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Review Open Access

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Glass-based coatings on biomedical implants: a state-of-the-art review

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Abstract: Bioactive glasses, invented by Prof. Larry L. Hench in the late 1960s, have revolutionized the field of biomaterials as they were shown to tightly bond to both hard and soft living tissues and to stimulate cells towards a path of regeneration and self-repair. However, due to their relatively poor mechanical properties (brittleness, low bending strength and fracture toughness), they are generally unsuitable for load-bearing applications. On the other hand, bioactive glasses have been successfully applied as coatings on the surface of stronger/tougher substrates to combine adequate mechanical properties with high bioactivity and, in some cases, additional extra-functionalities (*e.g.* antibacterial properties, drug release). After giving a short overview of the main issues concerning the fabrication of glass coatings, this review provides a state-of-the-art picture in the field and specifically discusses the development of bioactive and hierarchical coatings on 3D porous scaffolds, joint prostheses, metallic substrates (*e.g.* wires or nails) for orthopedic fixation, polymeric meshes and sutures for wound healing, ocular implants and percutaneous devices.

Keywords: Bioactive glass; Coating; Tissue engineering

1 Introduction and crucial aspects of bioactive glass coating fabrication

Bioactive glasses are a special subset of biocompatible ceramics which are able to strongly bond to living tissues (primarily bone) creating a stable interface [1] and to trigger a range of biological responses such as tissue regeneration and angiogenesis while degrading over time [2, 3]. These fascinating properties are related to a time-dependent modification of glass surface upon exposure to physiological environment. According to the classical mechanism of bioactivity proposed by Hench [4], the glass surface forms a biologically active layer of nano-crystalline hydroxyapatite (HA) that provides the bonding interface with host tissues while the dissolution products (*e.g.* Ca^{2+} and silicate ions) stimulate the cells to produce new tissue. The first bioactive glass was developed by Hench *et al.* in the late 1960s and belonged to the SiO_2-Na_2O-CaO-P_2O_5 quaternary system (45S5 Bioglass®) [5]; since then, many other silicate, borate and phosphate glass compositions have been proposed for a wide range of biomedical applications in contact to both hard and soft tissues, as recently reviewed elsewhere [6–8]. However, due to their poor mechanical properties (especially tensile strength and fracture toughness), bioactive glasses alone cannot be used for structural purposes where metallic alloys are still the materials of choice. Two valuable options to solve this problem involve either the combination of the glass with a fracture-tough phase, such as a metal or a polymer, to produce a composite [9], or the application of the glass as a coating on a mechanically stronger and tougher substrate [10].

In the biomedical field, coatings have been used in a variety of applications to modify the surface of implants and, in some cases, to create an entirely new surface that gives the implant additional properties which are quite different from those of the uncoated device [11]. Bioactive coatings are important for orthopaedic and dental implants: in fact, while the metals alone tend to be encapsulated with fibrous tissue after implantation, bioactive glasses have the potential to improve the stability of devices by bonding them to the host bone and, furthermore, can protect the substrate from corrosion, thereby avoiding the release of potentially toxic metal ions *in vivo* [12]. However, the nano-crystalline HA layer that forms on the surface of bioactive glasses is the result of a dissolution process. From a general viewpoint, bioactive glasses are by nature biodegradable according to various dissolution

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Table 1: Overview of the most common bioactive glass compositions used to manufacture coatings on biomedical implants (listed in order of apparition in the main text).

Glass name	Synthesis	Composition (mol.%)
45S5 Bioglass®	Melt-derived	$46.1SiO_2$-$26.9CaO$-$24.4Na_2O$-$2.6P_2O_5$
CEL2	Melt-derived	$45SiO_2$-$26CaO$-$15Na_2O$-$3P_2O_5$-$4K_2O$-$7MgO$
61S31C	Sol-gel	$60.8SiO_2$-$30.9CaO$-$5.8Na_2O$-$2.4P_2O_5$
58S	Sol-gel	$60SiO_2$-$36CaO$-$4P_2O_5$
A/W	Melt-derived	SiO_2-CaO-P_2O_5-MgO (apatite- and wollastonite-containing glass-ceramic)
64S	Sol-gel	$64SiO_2$-$31CaO$-$5P_2O_5$
MBG (80S15C)	EISA[a]	$80SiO_2$-$15CaO$-$5P_2O_5$
SCNA	Melt-derived	$57SiO_2$-$34CaO$-$6Na_2O$-$3Al_2O_3$
S50P3	Melt-derived	$50SiO_2$-$30CaO$-$14Na_2O$-$3P_2O_5$-$2MgO$-$1Al_2O_3$
S57A7	Melt-derived	$57SiO_2$-$30CaO$-$6Na_2O$-$7Al_2O_3$
S50B2	Melt-derived	$50SiO_2$-$35CaO$-$7Na_2O$-$6P_2O_5$-$2B_2O_3$
Biovetro®	Melt-derived	$(46\text{-}53)SiO_2$-$(9\text{-}20)CaO$-$(7\text{-}24)Na_2O$-$(0.1\text{-}2)MgO$-$(4\text{-}8)P_2O_5$-$(2\text{-}8)K_2O$-$(0.1\text{-}2)Al_2O_3$
52S	Melt-derived	$52SiO_2$-$30.5CaO$-$9.8Na_2O$-$6.2P_2O_5$-$1.5CaF_2$
2Ag-60S	Sol-gel	$60SiO_2$–$34CaO$–$4P_2O_5$–$2Ag_2O$
3Zn-42S	Melt-derived	$41.7SiO_2$-$36.3CaO$-$5.2Na_2O$-$4.7P_2O_5$-$1.3K_2O$-$7.8MgO$-$3ZnO$
5Cu-MBG	EISA[a]	$80SiO_2$-$10CaO$-$5P_2O_5$-$5CuO$

[a] Evaporation-induced self-assembling; a mesoporous glass with pore channels of few nanometres is obtained.

rates that depend on the material formulation and environmental pH; therefore, a highly bioactive coating may degrade over time causing instability of the prosthetic implant in the long term. This is probably the major reason why the clinical application of bioactive glass coatings is still limited and other bioceramics, such as thermally-sprayed HA which is osteconductive and non-resorbable, have been preferred by surgeons for a long time [13].

Another important issue about bioactive glass coatings concerns their thermal properties: when a coating is applied, the thermal expansion coefficient (TEC) of the glass should match that of the substrate to prevent the glass pulling away from the base implant upon processing [10]. The TEC of the well-known 45S5 Bioglass® ($15\times10^{-6}\,°C^{-1}$) is significantly higher than that of titanium alloys (about $9\times10^{-6}\,°C^{-1}$) and alumina (about $8\times10^{-6}\,°C^{-1}$), which are commonly used to fabricate orthopaedic and dental implants: therefore, the need has emerged to develop new glass formulations with a more suitable TEC for use as coating materials. In this regard, bioactive glasses belonging to the SiO_2-CaO-MgO-Na_2O-K_2O-P_2O_5 system have been widely investigated to match the TEC of the Ti6Al4V alloy [14–16]. Partial replacement of Na_2O and CaO with K_2O and MgO, respectively, was the most common strategy to design and adjust the TEC of the glass in a controlled way [14]. B_2O_3 can be also added to the glass formulation to decrease the TEC, although borosilicate glasses show a higher tendency towards dissolution in aqueous media (including biological fluids) compared to silicate materials [17]. Using multiple glass layers of different compositions has been also proposed to achieve a good compromise among thermal behaviour, optimal dissolution rate and osteointegration [14].

