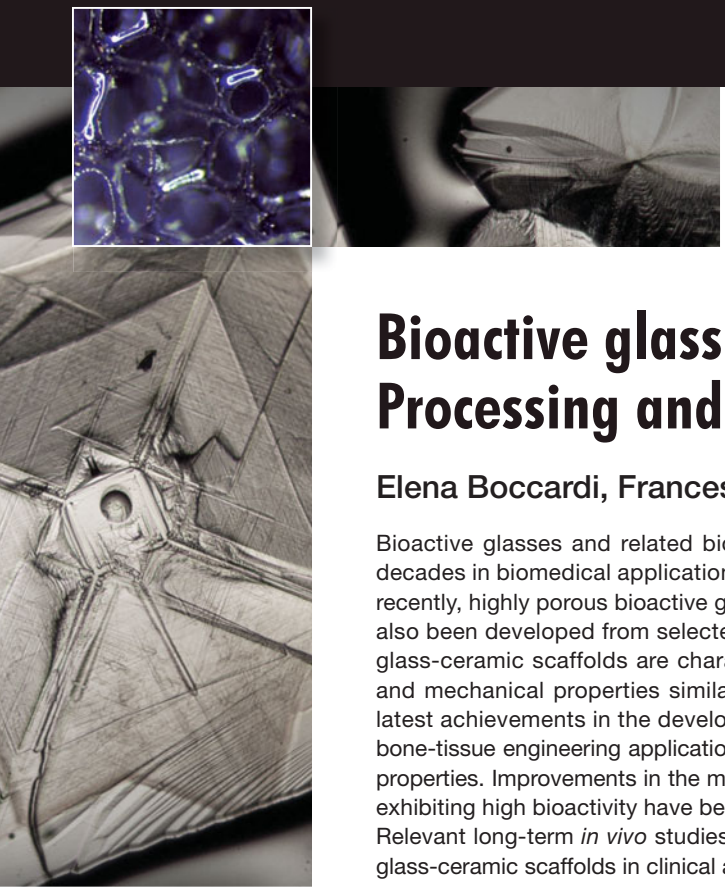


Bioactive glass-ceramic scaffolds: Processing and properties

Elena Boccardi, Francesca E. Ciraldo, and Aldo R. Boccaccini

Bioactive glasses and related bioactive glass-ceramics have been used for over three decades in biomedical applications such as bulk, particulate, or coatings materials. More recently, highly porous bioactive glass-ceramic scaffolds for bone-tissue engineering have also been developed from selected compositions of bioactive glasses. Current bioactive glass-ceramic scaffolds are characterized by an open porous network, high bioactivity, and mechanical properties similar to those of trabecular bone. This article reviews the latest achievements in the development of porous bioactive glass-ceramics intended for bone-tissue engineering applications, highlighting the fabrication technologies and scaffold properties. Improvements in the mechanical properties of bioactive glass-ceramic scaffolds exhibiting high bioactivity have been achieved by different approaches in the last 10 years. Relevant long-term *in vivo* studies are required to confirm the suitability of such bioactive glass-ceramic scaffolds in clinical applications.

Introduction

Glass-ceramics are partially crystallized inorganic materials obtained by controlled heat treatment of the parent glass above its crystallization temperature.[1–3] The resulting glass-ceramics contain one or more crystalline phases embedded in a residual glassy phase.[4,5] In the late 1960s, Hench[6] discovered the first bioactive glass with composition (wt%) $45SiO_2$-24.5CaO-$24.5Na_2O$-$6P_2O_5$, termed 45S5 bioactive glass. This was the first man-made material, which was shown to develop strong bonding to bone upon implantation, providing an alternative to inert materials in orthopedic and bone-replacement applications. Developing bioactive glass-ceramics has been a natural extension of the field of bioactive glasses in order to design bioactive materials with higher mechanical strength, but similar bioactivity to bioactive glass. Bioactive glass-ceramics are usually characterized by superior mechanical properties, including higher elastic modulus, failure strength, and hardness, than bioactive glasses.[3,7] However, the brittleness and low fracture toughness of bioactive glass-ceramics have remained major obstacles for their applications in load-bearing sites.[4,5]

