CaO favors network connectivity and enhances the stability of phosphate based glasses [121–123].

Bioactive glass-ceramics have also been fabricated from natural sources such as natural bone and thermally sprayed by plasma, as described by Dobrow et al. [1]. The authors reported the fabrication of coatings produced by adding calcium phosphate to a $CaCO_3$–SiO_2–P_2O_5 ceramic, the former coming from protein-free and sintered protein-free bovine bone. The coatings were applied on different substrates namely stainless steel, alumina, and a titanium alloy showing excellent adherence in all cases. Immersion tests in SBF showed that coatings containing protein-free calcium phosphate additives had lower dissolution rates than bulk counterparts having the same chemical composition. The substrate-coating interfaces were also studied after immersion in SBF for 7 and 21 days. After immersion testing, the interfaces of all substrate-glass coatings (studied by X-ray tomography and SEM) were free of cracks or gaps, although little micro-cracking was observed at the grain boundaries of the coating, especially at zones close to the substrate-coating interface. The use of additives coming from natural sources to bioactive glass-ceramics is promising as such additions can help to control the dissolution/ossification of the latter when exposed to simulated body fluid [1].

The ability of bioactive glasses to interact with the physiological environment promotes the occurrence of *in-vivo* osteogenesis on the implant surface, making it suitable for cell attachment and proliferation [35]. New bone can grow along the implant surface from the bone-like apatite layer formed on the bone-implant interface as long as extracellular and intracellular interactions occur between the implant and the surrounding tissue. It is important to point out that extracellular interaction depends on the material's surface features such as submicrometric topography and the presence of negatively charged molecules (*i.e.* silanols). The negatively charged surfaces promote protein adsorption followed by coagulation and activation of the interactions between osteoblast receptors and the corresponding protein ligands on the surface, which contributes to cellular adhesion. Proliferation rate of these cells onto the bioglass surface is mostly a function of submicrometric topographic configurations (*i.e.* roughness and porosity) [124]. For instance, *in-vivo* studies revealed that a topographic feature such as precipitation of microscopic needle-shaped crystals on the glass surface allows greater protein adsorption (mainly fibrin); it was also found that platelets aggregate on this fibrin network and secrete cytokines that recruit osteogenic cells to the implant site [125,126]. This fact promotes cell differentiation and proliferation on the implant surface. On the other hand, intracellular interactions depend on the release of ions coming from glass dissolution and on the concentration of Si and Ca that are responsible of genes activation, which are in turn involved in the osteogenesis process. Silicon and calcium release encourages cell division, triggering, and mitosis (*i.e.* rising of genetically identical daughter cells) [127]. The osteoinductive and osteoconductive properties of bioactive glasses has been studied by De Aza et al. [128] by performing different *in-vivo* experiments. Fig. 8 shows the results of an *in-vivo* study after fixation of tibial bioglass-based implants in rats, which resulted in the formation of a new bone layer over the surface of the implant. This study demonstrated that bioglass composition allows the adsorption of proteins and secretion of cytokines, that recruit osteogenic cells, to the implant site. These cells differentiate in osteoblasts and produce a collagen-rich matrix, which is further calcified [128]. Recent *in-vivo* studies have also obtained similar results [34,125,129]. It is important to point out that vascularization observed in bioglasses after *in-vivo* implantation (Fig. 9) is required to bond the implant with the host tissue during the osseous healing process. Both vasculogenesis, the embryonic development of the circulatory system, as well as angiogenesis, the expansion of blood vessels from existing vasculature thorough the implant, are fundamental steps in endochondral ossification (*i.e.* primary ossification) that have been shown to promote bone healing [130].