From a technological viewpoint, slurry-dipping, thermal spraying and sputtering are well-established and relatively easy processes to produce homogeneous bioactive glass coatings on flat substrates [12]; on the contrary, the fabrication of coatings on the surface of "real" implants with complex 3D geometries is a great challenge for materials scientists. Therefore, increasing interest has emerged in the last years to adapt, improve or modify the available processing techniques, as well as to develop new ones, in order to effectively apply bioactive glass coatings on curved, irregular and porous medical devices. This article provides a picture of the state of the art in the field, including the latest research efforts and achievements. Table 1 collects all the glasses mentioned in the text which have been used for the fabrication of coatings on scaffolds, prostheses and medical implants.

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Table 2: Overview of glass-based coatings on polymeric, ceramic or metallic scaffolds for bone tissue engineering.

Coating material	Scaffold material	Method of application	Coating function	References[a]
45S5 Bioglass®	PDLLA	Dipping, EPD	Improved bioactivity	[18, 19]
	Polyurethane	Dipping	Improved bioactivity	[20]
	SiC	EPD + firing	Improved bioactivity	[27]
CEL2	Polyurethane	Dipping	Improved bioactivity, mechanical reinforcement	[21]
61S31C (sol)	Polyurethane	EPD on the sol	Positive replica of the polymeric template	[22]
58S	Alumina/zirconia composite	Dipping + firing	Improved bioactivity	[26]
	Bovine HA	Prolonged dipping + firing	Mechanical reinforcement	[29]
A/W	HA	Dipping + firing	Improved bioactivity, improved mechanical properties	[28]
64S/gelatin /PCL	Magnesium	Freeze-drying	Improved bioactivity, reduced biodegradability of Mg scaffold	[31]
58S/PCL	Biphasic calcium phosphate	Dipping	Improved mechanical properties	[30]
SBA-15	Wollastonite-containing glass-ceramic	Dipping + calcination	Controlled drug release	[35]
MCM-41	SiO_2-CaO-K_2O-derived glass-ceramic	Dipping + calcination	Controlled drug release	[36, 38]
	Fluoroapatite-containing glass-ceramic	Dipping + calcination	Controlled drug release	[37]
	45S5 Bioglass®	Dipping + calcination	Controlled drug release	[39]
80S15C	Wollastonite-containing glass-ceramic (SCNA)	EPD + calcination	Improved bioactivity	[43]
	β-TCP	Spin coating + calcination	Improved bioactivity and bone-forming ability	[44]
MBG/PLGA	$CaSiO_3$	Dipping	Mechanical reinforcement, improved bioactivity, controlled drug release	[46]

[a] References follows numbering in the main text.

2 Coatings on porous scaffolds for bone tissue engineering

Biomaterials are often designed and processed to act as three-dimensional (3D) scaffolds which support tissue growth and safely dissolve once they have performed their function, thereby leaving the body to remodel the tissue to its natural form. Since the early 2000s, glass-coated porous scaffolds have increasingly attracted the interest of researchers working in the field of bone tissue engineering in the attempt to impart key extra-functionalities to the polymeric or ceramic base material, such as improved bioactivity and/or drug release ability. In the case of polymeric scaffolds, the presence of a glass coating can also contribute to mechanically reinforce the structure and adjust the resorption of the polymer matrix [9]. Table 2 summarizes the studies dealing with the deposition of bioactive glass-based coatings on the surface and struts of 3D porous scaffolds.

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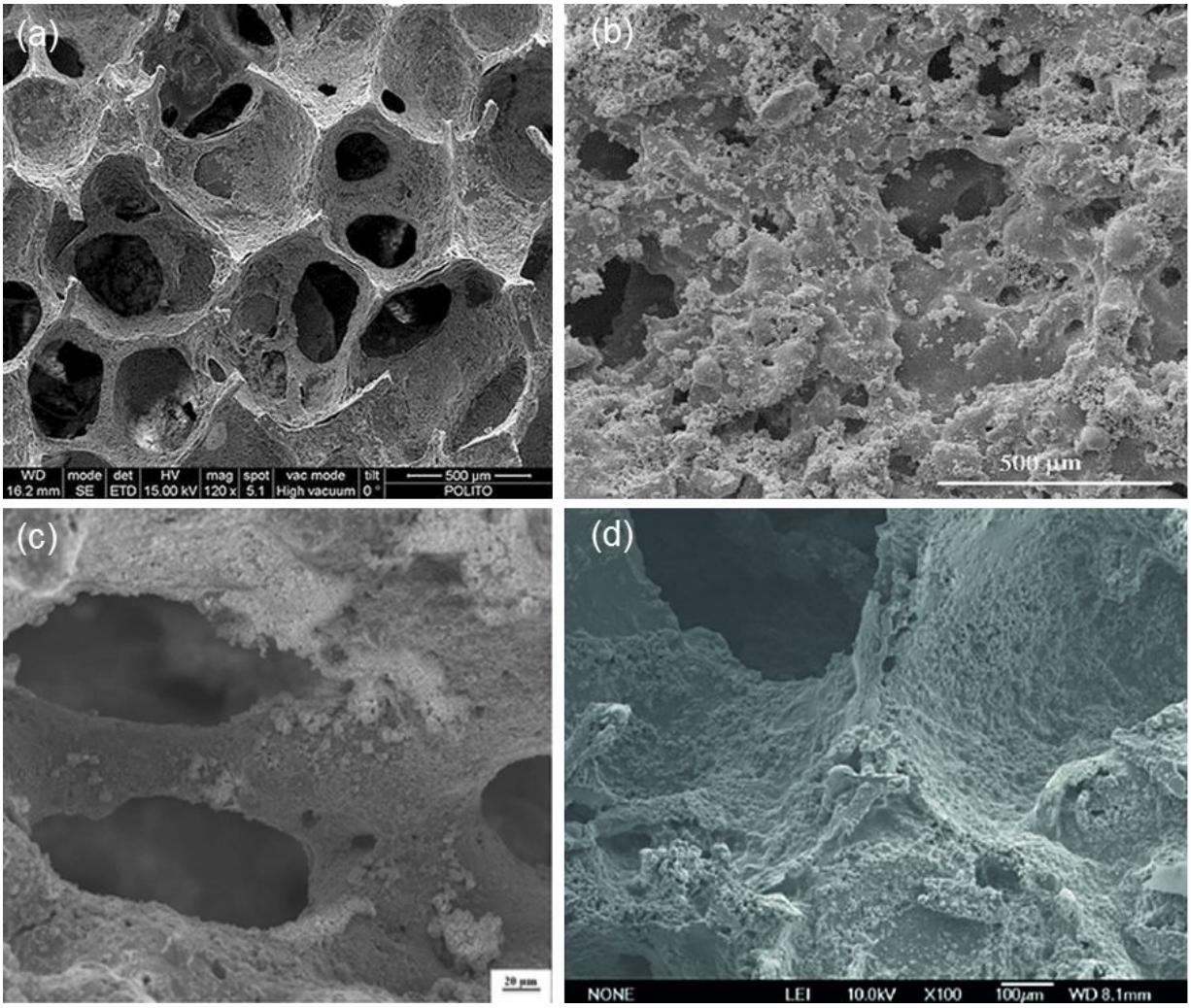

Figure 1: Glass-based coatings applied on the struts of 3D porous scaffolds: (a) CEL2-coated polyurethane foam (dipping procedure) (image adapted from Baino *et al.* [21] © Springer), (b) MCM-41 sphere on a fluoroapatite scaffold (dipping method) (image adapted from Vitale-Brovarone et al. [37] © Springer), (c) MBG particles deposited on a wollastonite-containing scaffold (EPD) (image adapted from Fiorilli *et al.* [43] © Springer), (d) $CaSiO_3$ scaffold coated with a PLGA/MBG composite layer (dipping method) (image adapted from Shi *et al.* [46]).