Bioactive glasses and bioactive glass-ceramics elicit specific biological reactions on their surfaces when in contact with the biological environment, which can stimulate cell attachment, proliferation, and differentiation.[8,9] In particular, once in contact with biological fluids, bioactive glasses and bioactive glass-ceramics develop a biological active hydrocarbonate apatite (HCA) layer, which is equivalent to the mineral phase of bone. This layer is essential for the binding of the material to bone.[10,11] Bioactive glasses and bioactive glass-ceramics can also degrade over time, releasing biologically active ions that have positive specific effects on cells (e.g., increase proliferation of human osteoblasts (cells that are able to form new bone matrix), as well as angiogenesis (induction of new blood vessel formation), and antimicrobial and anti-inflammatory effects *in vitro* and *in vivo*).[12] Investigations have started to emerge on the potential of bioactive glasses for the regeneration and repair of soft tissues.[13]

Several review papers are available covering the general field of bioactive glasses and bioactive glass-ceramics.[3,5,8,9,14] An extensive review on bioactive glass-ceramics in monolithic form has recently been published.[5] This article was designed to fill the specific lack of recent review articles concerning porous bioactive glass-ceramics intended for applications in bone-tissue engineering (i.e., scaffolds), discussing the latest achievements in processing methods, microstructure, and properties of such systems.

Current developments in porous bioactive glass-ceramic scaffolds

Tissue-engineering strategies involve the development of biological substitutes capable of inducing the growth of new

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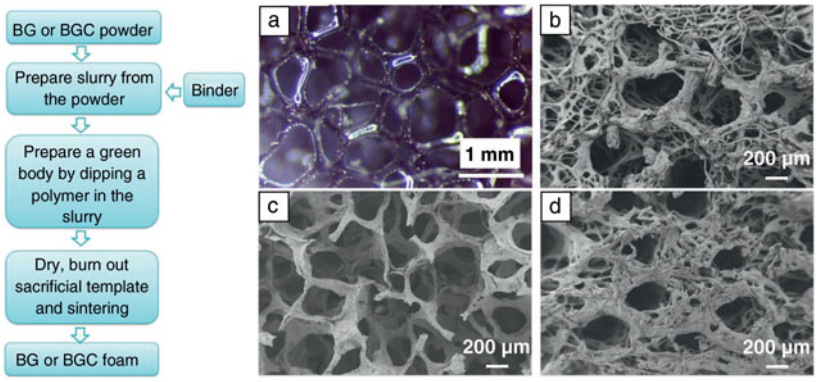


Figure 1. Flowchart for the production of bioactive glass (BG) and bioactive glass-ceramic (BGC) scaffolds via foam replica method.[16,17] (a) Polyurethane foam (45 ppi, [pores per inch]) and (b) natural marine sponge used to produce (c–d) bioactive glass-ceramic scaffolds of crystallized 45S5 ($45SiO_2$-24.5CaO-24.5Na_2O-6P_2O_5, wt%) bioactive glass composition. Micrographs courtesy of Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute of Biomaterials.

tissues.[15] This can be achieved by combining three-dimensional (3D) porous substrates, termed scaffolds, with cells and biological signals (e.g., growth factors).[3,15] The porous 3D scaffold should provide a mechanically stable environment (e.g., compressive strength comparable with that of trabecular bone), which is one of the two bone structures characterized by interconnected porosity and high vascularization, (2–12 MPa); adequate interconnected porosity (>90%); and pore size (150–500 µm) to enable cell adhesion, migration, and proliferation supporting the growth of new tissue.[3] A major current limitation in the field is that most of the available biomaterials are not simultaneously biologically active, mechanically competent, and bioresorbable. Bioactive glass-ceramics are a class of biomaterials that can have all of these attributes. Different bioactive glass-ceramic compositions and fabrication techniques for bioactive glass-ceramic scaffolds have been reported in the literature and these are discussed in this section with a focus on the most recent achievements.