Most of the studies concerning thermally sprayed bioactive glasses have been carried out under *in-vitro* conditions, and therefore mainly focusing on their osteoconductive behavior. For instance, Fig. 10 shows a bioglass coating prepared using APS. In this study, Monsalve et al. [93] studied the effect of adding a glassy-network modifier

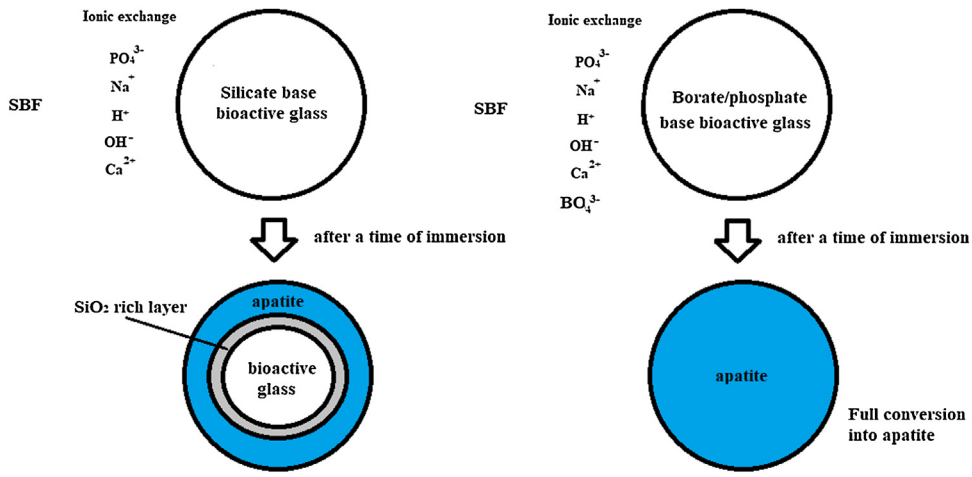

Fig. 8 – Schematic representation of the dissolution behavior of silicate, borate and phosphate bioactive glasses in simulated body fluid.

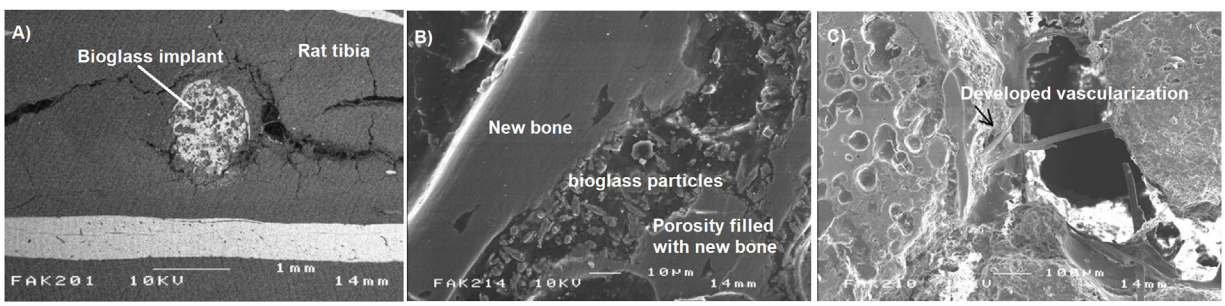

Fig. 9 – (A) Bioglass (wt.% 54.5 SiO_2-15 CaO-12 Na_2O-8.5 MgO-4 K_2O-6 P_2O_5) implant placed in the medullar canal of a rat tibia. (B) Bioglass implant after 12 weeks. (C) Developed vascularization between the bioglass implant and the surrounding tissue.
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on the bioactivity of a bioglass coating. In particular, the $31SiO_2$–$11P_2O_5$–(58–x)CaO–xMgO system was studied under *in-vitro* conditions using simulated body fluid to evaluate the effect of substituting calcium by magnesium in the glassy network. The authors obtained thick bioactive glass coatings with typical APS architectures, *i.e.* including molten particles, pores, and cracks. Interestingly, the bioactive glass coatings with and without magnesium additions exhibited signs of surface dissolution and bone-like apatite formation. Adding magnesium to the bioactive glass system resulted in thermal stabilization of the glassy network, as the Mg-doped coatings showed a higher crystallization temperature with respect to that observed in Mg-free counterparts. The crystallization of the bioglass powder during the spraying process promoted the formation of a bone-like apatite layer in the Mg-free coatings. The formation of a thick bone-like apatite layer was completed after performing an *in-vitro* test for 15 days, see Fig. 10.