2.1 Glass-coated porous polymers

The first example of a bioactive and resorbable glass-coated polymeric scaffold was reported by Roether *et al.* [18], who fabricated macroporous poly(DL-lactide) (PDLLA) foams coated with 45S5 Bioglass® particles (mean size below 5 µm). Stable and homogeneous glass coatings were produced by two processing methods, *i.e.* a slurry-dipping technique (in conjunction with a pre-treatment of the PDLLA foam in ethanol) and the electrophoretic deposition (EPD), which exploits the movement of charged particles suspended in a solution under an electric field with the aim of depositing them on a substrate [19]. *In vitro* bioactivity studies revealed the formation of a surface HA layer, the thickness of which increased with increasing time in simulated body fluid (SBF).

45S5 Bioglass®-coated polyurethane and polyurethane/PDLLA foams were also prepared by dipping cycles to improve the bioactivity of the polymeric substrate [20]. A similar approach was reported by Baino *et al.* [21] who coated polyurethane foams with a layer of CEL2 glass particles (Fig. 1a) that imparted high bioactivity to the otherwise inert polymeric scaffold and significantly increased the Young's modulus of the structure compared to the uncoated material (1.35 vs 0.12 MPa).

An interesting application of bioactive glass coatings on a porous polymeric template was recently reported by Cabanas-Polo *et al.* [22] who fabricated 3D scaffolds by the foam replication technique combining sol-gel and EPD process. In this approach, the sol precursor molecules were found to be positively charged and,

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Table 3: Overview of bioactive glass-based coatings on joint prostheses and surgical devices.

Coating material	Substrate/implant	Method of application	Coating function	References[a]
SCNA	Alumina cup	Dipping or airbrush spraying + firing	Joining	[53–55]
S57A7	Alumina/zirconia cup	Airbrush spraying + firing	Joining	[56]
S50P3	Alumina cup	Optimized sponge replica method	Improved bioactivity	[56]
S50B2	Alumina/zirconia cup	Optimized sponge replica method	Improved bioactivity	[57]
45S5 Bioglass®	Porous titanium	Infiltration	Improved bioactivity	[60]
	Stainless steel	Atmospheric plasma spraying	Improved bioactivity	[62]
	Polymeric sutures	Dry powder pressing, dipping	Improved bioactivity	[70–73]
	Nitinol wire	EPD	Improved bioactivity	[74]
Biovetro®	Titanium alloy femur stem	Plasma spraying	Improved bioactivity	[59]
52S	Ti6Al4V dental screw	Plasma spraying	Improved bioactivity	[61]
Chitosan/45S5 Bioglass®	Stainless steel	EPD	Improved bioactivity	[63, 64]
	Titanium alloy foams	EPD	Improved bioactivity	[67]
Chitosan/45S5 Bioglass®/ silver nanoparticles	Stainless steel	EPD	Improved bioactivity, antibacterial effect	[68]
Alginate/45S5 Bioglass®	Stainless steel	EPD	Improved bioactivity	[65]
PEEK/45S5 Bioglass®	Ti-6Al-7Nb	EPD	Improved bioactivity	[66]
	Nitinol wire	EPD	Improved bioactivity	[75]
PEEK/45S5 Bioglass®/ silver nanoparticles	Stainless steel	EPD	Improved bioactivity, antibacterial effect	[69]
58S/TiO_2	Nitinol nail	Dipping	Improved bioactivity	[76]

[a] References follows numbering in the main text.

upon electrophoresis, travelled from the surroundings of the counter-electrode to the cathode (a Ni wire fixed to a polyurethane non-conductive sponge), thereby creating a fairly homogeneous impregnation of the porous substrate. At the end of the process, the sol-coated polymeric template were left to dry and thermally-treated to obtain a glass (61S31C)-derived positive replica of the foam.

Besides being used as a coating material on preformed polymeric scaffolds, biomedical glasses have been widely employed over the last 15 years for the production of a variety of porous composites in which the inorganic particles are usually dispersed as bioactive and/or reinforcing inclusions in an organic matrix; the interested reader is addressed to some comprehensive reviews on this topic [9, 23, 24].

2.2 Glass-coated inorganic scaffolds

Bioactive glass coatings have been deposited on a wide range of porous inorganic substrates, including nearly-inert ceramics, hydroxyapatite and metals, to impart added value to the substrates, primarily bioactivity.

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Table 4: Overview of glass-based coatings on medical implants in contact with soft tissues.

Coating material	Substrate/implant	Method of application	Coating function	References[a]
2Ag-60S	Polymeric sutures	Dipping	Antibacterial effect	[81, 82]
3Zn-42S	Polymeric sutures	Dipping	Antibacterial effect	[84]
45S5 Bioglass®	Polyethylene orbital implant	Dipping	Improved angiogenesis (fibrovascularization)	[88, 89]
	Silicone tube (catheter)	Patented technology involving a pre-treatment of the tube in hexane/silicone solution	Soft tissue fixation	[100, 101]
5Cu-MBG	HA orbital implant	Dipping + calcination	Antibacterial properties and drug release (release of Cu^{2+} ion and ofloxacin)	[90]
A/W	Titanium "skirt" (flange) of a keratoprosthesis	Dipping + firing	Improved biocompatibility with ocular tissues	[94]
SiO_2/Ag nanoclusters	PMMA ocular prosthesis	Radio-frequency sputtering	Antibacterial properties (Ag^+ ions)	[91, 92]
	Polypropylene mesh for hernia repair	Radio-frequency sputtering	Antibacterial properties (Ag^+ ions)	[98]

[a] References follows numbering in the main text.

Miao [25] coated the struts of alumina foams with a thin film of lanthanum-doped alumino-silicate (LAS) glass to fill micropores and, therefore, improve the mechanical properties of these highly-porous substrate (above 80 vol.%). However, the resulting LAS-modified ceramic scaffolds exhibited no ability to bond to bone tissue; therefore, a 58S glass layer was then applied by dipping to impart bioactivity to the otherwise inert porous ceramics. The twice-coated and sintered scaffolds exhibited apatite forming ability upon contact with biological fluids and sufficient compressive strength to be proposed for maxillofacial reconstruction.

A similar approach was followed by Liu *et al.* [26] who applied a layer of 58S glass on the struts of alumina/zirconia (80 : 20 vol.%) composite scaffolds by dip coating. The glass-coated macroporous composite had a total porosity comparable to that of cancellous bone (60-66 vol.%), well-interconnected pores with large sizes (1-2 mm), adequate compressive strength for safe manipulation during surgery (5-8 MPa), and good bioactivity as demonstrated by the formation of a surface HA layer within 24 h in SBF.

45S5 Bioglass® coatings on porous SiC have also been produced by EPD; a postdeposition thermal treatment was applied to improve the cohesion of glass particles, in order to obtain a uniform coating with excellent coverage of the porous SiC struts [27]. *In vitro* studies carried out in SBF revealed the formation of a surface apatite layer, which demonstrates that even fully bioinert SiC can be "bioactivated" by the presence of a glass coating of suitable composition.