Foam replica method

The foam replica method (FRM) for the fabrication of ceramic foams was patented in 1963.[16] In 2006,[17] the technique was developed for the first time for the fabrication of bioactive glass-ceramic scaffolds based on 45S5 bioactive glass. Scaffolds produced by this technique are a positive replica of an open-cell porous template, which is usually a polyurethane foam (**Figure 1**a). After coating with a bioactive glass or bioactive glass-ceramic slurry, the template is burned out and the bioactive glass is sintered at high temperature, which, in the case of 45S5 bioactive glass, leads to crystallization.[17,18] The resulting 3D structures are characterized by an open and interconnected porous network that mimics the architecture of trabecular bone,[17,19,20] however, it is at the expense of a relatively low compressive strength of the structures.[3] Using this technique, foams with graded porosity can also be obtained.[19]

Baino et al.[21,22] recently developed a hemispheric highly porous bioactive glass-ceramic shell as a trabecular-like coating for the bioceramic acetabular cup (the semispherical component of a hip implant that allows movement inside the joint) in hip-replacement devices that demonstrates the versatility of the FRM. Moreover, the use of different templates, including marine sponges,[23] has been shown to lead to increased mechanical properties, especially the compressive strength, by a reduction of the total porosity of the scaffolds, without affecting the pore interconnectivity (Figure 1b,d).

The bioactivity of crystallized 45S5-based bioactive glass-ceramic scaffolds has been proven,[17] confirming earlier studies[24] that had shown that crystallization of bioactive glass reduces, but does not eliminate, the bioactive character of the 45S5 bioactive glass composition. It is also well known that bioactive glasses and bioactive glass-ceramics can be doped with a variety of metallic ions to enhance their biological activity[12,25] (**Figure 2***).

FRM is also versatile in terms of the type of starting slurry suitable for producing foams. Zhu et al.[26] proposed using a sol-gel synthesis solution to coat the sacrificial template. Cabañas-Polo et al.[27] applied electrophoretic deposition of a sol-gel solution in combination with FRM, accelerating the scaffold production time. Bioactive glass-ceramic scaffolds made by FRM have also been coated with ordered mesoporous silica particles,[28] biodegradable polymers,[29] and polymer microspheres,[30] transforming them in local drug delivery systems. In addition, polymer coatings on bioactive glass-ceramic foams usually lead to enhanced mechanical properties.[29,31,32]

The versatility and simplicity of FRM as well as the high reproducibility of the microstructure of the scaffolds produced explain the popularity of this method. A critical FRM challenge is to produce a uniform coating of the sacrificial template, which can be achieved by using slurries of suitable viscosity; the incomplete removal of excess slurry could lead to the presence of closed pores in the final bioactive glass-ceramic scaffolds, decreasing pore interconnectivity.[33]

Foaming techniques

Highly porous bioactive glass and bioactive glass-ceramic scaffolds can be produced by directly foaming a colloidal sol or a powder suspension, followed by a solidification treatment. The resulting foams exhibit a hierarchical structure with interconnected macropores (ranging from ~20 µm to 1–2 mm).[34] The main challenge is to prevent the foam struts from collapsing,

*Osteogenesis, physiological process that leads to the formation of new bone tissue; osteoclasts, cells that are able to degrade the bone matrix; angiogenesis, physiological process through which new blood vessels form; cementogenesis, physiological process through which cementum, a mineral phase found in teeth, forms.

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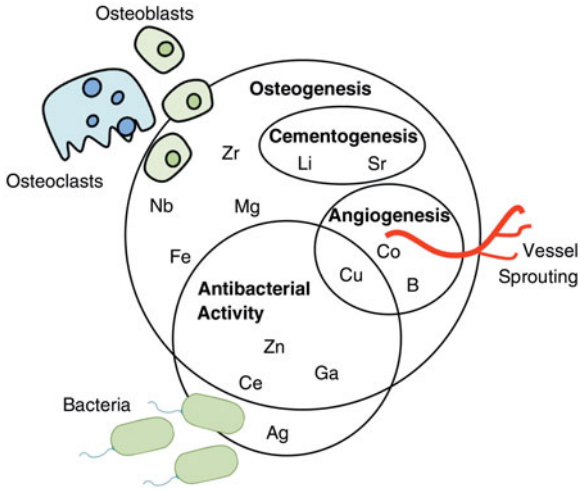


Figure 2. Selected examples of the biologically active ions being investigated to enhance the performance of bioactive glasses and bioactive glass-ceramics.[12,25]

which may result from the loss of the cellular shape of the bubbles. For this reason, a surfactant is used to stabilize the bubbles.