The widely known concept of bond and top coats in thermal spray has also been employed to fabricate thermally sprayed bioactive glass coatings. Cattini et al. [97] prepared a coating by SPS consisting of a hydroxyapatite bond coat and a bioglass top coat. In that study, the authors tried to improve the bioactive behavior of hydroxyapatite coatings prepared by SPS. The $4.7Na_2O$-42.3CaO-6.1-P_2O_5-46.9SiO_2 CaO-rich bioactive glass system was employed as a top coat and it was evaluated on simulated body fluid. Remarkably, the bilayer bioglass/HA coatings showed higher dissolution rate and bioactivity than pure HA coatings. Although both the bilayer and pure HA coatings were covered by a calcium–phosphate layer after *in-vitro* tests, the bioactive glass topcoat was completely converted into hydroxy-carbonate apatite in less than one week. This type of coating architecture has great potential for biomedical applications when fast osseointegration is required. In fact, a previous study [102] has suggested that an ideal architecture for this type of coatings can be a "graded" one; that is, a coating having a through-thickness continuously variable composition from pure HA, at the substrate-coating interface, to pure bioglass at the top surface. Although the formation of an apatite layer occurs on both bilayer and graded coatings, the mechanical performance of a graded architecture is better than that of a bilayer coating since the level of residual stresses in the latter can be very high, promoting a decrease in its adhesion strength.

The outstanding bioactive behavior of bioactive glasses have also been reported by different authors using other thermal spray techniques such as SPS, HVSFS, and FS [98,99,101,103]. For instance, Altomare et al. [106] prepared bioglass coatings by employing the HVSFS process. They found