Bioactive glass coatings were also applied on osteoconductive but non-osteoinductive calcium phosphate scaffolds to improve their biological performances. Jun *et al.* [28] fabricated porous HA foams via the sponge replica method and coated them with a bioactive A/W glass-ceramic layer by a dipping procedure. It was observed that all of the scaffolds retained a highly porous structure (above 93 vol.%) with well-interconnected pores and the A/W coating significantly increased the compressive strength of the HA scaffolds due to the formation of a dense, strong and smooth glass-ceramic "sleeve" around the weak HA struts (1.0 vs. 0.1 MPa). The *in vitro* bioactive behavior of the scaffolds was markedly improved by the glass-ceramic coating as demonstrated by the formation of a surface nano-crystalline apatite layer as well as the higher proliferation rate and alkaline phosphatase activity of osteoblast-like cells compared to the uncoated material.

Highly porous (83 vol.%) scaffolds of bovine-derived HA were also coated with a thin layer of 58S glass by a prolonged dipping procedure to improve the compressive strength of the material (from 0.22 to 1.49 MPa) [29].

A significant improvement of the mechanical properties of biphasic calcium phosphate scaffolds was achieved

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by applying polycaprolactone (PCL)/nano-sized 58S glass composite coatings containing various amounts (1-90 wt.%) of inorganic phase (compressive strength: 0.2-1.5 vs. 0.1 MPa, elastic modulus: 20-50 MPa vs. 15 MPa) [30]. After examining the fracture surfaces, the authors of this study reported that there was no sign of detachment of the nanocomposite layer from the substrate surface, which indicates a strong interfacial bond of the coating to the calcium phosphate material. Furthermore, the nanocomposite layer stretched considerably before breaking off and the coating presented a ductile fracture surface due to the excellent ductility of PCL [30]. Fabrication of bioactive glass and, in general, bioceramic monolithic coatings on metallic substrates is challenging due to a series of problems associated with high-temperature sintering required for the consolidation of the bioactive layer, including the risk of oxidation of the metal surface and TEC mismatch [10]. Therefore, there is increasing interest in the development of polymer/glass coatings that can adhere to the metallic substrate at low temperatures. In this regard, a multilayer coating composed of PCL and gelatin reinforced with 64S glass particles has been applied on the surface of magnesium (Mg) scaffolds by means of a freeze-drying process [31]. The presence of the bioactive coating induced the growth of a surface apatite layer on the scaffold struts and reduced the degradation rate of the substrate material: in fact, it was observed that uncoated Mg scaffolds were fully degraded after 3 days in SBF, whereas about 87 wt.% of PCL/gelatin/glass-coated samples remained after immersion for 14 days. This was an important finding that could expand the biomedical applications of Mg scaffolds and implants, the use of which is very limited in bone tissue engineering due to the too fast degradation of the metal in contact with biological fluids to allow an adequate support to hard tissues [32].

2.3 Hierarchical scaffolds with a mesoporous coating

Another key added value that can be imparted to bone tissue engineering scaffolds by means of an appropriate coating is the ability to incorporate and deliver therapeutic agents in a controlled way according to predetermined release kinetics. In most cases, polymeric or polymer-coated ceramic scaffolds have been proposed for this purpose since drugs can be incorporated in the organic phase and subsequently released as the polymer degrades [33].

The advent of silicate mesoporous materials, which being amorphous can be formally considered as SiO_2-based glasses, revolutionized the field of drug release over the last two decades allowing a finely controlled release of biomolecules to be successfully achieved from inorganic matrices, too [34]. Using silica mesoporous materials for the fabrication of multifunctional hierarchical scaffolds was proposed in the attempt to combine the attractive properties of bioactive glass-derived macroporous scaffolds, *i.e.* mechanical support to host and regenerated bone and stimulation of bone cells towards osteogenesis, with the drug uptake/release ability supplied by the mesoporous material. The first prototype of such a construct was developed by Cauda *et al.* [35] who coated bioactive glass-ceramic scaffolds with a thin layer of SBA-15 spheres (mesopores within 5-8 nm arranged according to a hexagonal symmetry). This early study was then extended to MCM-41 (Fig. 1b), which possesses narrower pore size (2-3 nm, hexagonal symmetry of pore arrangement) compared to SBA-15 [36–38]; in both cases, the silica mesoporous coating deposited on scaffold struts was found to play a key role in enhancing the drug adsorption ability of the porous construct. A similar approach was also proposed by Boccardi *et al.* [39] who synthesized submicronic MCM-41 spheres directly on a 45S5 Bioglass®-derived foam through a modified Stöber method.

From the viewpoint of regenerative medicine, the major limitation of pure SiO_2 mesoporous materials is their moderate reactivity in biological environment: in fact, although MCM-41 and SBA-15 were shown able to form a surface apatite layer upon prolonged immersion in SBF [40, 41], the reaction kinetics are too slow to consider them as effective bone-bonding materials. With these concerns in mind, researchers introduced other oxides (primarily CaO and P_2O_5) in the composition of mesoporous materials to obtain nano-textured bioactive glasses with exceptional apatite forming ability [42]. Fiorilli *et al.* [43] exploited the electrophoretic mechanism to deposit mesoporous bioactive glass (MBG) particles onto the struts of a wollastonite-containing macroporous scaffold (Fig. 1c) to combine the excellent bioactivity of the mesoporous phase with the high mechanical strength (above 15 MPa under compressive loads) of the glass-ceramic skeleton that, without the coating, was a nearly-inert material.

For the same purpose, spin coating method was experimented by Zhang *et al.* [44] to deposit a thin layer (about 100 nm) of MBG on the struts of a 3D-printed β-TCP scaffold to improve its bone forming ability; early *in vivo* tests (rabbit model) revealed that this hierarchical macro-mesoporous construct significantly improved the mineralization ability, attachment/viability and osteogenic/angiogenic gene expression of osteoblastic cells as well the formation of new bone compared to the uncoated material.

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It is worth pointing out that using MBG as a coating on a strong substrate also allows overcoming the mechanical limitations of mesoporous materials (dramatic brittleness) due to the inherent nanoporosity [45].

Shi *et al.* [46] fabricated MBG/poly(lactic-*co*-glycolic acid) (PLGA)-coated $CaSiO_3$ scaffolds by dipping the macroporous template in a PLGA solution with different amounts of suspended nano-sized MBG particles (Fig. 1d). The mechanical strength of MBG/PLGA-coated scaffolds were greatly improved due to the addition of nano-sized MBG particles compared to uncoated and PLGA-coated $CaSiO_3$ scaffolds (1.5-2 vs. 0.4 MPa). Furthermore, the bioactive coating enhanced the *in vitro* mineralization ability, the proliferation and early cell differentiation of osteoblasts, and the mesoporous channels inside the MBG particles allowed a controlled release of ibuprofen to be achieved.

Although the above-mentioned experimental devices were usually found functional for the intended scope (*e.g.* improved bioactivity, drug release), most approaches followed to deposit a mesoporous layer on the struts of a ceramic/glass-ceramic scaffolds (dipping, EPD) still need to be optimized to improve the coating uniformity and homogeneity (Figs. 1c and 1d).