One of the most successful foaming methods is gel casting,[35] in which *in situ* polymerization of monomers can be initiated, forming a 3D polymeric network, a gel, which produces mechanically stable structures.[34] The samples are then sintered to provide mechanical strength. The total porosity and the pore size can be controlled by the surfactant concentration. A further development of this technique is sol-gel foaming.[35] In this method, a sol-gel glass synthesis solution is prepared and a surfactant is added, the foam is generated by vigorous agitation, the sol is transferred to a mold for aging, and finally, the porous body is heat-treated.[35]

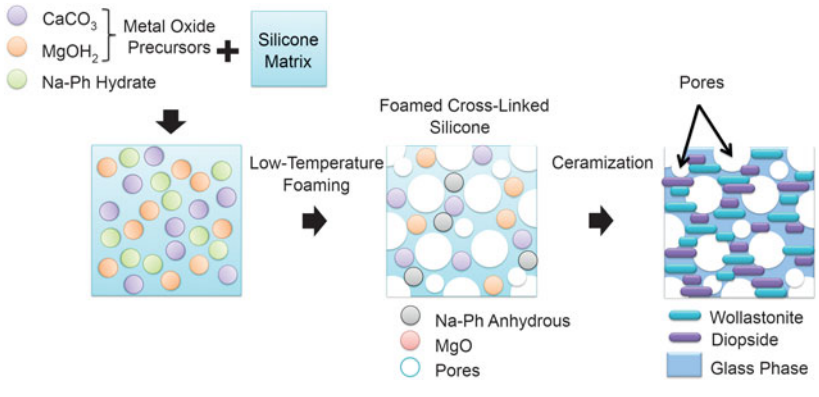


Figure 3. Schematic diagram of the production of wollastonite-diopside ($CaSiO_3$-$CaMgSi_2O_6$) polymer derived glass-ceramic foams, using sodium hydrate phosphate filler (Na-Ph hydrate). The process leads to the fabrication of highly porous glass-ceramic foams by mixing preceramic polymers (e.g., silicone resins that act as a silica precursor) and powdered metal oxide precursors.[38]

A more recent technology developed for bioactive glass-ceramic foams involves the use of polymer-derived ceramics.[36] In this approach, metal oxide precursors in the form of micro- or nano-sized particles are added to a polymeric precursor (e.g., a silicone resin), allowing the production of silicate bioceramics (**Figure 3**). The foaming is obtained by water release from specific hydrated fillers. The foams are then sintered. Fiocco et al.[37,38] showed the possibility of obtaining wollastonite-diopside ($CaSiO_3$-$CaMgSi_2O_6$) foams with 77% porosity and compressive strength of 1.8 ± 0.3 MPa.

The quality of the obtained porous scaffolds can be improved by selecting different silicon precursors (e.g., polysiloxane) and by using CO_2-assisted extrusion. Another approach to produce porous bioactive glass-ceramics involves a powder-metallurgy technique.[39] In this method, bioactive glass powder is dry mixed with a solid polymeric binder and a foaming agent. The mixture is then molded and heat-treated.[40] The resulting scaffolds showed compressive strength values in the range of 5–40 MPa (i.e., in the upper range of values reported so far for this type of porous materials). The scaffolds exhibited highly interconnected pore structure and tunable porosity (55–77%), and they retained satisfactory compressive strength after immersion for one month in simulated body fluid (6 MPa).[41]

The major drawback of this method is that the process could yield a structure with unconnected pores that are essential for bone integration and vascularization.[42] Interconnected porosity is a key property required in bone-tissue engineering scaffolds as it is essential to enhance cell invasion and new tissue growth. In addition, the ability of these scaffolds to promote vascularization has not been yet investigated, as opposed to bioactive glass-ceramics produced by FRM.[43]

Additive manufacturing technologies

Additive manufacturing technology (AMT) is the usual term given to fabrication processes where 3D structures are fabricated layer by layer without any specific tooling to obtain the targeted geometry.[44,45] Of relevance for bone-tissue engineering, these methods allow for the customization the final cellular scaffolds from the patient-specific (bone) defect using a computer-aided design file.[45]

Tesavibul et al.[46] were the first to process 45S5 bioactive glass powder, obtaining porous bioactive glass-ceramic scaffolds with 50% porosity through stereolithography ceramic manufacturing (SLCM). SLCM starts with a layer-by-layer buildup of a photoreactive polymer filled with bioactive glass or bioactive glass-ceramic powders.[45] Gmeiner et al.[47] recently demonstrated the possibility of processing different bioactive glasses and bioactive glass-ceramics by SLCM using raw materials with specific particle sizes (0.16–4.3 μm).[45] They succeeded in reproducing the microstructure of a human femoral bone with a precision