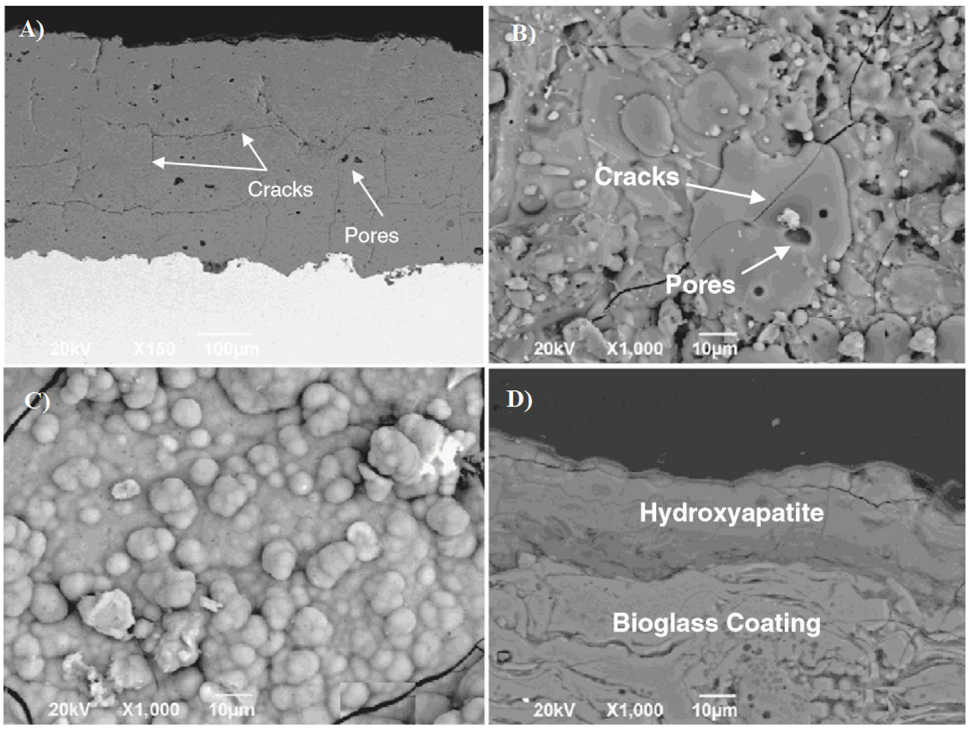

Fig. 10 – Atmospheric Plasma Spray Bioglass Coating ($31SiO_2$–$58CaO$–$11P_2O_5$ mol%); (a,b) as sprayed; (c,d) after 15 days in SBF.
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that the interaction mechanisms between a 45S5 bioglass® coating and simulated body fluid were similar to those of a bulk bioglass having the same chemical composition and involved the seven stages for HA formation already mentioned. The results also showed that the 45S5 bioglass® coating presented a particularly fast dissolution rate, as it developed a continuous bone-like apatite layer on its surface after only one day of immersion in SBF. Monsalve et al. [110] obtained similar results after studying the $31SiO_2$–$11P_2O_5$–(58–x)CaO–xMgO bioactive glass system deposited by flame spray.

Bioactive glass coatings can be obtained by different thermal spray techniques and can show bioactive behavior in simulated body fluid. Previous reports dealing with the bioactive behavior of these coatings suggest that they show a fast dissolution kinetics, which depends on their chemical composition [131,132]. There is little published evidence in the literature regarding *in-vitro* cell viability tests of bioglass coatings deposited by thermal spray. A study dealing with cell interaction of 45S5 bioglass® coatings, deposited by HVSFS, was carried out by Altomare et al. [106]. The coatings produced in that work experienced homogeneous cell spreading all over their surface, showed good characteristics as a substrate for human osteoblast-like cell adhesion and proliferation, and also maintained biocompatibility characteristics typical of bulk bioglasses during testing. Another interesting study was carried out by Jallot et al. [111] using APS coatings. In particular, they studied the $50SiO_2$–$20Na_2O$–$16CaO$–$6P_2O_5$–$5K_2O$–$2Al_2O_3$–1Mg bioactive glass system with small additions of alumina (2 wt.%) to produce bioactive glass coatings with controlled solubility during *in-vivo* tests. Alumina is well-known to remarkably reduce the reactivity of bioactive glasses. Interestingly, the obtained bioactive glass coatings showed an increased *in-vivo* stability and presented a reduced dissolution by the formation of a silica–alumina-rich layer during the first months after implantation. As previously mentioned, the architecture of the coatings also has an important role on their bioactive response. The bioactive response of bioactive glasses can be controlled not only by playing with a gradual coating composition (graded architectures) but also by tuning the porosity. For instance, Bolelli et al. [104] reported that highly porous SPS coatings were very reactive in simulated body fluid and behaved as a rapidly resorbable material. In that work, bioactive glass coatings obtained by HVSFS presented a denser microstructure and a slower dissolution kinetics than counterparts produced by SPS.

6. Latest developments and perspectives

In general, clinical and *in-vivo* studies on both homemade and commercially available bioactive glasses have shown that they can perform better than other bioceramic counterparts. After many years of research on bioactive glasses, the 45S5 bioglass® composition has shown better performance on biological environments over many other bioactive glass compositions. So far, the famous 45S5 bioglass® composition has been employed in tens of thousands of patients to repair bone defects since it has the ability to dissolve and stimulate bone regeneration [35]. However, this composition suffers

several drawbacks, which has hindered its use in many other biomedical applications. The main disadvantage of the 45S5 bioglass® is the difficulty for producing scaffolds, fibers, and coatings employing this material; in particular, this composition has the tendency to crystallize at temperatures easily attained when these materials are processed [133]. It has been reported that crystallization is very harmful for bioglasses since it reduces their biological activity [134]. Thermal spraying is a good alternative method for processing bioglasses; especially suspension and combustion flame processes can be an excellent choice since both can produce entirely glassy coatings [104].