3 Coatings on endoprostheses and devices for surgical fixation

3.1 Orthopaedic and dental implants

The hip prosthesis has been the most active area of joint replacement research and development since the beginning of the 20th century. Today, the most commonly used bearing couples in hip joint replacements consist of a cobalt-chrome (CoCr) alloy (femur head) articulating against an ultrahigh-molecular-weight polyethylene cup (acetabular component). Ceramics (alumina and alumina/zirconia composites) have been increasingly used as a valuable alternative to metal-on-polyethylene bearing couple due to excellent anti-wear properties and bioinertness [47]. The polymeric or ceramic prosthetic acetabular cup is fixed to the patient's bone by means of a metal-back provided with screws or anchoring flanges, with or without the use of an acrylic cement. The use of HA as a bioactive coating on the metal-back has been experimented, but the results and actual benefits seem to be still controversial [48]. Griss *et al.* [49] implanted a 45S5 Bioglass®-coated alumina total hip prosthesis (acetabular cup and femur stem) in sheep and found that, although new bone formation was observed at the bone-implant interface, problems of instability occurred in the long-term. Similar results and problems were reported by Hamadouche *et al.* [50] who experimented alumina implants coated by a sol-gel glass in rabbits. While in these early studies monolithic glass coatings were employed, Verné *et al.* [51] first claimed the concept that a single-piece ceramic acetabular cup can be fixed to the patient's bone by means of a porous coating made of bioactive glass. This novel bone-like glass coating aims to overcome the current limitations associated to implant modularity (need for a perfect assembling of the cup into the metal-back during surgery), traumatic fixation and toxicity due to metal ion release and/or cement degradation. This novel prosthetic acetabular cup is constituted by three layers, *i.e.* an alumina/zirconia composite substrate, a bioactive glass-based trabecular coating and a glass-derived interlayer with the aim of improving the adhesion between the bioceramic cup and the trabecular coating [52]. The key element of this 3-layer system is the outer bone-like coating, as new bone is expected to grow *in vivo* within its 3D network of highly interconnected macropores, thereby creating a tight interfacial bond between prosthetic cup and host bone. Fabrication of an early prototype of such implant was a highly challenging task: in this regard, optimized dipping procedures and airbrush spraying of glass slurries were experimented to manufacture the non-porous interlayer on the curved surface of the cup (Fig. 2a) [53, 54], while the outer trabecular coating was successfully produced by properly adapting the sponge replica method to the 3D radial geometry of the prosthesis (Figs. 2b and 2c) [55–57]. In these studies, the issue of estimating reliably the adhesion strength of the bioactive coating to the curved substrate was also tackled: specifically, the recommendations of the relevant ASTM standard dealing with pull-out tests on flat samples [58] were properly adapted for a "nearly-flat" geometry and appropriate testing tools were manufactured for this purpose [53].

In the field of metallic implants, a special mention should be dedicated to the study reported by Alonso-Barrio *et al.* [59] who implanted clinically (70 human patients) titanium-based prosthetic femur stems having the proximal two-thirds coated with a 80-μm thick layer of Biovetro®. Survival rate for this stem was 91.4% after a 8-year follow-up, and clinical evaluation including pain, mobility and gait revealed that results were excellent or good in 77% of cases, whereas 23% of patients had fair or poor results. Interestingly, the authors of this study concluded that, however, Biovetro® coating produced worse osteointegration compared to plasma-sprayed HA due to the appearance of a fibrous interface with a macrophage

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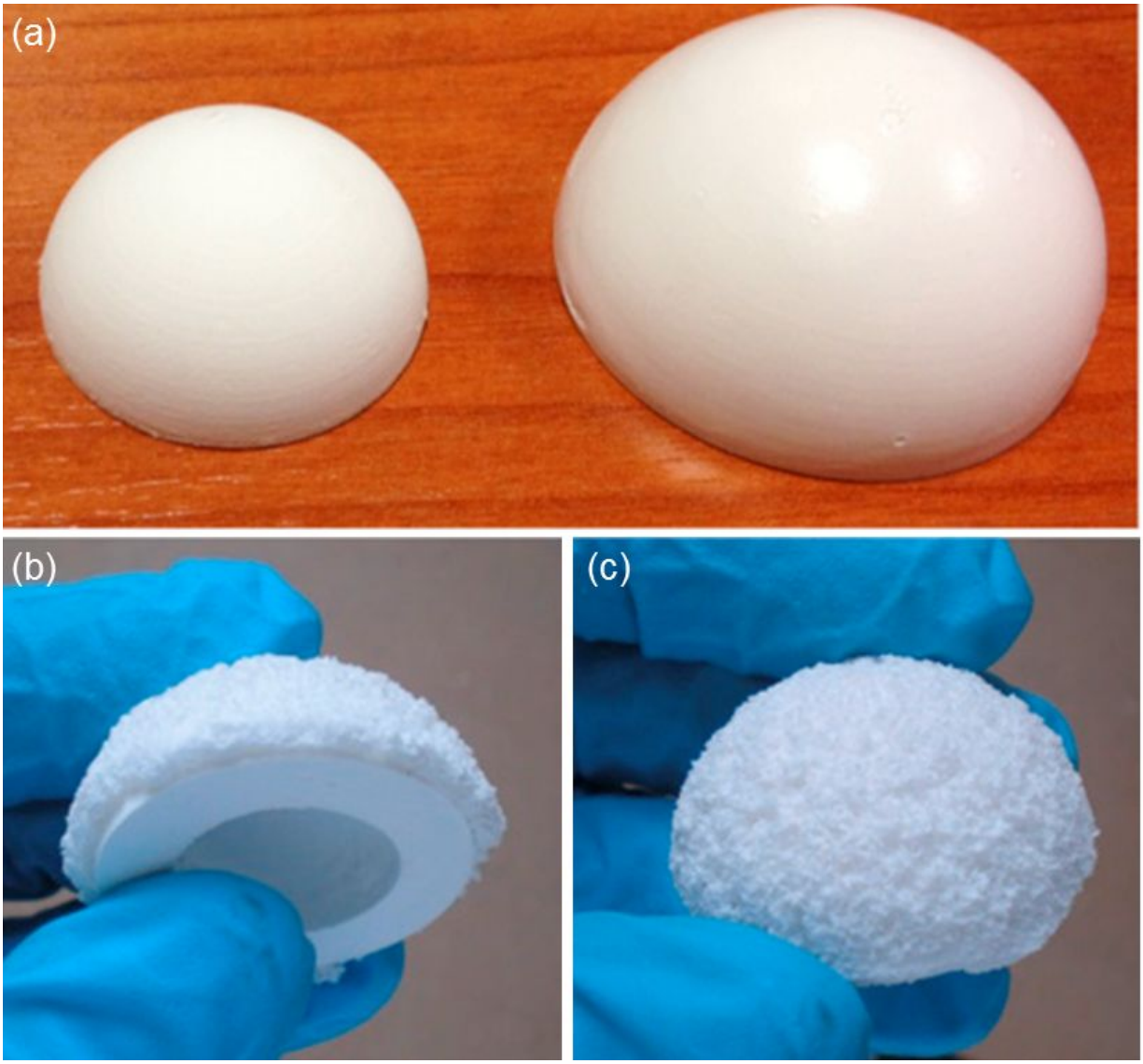

Figure 2: Bioactive glass coatings on alumina/zirconia composite acetabular cups for hip joint prosthesis: (a) SCNA-derived coating produced by a slurry-dipping procedure (left: "green" sample, right: sintered coating), (b) and (c) three-fourth views of a full prototype with a S50B2-derived trabecular coating produced by an optimized sponge replica method (images adapted from Baino *et al.* [57] © Elsevier).

foreign body reaction, less new bone, a significant delay in bone maturation and insufficient mineralization of the newly-formed bone.