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of micrometers. The authors also reported the possibility to increase the structural strength[45] of these scaffolds by adding artificial support structures (e.g., barrel rings, shifted honeycomb structure). The strength values were increased by a factor of three.[45,47]

Three-dimensional printing has mainly been used for the production of bioactive glass-ceramic composite scaffolds.[48,49] A liquid binder is printed onto a powder bed layer by layer, gluing the powder together in the desired areas until the 3D structure is completely printed.[45] Zocca et al.[50] developed 3D printed Li-aluminosilicate crystallized scaffolds characterized by 60% porosity and 15 MPa maximum compressive strength. More recently, a nonsacrificial preceramic binder (e.g., silicon resin), combined with reactive fillers (e.g., calcium carbonate, $CaCO_3$, and bioactive glasses) was used to produce complex porous wollastonite 3D printed structures.[51] The resin plays a dual role: first, as a binder during the printing process, and second, as a reactive phase to form the desired bioceramic during the thermal treatment. Highly porous (80%) structures exhibiting a compressive strength of 1.0 ± 0.3 MPa were produced.

Lee et al.[52] proposed in early investigations the selective laser sintering (SLS) technique for the development of ceramic porous structures. This technique is analogous to 3D printing, consisting of a free-flowing powder fused by a laser in defined areas.[45,53] Liu et al.[54] showed that the processing of 45S5 bioactive glass by SLS led to the same crystalline phases obtained in conventionally sintered 45S5 bioactive glass, namely combeite ($Na_2Ca_2Si_3O_9$) as the main phase and rhenanite ($NaCaPO_4$) as the secondary phase, which confirms SLS as a suitable alternative method to fabricate this type of scaffold.

The dispense plotting technique, also known as direct ink writing or robocasting, is a method in which a paste-like material is extruded through a nozzle onto a building platform.[55] Eqtesadi et al.[56] fabricated 45S5 bioactive glass-based scaffolds with 60–80% porosity and compressive strength of 2–13 MPa by this technique. Shao et al.[57] reported a study on low-melting-point bioactive glass evaluating the effect of pore morphology on the mechanical properties of the scaffolds (compressive strength of 48 MPa and porosity of 60%). Pierin et al.[58] used the same technique and produced for the first time a porous bioactive glass-ceramic scaffold using an ink made of a pure preceramic polymer ($[CH_3]_{0.96}$ $[OR]_{0.04}$ $SiO_{1.5})_n$ (where the cross-linking groups [OR] are –OH and $–OC_2H_5$) with 64% porosity and compressive strength of 2.5 MPa, which increased to 3.1 MPa with the addition of 0.1 wt% graphene oxide.

While AMTs for bioactive glass-ceramics continue to be developed, novel combinations of bioactive amorphous and crystalline phases are expected, which should enhance the biological activity of the scaffolds without compromising their mechanical stability. However, the main disadvantage of the techniques involving organic inks and resins is the difficulty in removing unprocessed powders trapped in the pores of the scaffolds, which requires optimized heat treatment in each case.[59]

Freeze casting

Freeze casting generally involves freezing a ceramic slurry, inducing the formation of ice crystals along the freezing direction and agglomeration of bioactive glass or bioactive glass-ceramic particles between the crystals.[60] The obtained structure undergoes sublimation to remove the ice. The obtained green body is then thermally treated to consolidate the structure.[61] Similar methods have been used for the production of porous polymeric composite scaffolds containing bioactive glass and bioactive glass-ceramic as the filler.[62,63] Limited work has been reported in the literature on bioactive glass-ceramic scaffolds developed by this method, and the resulting foams are mainly characterized by relatively small pores (≤100 μm).[64,65] Thus, a drawback of this technique is the presence of small pores in the final structure and the long processing time required to produce scaffolds of relevant dimensions.[66]

Table I[67–80] lists a summary of the latest achievements in the field of 3D bioactive glass-ceramic scaffolds, reporting the fabrication techniques used and the main properties of the scaffolds.