Recent investigations have focused on the development of bioglasses with improved crystallization resistance with respect to 45S5 bioglass®. Novel bioactive glass systems have a limited tendency to crystallize and can be processed to preserve their amorphous nature. For instance, Bellucci and Canillo [135] developed a bioactive glass composition (in mol%: 2.3 Na_2O; 2.3 K_2O; 25.6 CaO; 10.0 MgO; 10.0 SrO; 2.6 P_2O_5; 47.2 SiO_2) with a higher crystallization temperature and a larger processing window than 45S5 bioglass®. The sintered samples obtained by the authors were fully amorphous and exhibited a pronounced bioactivity while tested in *in-vitro* tests. In this context, there is still a significant opportunity to explore these new bioglasses if they are produced by thermal spraying. In particular, bioglasses with a large processing window can be interesting for thermal spray processes, since entirely glassy coatings could be obtained with the correct selection and optimization of spraying parameters. Furthermore, this type of bioactive glasses opens up the possibility of spraying fully amorphous coatings with conventional thermal spraying techniques, thereby avoiding the use of suspension-based processes.

Another interesting research topic reported recently is the development of multifunctional bioactive glasses that simultaneously can promote bone formation (osteogenesis) and stimulate the production of new blood vessels (angiogenesis). Although bioactive glasses have demonstrated to stimulate angiogenesis during *in-vitro* and *in-vivo* tests, the bioactive glass response has not been as satisfactory as expected. Therefore, to improve and control osteogenic and angiogenic responses, ions such as Co, Ce, Cu, Sr, and Ag are often introduced into the bioactive glass composition [136]. The introduction of these elements in the bioactive glass composition must be performed carefully since any excess of these elements in humans can potentially result in cytotoxicity. Recent studies have shown that the *in-vitro* angiogenic cell response of $40SiO_2$–(54-x) CaO–x MeO–$6P_2O_5$ and $80SiO_2$–(16-x)CaO–x MeO–$4P_2O_5$ (where x = 0 or 1; Me = Cu or Co) bioactive glass, related to the presence of elements such as Cu and Co in glass structure, strongly depends on the CaO/SiO_2 molar ratio [137,138]. This finding is quite interesting as, for a therapeutic use, such ratio must be fine-tuned for having a controlled amount of Cu and Co in the glass structure in order to promote the expected angiogenic response and also to avoid the release of both ions in the human body. This topic requires additional studies in order to determine the composition-structure-properties correlations for optimizing the bioactive glass obtained.

Alternatively, other authors have investigated bioactive glass compositions that can attack chronic osteomyelitis, which is a bone infection caused by bacteria in post-surgical interventions. Osteomyelitis occurs in the form of inflammation around the bone/implant interface, resulting in bone damage. Osteomyelitis often requires extensive parenteral treatments such as the application of antibiotics and/or removal of the infected part. The S53P4 bioglass® (in mol%: 53.85 SiO_2; 22.65 Na_2O; 21.77 CaO; 1.72 P_2O_5) is one of the glass compositions designed to have antibacterial properties [139]. Based on this glass composition, various studies [140–143] have been focused on the effect of antibacterial ions, such as Ce, Ga, Cu and Bi, added to bioactive glass systems to avoid proliferation of different bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus sanguis*, and *Escherichia coli*.

In addition, a recent investigation has proposed the use of magnetic-bioglass powders for bone restauration in regions affected by malignant tumors [143]. This study has reported that the propagation of magnetic ions such as Fe^{3+} can improve mitochondrial activity, gene expression of cells for bone formation, and reconstruction of bone defects. Interestingly, the development of Fe-bioglass scaffolds creates a magnetic bioactivity structure that can be employed for bone tumor treatment.

In this context, many bioglass compositions are currently available to produce bioactive glass coatings *via* thermal spraying. Each composition has its own pros and cons and, according to specific clinical requirements, they can be used to develop multifunctional thermally sprayed coatings. One of the largest challenges that the thermal spray industry is facing involves a large available combination of specific compositions and spraying process for processing functional coatings with desired properties. In other words, the choice of the 'best' deposition method will strongly depend on the specific nature of the bioglass and the biomedical device to be coated. Some of the available compositions may produce multifunctional bioglass coatings that can be sprayed only by employing suspension-based techniques; others can be sprayed using conventional processes. Future contributions should be focused on the study of deposition techniques, spraying parameters, and bioglass compositions that can generate multifunctional coatings to stimulate certain genes, regulate bone growth, and ensure antibacterial properties of implants.