More recently, Drnovšek *et al.* [60] infiltrated the outer porous titanium layer of Ti6Al4V cylindrical implants (diameter 3 mm, length 6 mm) with 45S5 Bioglass® particles with size from 100 nm to 1 µm. The thickness of the vacuum plasma-sprayed porous titanium layer was 300 µm, with interconnected pores in the range of 20 to 100 µm. The implants with or without the bioactive glass coating were inserted bilaterally in tibial holes of ten New Zealand white rabbits. After ten weeks *in vivo*, 45S5 Bioglass® was fully resorbed and about 38% of the pores throughout the thickness of the porous titanium layer were filled with new bone. In the absence of the bioactive coating, only 22% of the pores were filled by new bone, which was found mostly in the outer part of the porous titanium layer. Although the observed percentage of pores occupied by new bone in the glass-coated implants seems not to be exceptionally high (38%), the increase from 22% to almost a double value demonstrates the key role played by the bioactive layer in stimulating bone ingrowth during the first weeks after implantation.

In another interesting study, Schrooten and Helsen [61] combined an experimental approach with finite element analysis to evaluate the adhesion strength of

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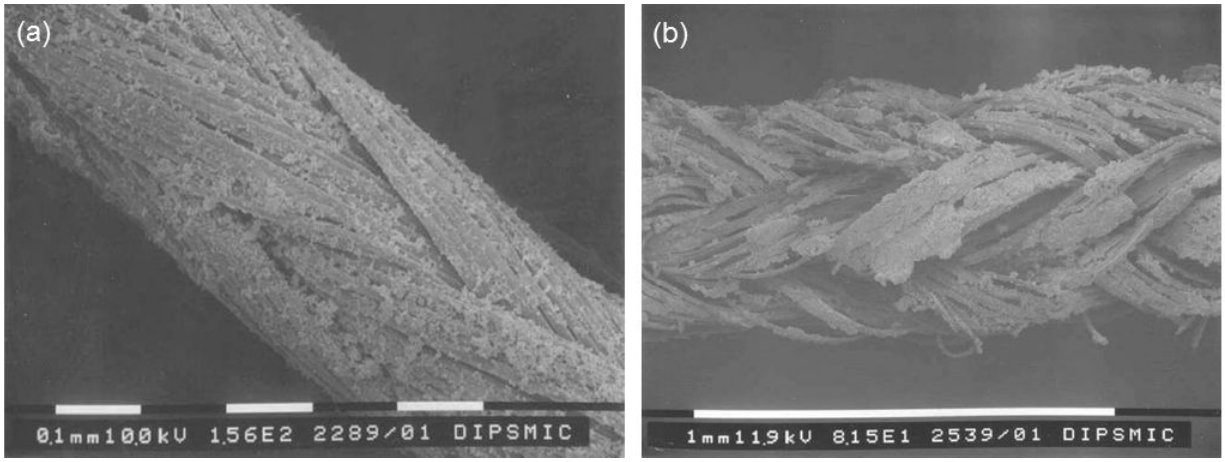

Figure 3: 45S5 Bioglass®-coated Vicryl sutures produced by slurry dipping before (a) and after soaking for 28 days in SBF (b) (images adapted from Bretcanu *et al.* [72] © Springer).

52S glass coatings applied on Ti6Al4V dental implants by means of plasma spraying. It was shown that the coating could withstand an externally generated tensile stress of 47 MPa without any damage; adhesion tests performed after 2 months in SBF revealed that the coating adhesion strength decreased of about 10% but the glass-Ti6Al4V interface remained fully intact at all times.

Atmospheric plasma spraying was also experimented to produce 45S5 Bioglass® coatings on AISI 304 steel flat substrates [62].

A relatively recent and highly promising area of research concerns the development of coating systems involving a polymer matrix with bioactive glass inclusions. The use of these coatings is particularly attractive in the case of metallic implants as there is no need for a high-temperature thermal treatment, which is necessary if monolithic glass or ceramic coatings are used but is often incompatible with metal substrates. These "soft" composite coatings can also create a better transition between the metallic implant and the bone.

EPD proved to be a valuable strategy to produce such type of coatings on both flat surfaces (*e.g.* 45S5 Bioglass®/chitosan [63], Sr-/Zn-doped 45S5 Bioglass®/chitosan [64] and 45S5 Bioglass®/alginate composite coatings on AISI 316L stainless steel [65], 45S5 Bioglass®/polyetheretherketone (PEEK) on Ti-6Al-7Nb alloy [66]) and 3D porous structures (45S5 Bioglass®/chitosan coatings deposited on Ti-4Al-6V foams [67]). Antibacterial 45S5 Bioglass®/polymer-based layers embedding silver nanoparticles were also produced on AISI 316L stainless steel by EPD [68, 69].

3.2 Devices for surgical fixation

Application of a bioactive glass coating on polymeric meshes is useful to induce the formation of a nanocrystalline HA layer on the surface of the suture, the degradation of which can therefore be designed and modulated. Stamboulis *et al.* [70] produced 45S5 Bioglass® coatings (particle size below 5 μm) on polyglactin 910/polydioxanone surgical meshes by means of dry powder pressing or slurry-dipping processes and demonstrated the excellent *in vitro* bioactivity of the surface-modified polymeric sutures. Commercial Vycril® sutures were also coated with 45S5 Bioglass® particles by means of similar procedures (Fig. 3a) [71], and it was noted that the slurry-dipping process gave the better results in terms of uniformity/reproducibility of the coating (thickness 15-20 μm) and bioactive behavior (faster kinetics of HA formation in SBF), although the suture showed a degraded structure after immersion for 28 days in SBF (Fig. 3b) [72]. Interestingly, these glass-coated sutures exhibited a decrease in tensile strength compared to uncoated ones (385 vs. 467 MPa) [73]: the possible explanations were associated to mechanical damage of the suture surfaces by the hard inorganic particles upon coating preparation and/or the possible infiltration of glass particles into the voids of the braided structure of the suture.

Although this application was initially developed in the context of bone repair due to the bone-bonding ability of bioactive glasses, recent studies have been addressed to wound healing and, therefore, this topic is discussed in more detail in the section 4.1.

Besides polymeric sutures, other devices used for the surgical fixation of implants, such as metal wires, have been coated with a bioactive glass layer. In this regard, EPD

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was found a very suitable technique to deposit monolithic 45S5 Bioglass® [74] and PEEK/45S5 Bioglass® composite coatings [75] on shape-memory nickel-titanium (Nitinol) wires. PEEK is suitable for a number of medical device applications since it combines excellent chemical and hydrolysis resistance, high strength and excellent tribological properties; bioactive glass particles were incorporated into the coating to impart bioactivity as an extra-functionality. A post-EPD process at moderate temperature (340°C for 20 min, heating rate 300°C/h) was applied to improve the densification and adhesion of the coating to the substrate (final thickness: 15 μm) [75].