Discussion

Bioactive glass-ceramics are partially crystallized inorganic materials obtained by heat treatment of parent bioactive glasses above the crystallization temperature (i.e., the temperature corresponding to the structural change of the glass into a crystalline solid).[1–3,81]

Since the first series of scaffolds based on 45S5 bioactive glass was developed 10 years ago,[17] the high potential for applications of bioactive glasses and bioactive glass-ceramics as 3D scaffolds for bone-tissue engineering has prompted substantial research in the field using melt-derived bioactive glass powders. However, due to their relatively low compressive strength, no clinical applications have been reported for these scaffolds, despite their notable characteristics in terms of osteogenic (formation of boney tissue) and angiogenic (formation of new blood vessels) responses.[3,43,74] FRM is still the most widely used technique for the production of porous bioactive glass-ceramic scaffolds. By modifying the glass composition or choosing alternative sacrificial templates, it is possible to obtain bioactive glass-ceramic scaffolds with compressive strength values comparable to those of human trabecular bone (2–12 MPa). Coating and infiltrating bioactive glass-ceramic scaffolds with biodegradable polymers is also being explored to enhance the resulting mechanical properties.[29,31,32]

Improving foaming techniques is an alternative approach to develop robust bioactive glass-ceramic scaffolds, for example, by using polymeric precursors or by developing powder-metallurgy methods for the production of 45S5-based bioactive glass-ceramic scaffolds with high pore interconnectivity and increased mechanical properties, opening the possibility to machine the obtained foams to required shapes for the intended applications.[41]

More recently, research efforts have increased in the use of AMTs, especially the robocasting method, to produce

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Table I. Summary of the latest achievements in the field of 3D bioactive glass-ceramic scaffolds, including processing method used and main properties obtained. (*Bioactivity test performed without following the proposed standard in References 67 and 68.)

Manufacturing	Material	Porosity (%)	Pore Size (μm)	Compressive Strength (MPa)	HCA Formation (days)
FRM—alternative BG/BGC compositions to 45S5 BG	13–93[69]	85 ± 2	100–500	11 ± 1	7*
	CEL2[70]	64.5 ± 2.0	100–500	5.2 ± 2.0	7*
	SCNA[71]	42–65	200–800	17.8 ± 6.9	
FRM—polymeric coating	Gelatin coated Biosilicate[29]	Non-coated 95	200–500	Non-coated 0.06 ± 0.01	3*
		Coated 93		Coated 0.8 ± 0.05	7*
	Cross-linked gelatin coated $60SiO_2$-30CaO-10MgO mol%[72]	Coated 93	300–600	0.032 ± 0.01	—
	PCL/zein coated 45S5 Bioglass scaffold[73]	>91	300	Non-coated 0.004 ± 0.001	14*
				Coated 0.15 ± 0.02	
				Coated after 28 days in SBF 0.094 ± 0.004	
FRM—specific ion release	Ag-doped 45S5 Bioglass[74]	65	—	0.62 ± 0.04	14*
				After 14 days in SBF 0.50 ± 0.04	
FRM—modified and novel templates	Natural marine sponges based 45S5 Bioglass[75]	68 ± 0.2	215	4.0 ± 0.47	1
		Interconnected >99		After 28 days in SBF 1.2 ± 0.2	
		After 28 days in SBF 80			
	CEL2 glass-based scaffold with different porosity[76]	66–82	—	0.5–6	—
FRM—ordered mesoporous materials coating	SCNA scaffolds coated with SiO_2-P_2O_5-CaO MBG glass[77]	50–80	100	Non-coated 18.4 ± 3.7	2*
				Coated 19.7 ± 5.5	
	45S5 Bioglass scaffolds coated with MCM-41 particles[28]	93	670	—	7 (TRIS)
		Interconnected > 99			
	$70SiO_2$-30CaO mol%[78]	85	200–500	2.26	3*
3D Printing	HA/A-W glass[47]	51 ± 1 (T_{sint} = 1200°C)	500	76.82	1*
	Wollastonite[51]	80	—	1 ± 0.3	—
Robocasting	6P53B[79]	60	500	136 ± 22	—
	45S5 Bioglass[56]	60–80	—	2–13	—
SLCM	45S5 Bioglass[46]	50	500	0.33	—
Foaming	$49.46SiO_2$-36.27CaO-$6.6Na_2O$-$1.07P_2O_5$–$6.6K_2O$ mol%[80]	80	379	2	3
	45S5 Bioglass[42]	68	100–500	12	2
				After 28 days in SBF 6	