Moreover, by understanding the glass structure and the effects of doping elements on the bioglass processing window, a large research field able to explore different bioactive glass compositions and thermal spray techniques opens up. Such understanding can result in the development of fully amorphous glasses with different optimized microstructures for specific clinical uses. For example, one point to exploit is the development of bioglasses having a high crystallization temperature and a low glass transition temperature that can be produced by low thermal energy thermal spray processes such as cold gas spray (CGS). The CGS process is a thermal spray method that mainly employs the kinetic energy of particles to build-up coatings. In this process, high pressures and low temperatures (compared with those of combustion and plasma processes) yield supersonic gas velocities and

large particle accelerations. The particles are propelled toward the surface of the substrate, where they impact and deform plastically to form a strong bond with the substrate material [144]. The CGS technique can be useful for producing coatings from metastable and oxidation sensitive materials. Recent studies have demonstrated that is possible to spray metallic glass coatings using CGS [145–147]. Interestingly, the deposition of bioglasses by CGS might be carried out by following the same methodologies developed for processing metallic glass coatings, bearing in mind the amorphous nature of both materials. However, future studies must explore this field to reveal the feasibility of producing bioglasses by this method.

7. Concluding remarks

Bioactive glasses have demonstrated clinical success and have a great potential as coatings in biomedical applications thanks to their good *in-vitro* and *in-vivo* properties. Hence, several thermal spray techniques (combustion and plasma spray processes in particular) have been used to prepare bioactive glass coatings. The coatings obtained have demonstrated biocompatibility and bioactivity in simulated body fluid. However, there is still a long learning curve to follow concerning their optimization, functionality, and biomedical applications. For instance, there is a lack of studies concerning *in-vitro* cell viability tests and *in-vivo* studies on this type of coatings. Although systematic studies on bioactive glass coatings have revealed that graded coatings are the best choice from the perspective of mechanical and bioactive properties, studies concerning the production of different coating microstructures and architectures, their long term-stability, and their effect on bioactivity are still an open issue.

Our summary of previous research studies has revealed that suspension-based techniques such as SPS, SPPS, and HVSFS are appropriate for producing bioactive glasses, since these techniques either achieve lower processing temperatures than conventional thermal spray processes or can be employed for processing thinner coatings with controlled amounts of crystalline or amorphous phases. However, it is also possible to produce thermal spray coatings using conventional APS and FS processes. The trade-off occurs in some cases in the glassy phase content; the design of the glass composition plays an important role in selecting a specific thermal spraying technique and the corresponding spraying conditions. Modifying the bioactive glass composition to favor the deposition of bioactive glass coatings by thermal spraying may be a good option for continuing the development of these types of bioactive systems. However, this kind of research must constantly strive to optimize the mechanical and bioactive properties of bioglasses. Future studies could, for instance, investigate the effect of doping elements on the bonding aptitude and bioactivity of coatings. Feasibility and optimization of the microstructure of bioactive glass coatings is also a field to explore using various thermal spraying techniques, including CGS, VPS and HVOF.

Some key points about bioactive glass coatings are presented below:

1) Crystalline phases degrade the bioactivity of bioactive glasses. Therefore, fully glassy coatings should be obtained to maintain the performance of the coating as close as possible to that of a bulk bioglass having the same chemical composition. In this context, ideal spraying conditions are those that can avoid the crystallization temperature of the glassy phase.
2) The bioactive behavior of bioactive glasses also depends on the chemical composition of the glass. Doping a specific bioglass composition can either improve or hinder glass bioactivity. Bioactive glass coatings can then be fabricated with controlled bioactive behavior.
3) Depending on the thermal spraying technique, bioactive glass coatings can have both high density and good bond strength or, conversely, high porosity and low bond strength. It is difficult to evaluate one thermal spray technique as a general choice to produce bioactive glass coatings on implants since different characteristics are required for each application. For instance, some medical devices are required to be fixed as fast as possible; others need to last longer. Therefore, thermal spray processes can be complementary and can be helpful for specific clinical needs (*e.g.* reabsorbable coatings, support coatings, *etc.*).

Conflicts of interest

The authors declare no conflicts of interest.

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