Esfahani *et al.* [76] dip-coated Nitinol nails with a composite layer made of nano-sized 58S particles (50-60 nm) and titanium oxide (TiO_2) produced via a sol-gel route. It was observed that the presence of glass particles in the TiO_2 matrix enhanced gradually the hardness of the coating and direct pull-out test recorded a coating-substrate bonding strength larger than 16 MPa. Furthermore, *in vitro* bioactivity studies revealed the formation and growth of HA agglomerates on the surface of the 58S/TiO_2-coated Nitinol alloy.

4 Coatings on implants for non-osseous applications

Until the early 1980s biomaterials scientists believed that only calcified tissues could form a bond to bioactive materials. Wilson *et al.* [77] first showed that melt-derived bioactive glasses in the SiO_2–CaO–Na_2O–P_2O_5 system can also bond to soft collagenous tissues when the material composition exceeds 52 wt.% of SiO_2. Today bioactive glasses are still mainly employed for hard tissue repair and regeneration in the clinical practice, but especially in the last decade a wide range of non-osseous tissue engineering applications has emerged which seemed impossible when research began. The interested reader is addressed to a couple of recent reviews that provide a comprehensive picture of the potential of biomedical glasses in contact with soft tissues [78, 79].

4.1 Wound healing

Wound healing represents a major challenge in medicine and is commonly associated to a number of clinical scenarios including skin regeneration, chronic wounds (*e.g.*, non-healing diabetic ulcers) and surgical sutures. The skin plays an important role in the prevention of infections from pathogens; once a trauma is suffered, the damaged skin should be immediately covered with a dressing material able to maintain a moderately moist environment for regeneration of the skin, and prevent infection by exerting an antibacterial effect [80]. Blaker *et al.* [81] coated resorbable polymeric sutures with silver-doped bioactive glass (2Ag-60S) powder by a dipping procedure and reported the *in vitro* bioactive behavior and bactericidal effect of the composite. In a next study, Pratten *et al.* [82] carried out *in vitro* experiments using *Staphylococcus epidermidis* to compare the antimicrobial activity of commercial Mersilk® sutures coated with 45S5 Bioglass® and 2Ag-60S powder and reported that Ag-doped sutures showed a significantly greater effect in limiting bacterial attachment compared to 45S5 Bioglass®-coated and as-such sutures. Besides silver, which is known as a potent antibacterial agent [83], other elements such as zinc have been used to dope bioactive glasses. Salah Ahmeed *et al.* [84] recently reported the *in vitro* antibacterial activity of Mersilk® sutures coated with 3Zn-42S bioactive glass against *Staphylococcus aureus*, *Streptococcus mutans* and *Lactobacillus*.

A comprehensive overview of the use of biomedical glasses for wound healing, not restricted to bioactive coatings, has been published by Shah Mohammadi *et al.* [85].

4.2 Ocular applications

Due to its biocompatibility and transparency to visible light, glass has been used for centuries in ophthalmology for fabricating external lenses to correct refractive deficiencies of the eye. In these "traditional" applications, glass has been employed as an optical element of ophthalmic devices; in recent years, some highly innovative applications of bioactive glasses and glass-ceramics have emerged to impart key added values to ocular implants, such as angiogenesis and antibacterial properties [86].

Orbital implants are porous or non-porous devices that aim to replace the orbital volume after surgical removal of the globe (evisceration, enucleation) due to malignant tumors, oculo-orbital traumas or untreatable infections [87]. The most commonly used orbital implants are porous spheres made of HA, polyethylene or alumina in which fibrovascular tissue is expected to grow postoperatively. A novel implant, constituted by a sphere of porous polyethylene coated by a thin layer of 45S5 Bioglass®, has been recently introduced on the market and sold under the commercial name of Medpor-Plus. Naik *et al.* [88] investigated the fibrovascular in-growth of Medpor-Plus orbital implants compared to conventional porous polyethylene spheres in ten enucleated patients and found a statistically

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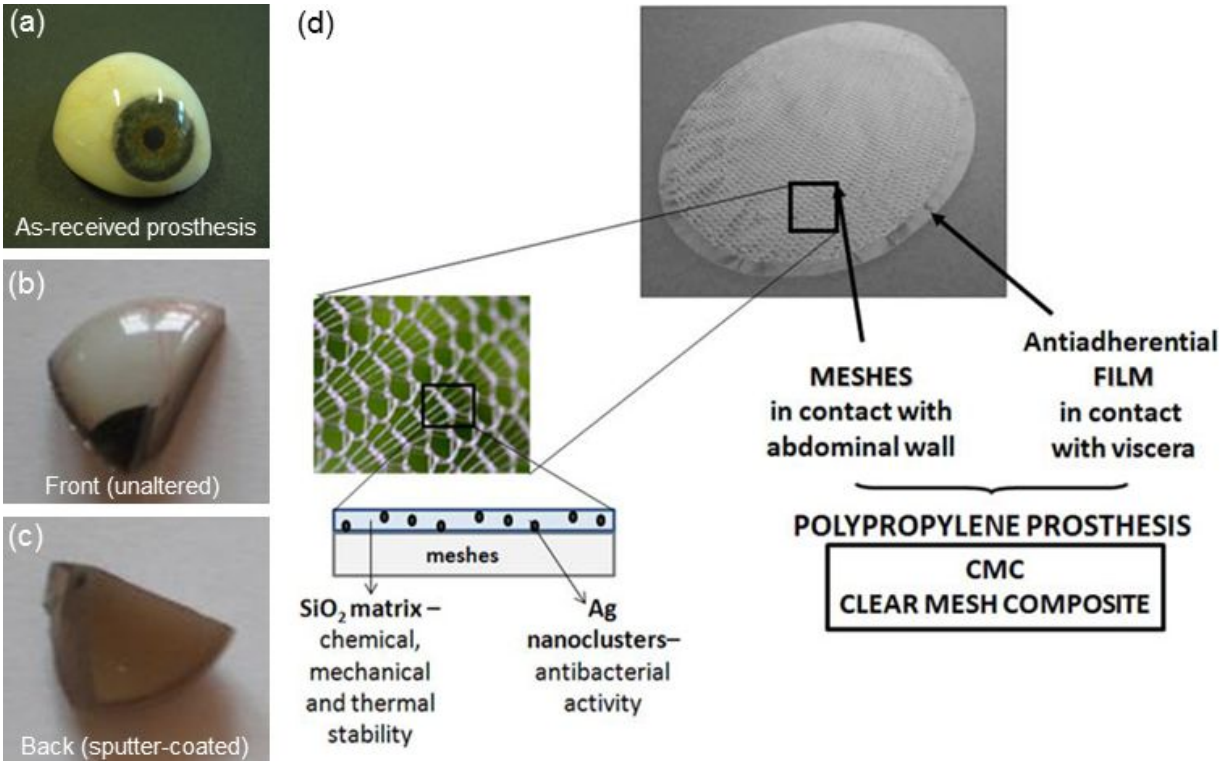

Figure 4: Ag nanocluster/SiO_2 glass coating applied by radio-frequency sputtering on (a-c) a PMMA ocular prosthesis (images adapted from Baino *et al.* [91] © Elsevier) and (b) a polypropylene prosthesis for hernia repair (image adapted from Muzio *et al.* [98] © Wiley).

significant increase in the rate of fibrovascularization of glass-coated polyethylene implants under MRI investigations. In a more recent study, Ma *et al.* [89] examined the overall postoperative outcomes of 170 enucleated patients receiving a Medpo-Plus implant and reported an overall success rate of 94.7%.