Note: HCA, hydrocarbonate apatite; FRM, foam replica method; BG, bioactive glass; BGC, bioactive glass-ceramic; CEL2, $45SiO_2$-26CaO-$15Na_2O$-$3P_2O_5$-$4K_2O$-7MgO mol%; SCNA, $57SiO_2$-34CaO-$6Na_2O$-$3Al_2O_3$ mol%; PCL, polycaprolactone; MBG, mesoporous bioactive glass; MCM, mobil composition of matter; HA/A-W hydroxyapatite/apatite-wollastonite; 6P53B, $52.7SiO_2$, $10.3Na_2O$, $2.8K_2O$, 10.2MgO, 18.0CaO, $6.0P_2O_5$ (wt%); SLCM, stereolithography ceramic manufacturing; SBF, simulated body fluid; TRIS, tris-(hydroxymethyl) aminomethane; T_{sint}, sintering temperature; 45S5, $45SiO_2$-24.5CaO-$24.5Na_2O$-$6P_2O_5$, in wt%.

mechanically competent bioactive glass-ceramic scaffolds.[45,49,56] With these techniques, scaffolds exhibiting high bioactivity and mechanical properties comparable to those of trabecular bone have been produced.

One major issue is the impossibility in directly comparing most of the fabricated scaffolds in terms of their bioactivity. For example, a common procedure to measure bioactivity has not been followed in most of the reviewed studies. Authors refer

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to Kokubo's approach[67] only for the preparation of simulated body fluid ([SBF], a solution with a similar ionic concentration to human blood plasma), but no specific information on the material weight/SBF volume ratio is reported or different SBF exchange protocols have been used. Kokubo et al.[67] established a protocol to evaluate the ability of HCA to form on material surfaces in SBF at a fixed material weight/SBF volume ratio. In fact, higher material weight/SBF volume ratios can induce faster HCA precipitation on scaffold surfaces, providing false positive results.[82]

Incorrect results (e.g., overestimation of bioactivity) are also associated with the high reactivity of some bioactive glass-ceramic compositions, in particular, when they are tested in SBF buffered with tris-(hydroxymethyl) aminomethane.[82] Maçon et al.[83] put forward a protocol for the bioactivity evaluation of bioactive glasses and bioactive glass-ceramics, which is the result of an international round-robin test supported by technical committee 4 (TC04) of the International Commission on Glass. This method should be considered to generate data to compare the bioactivity of bioactive glasses and bioactive glass-ceramics fabricated by different methods.

Conclusions

The available research outputs suggest an improvement in the mechanical properties of bioactive glass-ceramic scaffolds through dedicated research efforts from the last 10 years, opening the possibility for using bioactive glass-ceramic scaffolds in clinical applications. More research is required to compare different bioactive glass-ceramic compositions and to assess the relative merits and drawbacks of the different techniques developed for the production of bioactive glass-ceramic scaffolds. In this context, conducting relevant long-term *in vivo* studies in critical bone defects (nonhealing bone defects related to tumor resectioning or injuries) animal models remains an important future task to start closing the gap between basic research and clinical applications of bioactive glass-ceramic scaffolds.

Looking into the future, it can be stated that the main advantage of bioactive glass-ceramic scaffolds, compared to the already available bioactive glass-ceramic bulk or particulates, is the possibility to develop a patient-specific 3D structure that can fill bone defects while also supporting cell attachment, cell ingrowth, and regeneration of the damaged tissue with progressive degradation of the implanted porous scaffold. As reviewed in this article, novel bioactive glass-ceramic scaffolds with required mechanical properties and suitable interconnected porosity are now available due to the development of novel techniques and improvements in existing ones, opening for the first time the possibility of applications of bioactive glass-ceramic scaffolds in the clinic.

Future developments should consider enhancing the biological activity of the scaffolds by designing bioactive glass compositions with multifunctional bioactivity and therapeutic ion-release function (e.g., with antibacterial, osteogenic, and angiogenic properties),[12] which could lead to scaffolds with high regenerative capability without the need for cost-intensive and complex recombinant proteins or growth factors.

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