Other authors applied surface coatings to orbital implants in order to impart an antibacterial effect. Ye *et al.* [90] coated HA implants with a copper-containing MBG (5Cu-MBG) coating to combine the bactericidal effects of Cu^{2+} ions released as the coating degrades and ofloxacin, an antiseptic drug that was encapsulated in the glass mesopores. Preliminary *in vitro* analyses validated the twofold effect of the proposed system against both gram-positive (*Staphylococcus aureus*) and gram-negative bacteria (*Escherichia coli*), thus opening new perspectives for the prevention and treatment of implant-related ocular infections.

Silver nanocluster/SiO_2 glass composite coatings have been also deposited via radio-frequency sputtering on the surface of poly(methyl methacrylate) (PMMA) ocular prostheses to be coupled with orbital implants (Figs. 4a-4c), and it was reported that the material elicited a potent antibacterial effect *in vitro* against *Staphylococcus aureus* due to the sustained release of Ag^{+} ions [91, 92].

Bioactive glass coatings have also found a sporadic application in the manufacturing of artificial corneas (keratoprostheses), which are implanted when transplant of corneal tissue is unfeasible [93]. Keratoprostheses are basically constituted by an optical core (transparent PMMA cylinder) that is anchored to host tissue by a porous "skirt". Linnola *et al.* [94] deposited a bioactive A/W glass-ceramic coating on a keratoprosthetic titanium skirt in the attempt to avoid the ingrowth of epithelium into the anterior chamber, which could open a canal for infections, cause the extrusion of the prosthesis and induce postoperative glaucoma. The outcomes of A/W-coated and uncoated kerathoprostheses were evaluated in 22 New Zealand albino rabbits after enucleation (11 for each of the two groups): a predominant epithelial ingrowth was observed with the uncoated devices, which supported the idea that a bioactive coating was able to rapidly anchor the prosthesis to the corneal tissue thereby preventing epithelial down-growth from the surface along the prosthesis into the interior of the eye. However, the A/W coating was prone to degradation in the long-term and tended to detach from the titanium substrate; perhaps these were the major reasons why the studies, although promising, were discontinued.

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A passivation layer of pure SiO_2 glass (thickness 500 nm) was also applied on the Si electrodes of an early prototype of artificial retina [95]. Animal experiments in rabbits and pigs revealed a degradation of the SiO_2 layer accompanied by pit corrosion of the Si substrate for implantation periods above 6 months. In order to overcome this drawback, the researchers' interest was then addressed to other materials to fabricate both the substrate (*e.g.* nanoporous TiN) and the passivation layer (high-performance polymers) [96].

4.3 Prostheses for hernia repair

A number of biological and synthetic prostheses are commercially available for abdominal hernia repair; the most commonly used devices are made of polypropylene and comprise a single polymeric mesh or a two-layer system [97]. Very recently, Muzio *et al.* [98] deposited a silver nanocluster/SiO_2 glass composite coating on a polypropylene prosthesis comprising a porous mesh in contact with the parietal side and a 70-µm thick smooth layer that prevented adhesion with intestine and viscera (Fig. 4d). Only the mesh layer, being more prone to bacterial colonization due to its wrinkled surface structure, was sputter-coated with the silver nanocluster/SiO_2 glass film (thickness of few tens of nanometres). During *in vitro* experiments, the coating promoted the growth of human mesothelial cells, the role of which is crucial in healing the abdominal wall, and exhibited a bactericidal effect against *Staphylococcus aureus* due to the release of Ag^+ ions.

4.4 Fixation of percutaneous catheters

Catheters for peritoneal dialysis are made of highly biocompatible polymers, such as silicone, which is successful in minimizing the foreign body reaction and enhancing the longevity of the device [99]. Typically, a thin fibrous capsule develops around the catheter without a tight adhesion. Therefore, a space between the device and the interposed fibrous layer may exist, which allows bacterial migration from the percutaneous site into the peritoneum with serious consequences for the patient. Polymeric cuffs can be used for anchorage, but they may be susceptible to infections that are difficult to eradicate and can lead to the loss of the catheter. The capability of 45S5 Bioglass® to bond to soft collagenous tissues was the basis of the pioneering work carried out by Marotta *et al.* [100], who patented a technology to produce stable and well-adherent bioactive coatings on silicone catheters by applying a pretreatment in hexane/silicone solution to the outer surface of the polymeric tube. Ross *et al.* [101] implanted segments of 45S5 Bioglass®-coated silicone tubes (length 2.5 cm) in rats, using uncoated tubes as controls. Histological analysis of the tissue-implant interfaces at 2, 4 and 6 post-insertion weeks showed that uncoated tubes had no adherence to the surrounding tissues with a physical separation of about 50 µm, whereas the glass-coated devices were tightly fixed to the soft tissues. Although this early animal study demonstrated that 45S5 Bioglass® coatings enhanced the stabilization of the device, surprisingly no other report has been found in the literature on this topic and the research was apparently discontinued. On the contrary, this research area would deserve careful and intensive investigation in the future to achieve rapid and stable interfacial bonding of catheters and other percutaneous devices for a variety of clinical needs.

5 Conclusions and open challenges

As witnessed by the large amount and variety of studies reviewed in this article, in the last years the range of applications of bioactive glass coatings expanded dramatically beyond the "traditional" bone-bonding ability of orthopedic and dental implants. Glass-based coatings have been successfully applied on 3D porous scaffolds for tissue engineering as well as on devices in contact with soft tissues, such as ocular implants, polymeric meshes for wound dressing and percutaneous catheters. Along with new applications, new deposition techniques, *e.g.* EPD and radio-frequency sputtering, have been experimented to produce well-adherent and long-lasting coatings on a number of non-porous and porous metallic, ceramic and polymeric substrates. Every method has its advantages and limitations, and it is impossible to define universally the "best" processing strategy as this choice strongly depends on the specific nature of the biomedical device to coat and the characteristics of the coating material.

Likewise, it is not easy to compare reliably the performance of different glass coatings applied on non-flat substrates, since very often no standard methods or procedures have been established to characterize bioactive glass coatings deposited on "real" implants. For example, the adhesion strength of the coating to the substrate is a fundamental parameter, but international recommendations exist only for testing flat samples. Therefore, available standards are often modified, adapted or implemented case by case, which makes a direct comparison among the data available in the literature difficult to do.

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Another key issue is the assessment of the long-term stability of bioactive coatings *in vivo*, *i.e.* under "real" working conditions. In fact, it is well known that the human body is a highly reactive environment from chemical and biological viewpoints, and thus studies on long-lasting performance of the coatings are necessary to investigate the response of materials after a long time of implantation; however, there still is a paucity of contributions addressed to this topic in the literature. Investigation of *in vivo* performance of biomedical implants is a long, time-consuming and expensive way that begins with animal studies; it is impressive that, except for few cases (*e.g.* Biovetro®-coated femur stems), the majority of glass-coated implants reviewed in this article have not yet been involved in early human trials and just a single device (45S5 Bioglass®-coated polyethylene orbital implant, Medpor-Plus) has been cleared via the 510(k) process by FDA in 2002 and then marketed worldwide.

In summary, there is interest in fabricating novel bioactive glass and composite coatings that can carry added values to scaffolds and implants, as well as in developing more reliable characterization methods to test and compare the performance of these coatings. The increasing need for biomedical devices to meet the requirements of an ageing population will indeed urge the research in the field of bioactive glass coatings, which will bring further prestige to the long history of glass in medicine.

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