Bioactive Glasses: Advancing from Micro to Nano and Its Potential Application

Mengchao Shi, Jiang Chang and Chengtie Wu

Abstract Bioactive glasses or bioglasses in short (please consult the Editor's note in order to clarify the usage of the terms bioglass, bioactive glass and biocompatible glasses) have attracted much attention in application for bone regeneration since 1970s. With the development of the preparation strategies from conventional quenching to modified sol–gel methods, bioglasses of different structures and varied compositions have been reported as their physicochemical and biological properties being well-studied. Mesoporous bioglasses, which possessed unique mesopore channels for drug delivery, has become a hotspot in the last decade. In this chapter, the fabrication of bioglasses including porous scaffolds, coatings, fibers and particles especially the development of its nanoscale form, and several bioglasses involved composite materials are discussed. Recent studies on therapeutic ion substitution (e.g. Sr, Co) of bioglasses and their biological properties both in vivo and in vitro are mentioned. The potential application of bioglasses in different forms for the hard tissue engineering (e.g. dental implantation, bone regeneration), and some recent reports on soft tissue engineering (e.g. would healing) are also referred to. As one of the most promising candidate for bone/soft tissue regeneration application, both the great chances and challenges, and the potential direction of bioglasses for its development are summarized.

M. Shi · J. Chang (✉) · C. Wu (✉)
State Key Laboratory of High Performance Ceramics and Superfine Microstructure, Shanghai Institute of Ceramics, Chinese Academy of Sciences, Shanghai 200050, People's Republic of China
e-mail: jchang@mail.sic.ac.cn

C. Wu
e-mail: chengtiewu@mail.sic.ac.cn

J. Marchi (ed.), *Biocompatible Glasses*, Advanced Structured Materials 53,
DOI 10.1007/978-3-319-44249-5_6

1 Introduction

1.1 Origin of Conventional Bioactive Glasses (BG)

Invented by Professor Larry Hench at the University of Florida in 1969, bioglasses (later termed 45S5 Bioglass®) were the first man-made biomaterials that can bond closely with the host bone tissue. The "grandfather" composition (46.1 mol% SiO_2, 24.4 mol%, Na_2O, 26.9% mol% CaO and 2.6 mol% P_2O_5) of Bioglass® made it possible to form a strong bond with bone which could not be removed unless breaking the bone [1, 2]. This launched the field of bioactive ceramics, including variation of 45S5 Bioglass, glass-ceramics, hydroxyapatite, calcium phosphates and so on. It has also been the milestone of the third-generation of biomedical materials, or the bioactive material, which was defined as to stimulate a beneficial response from the body, particularly bonding to host tissue [3]. In the past 45 years, bioglasses, taking 45S5 as a golden standard, with its generally excellent bioactivity, osteoconductivity, osteostimulation and potential to enhance angiogenesis, have been widely studied by researchers and applied as bone filling materials and bioactive coatings for dentistry, orthopedics and small bone implants in hard/soft tissue regeneration application [4, 5].

The mechanism behind new bone formation on bioglasses is attributed to a hydroxycarbonate apatite (HCA) layer on the surface, which is associated with the release of Na and Ca ions [6, 7]. The HCA is similar to bone mineral and could interact with collagen fibrils to integrate with the host bone. Further studies have revealed that the dissolution products, including Ca and Si ions from 45S5 could stimulate osteoblast proliferation and differentiation [8].

Apart from the silicate based bioglasses borate based bioglasses were developed in 1990 by replacing partial silica with boron to gain more desirable bioactivity [9]. The glasses possess lower chemical durability and could convert more rapidly and thoroughly to apatite. The sintering behavior is more controlled than 45S5 Bioglass®. As a trace element required for bone health, the biosafety of boron is concentration dependent and the excessive amount could be toxicity [10, 11]. Potential application of borate glasses and the composites have recently been reported in some literatures [12, 13]. Another bioglass is phosphate based glasses that proposed in 1980 [14]. With P_2O_5 being the network former oxide, the asymmetric structure of P–O–P bonds hydrated easily and lead to the good biodegradability. It has been studied as controlled release vehicles of antibacterial ions including zinc, gallium, silver and copper in recent years [4]. In this chapter, we mainly focused on the most widely investigated silicate based bioglasses, from the conventional 45S5 Bioglass® prepared by melting quenching approach to the developed ones synthesized by the chemistry-based sol–gel methods.

45S5 Bioglass® was first synthesized by mixing all the powder containing silicon, calcium, sodium salts/oxides and phosphate and melting them at high temperature (1300–1500 °C). It is essential for the temperature to be at the sintering window (the temperature difference between T_g and $T_{c,\ onset}$) [9, 15, 16]. Being

effected by the particle sizes, structure of silica network and the whole composition, the sintering window is too small to avoid crystallization, which could have negative impact on the bioactivity of bioglasses. Bioglasses cannot induce the HCA layer formation if the content of SiO_2 exceeds 60 % since the network is too stable to release Na or Ca, leading to insufficient OH groups on the glass surface. Besides, another disadvantage is the lack of microporous structure and low specific surface area of melt glasses, let alone the high energy consuming during the sintering process [17, 18]. Later after that, a new approach named sol–gel method was applied in bioglasses preparation, through which larger surface area, porosity, higher SiO_2 content and varied compositions could be attained. Details will be discussed in Sect. 1.2.

1.2 Development of Mesoporous Bioactive Glasses (MBG)

In 1990s, the discovery of ordered mesoporous silica sieves known as MCM41 by Mobil Oil Company launched the field of unique mesoporous materials [19]. The material possesses higher surface area, tunable pore volume and size, possibility of surface modification and has been widely studied the field of catalysis, adsorption/separation, electronics and biomedical applications [20, 21]. Years after that, studies on mesoporous materials were expended into the bone regeneration since the investigation of in vitro apatite formation found that HCA layers could be deposited on the surfaces of several types of mesoporous materials (e.g. phosphorous-doped MCM-41, SBA-15) [22]. Interestingly, the mesoporous silica materials present a similar chemical surface to bioglasses, which may led to its application as bone regenerators. However, scientists have noticed that the compared with pure silica content, bioglasses with a combined composition of SiO_2–CaO–P_2O_5 showed more active apatite formation ability [23, 24]. It is of great interests to introduce mesoporous structure to bioactive glasses to improve the bioactivity.

Meanwhile, problems such as bacterial infection in bone reconstruction process have caused great pain of patients. Conventional treatments including systemic antibiotic administration, surgical debridement and wound drainage are not always efficient, which may lead to extra surgeries. One of the best solution is to introduce a proper local drug release system into the implant site [25, 26]. Under this circumstance, the in situ introduction of mesoporous structure, which could endow the bioactive glasses with drug/growth factor loading capacity stood out as a wise candidate. Apart from the antibacterial drugs, growth factors enhancing the osteogenesis and angiogenesis could also be delivered [27, 28]. In the year 2004, mesoporous bioactive glass (MBG) was first synthesized by Yan et al. using non-ionic block copolymers as template via the evaporation-induced self-assembly process [29]. The prepared MBG possessed highly ordered mesoporous channels and large specific surface area, pore volume and pore size (351 $m^2\ g^{-1}$, 0.49 $cm^3\ g^{-1}$ and 4.6 nm by BET, respectively), showing a significant improvement

compared to BG with some composition. The mineralization property of MBG tested in simulated body fluid (SBF) was also greatly enhanced. After that, different types of MBG such as particles, fibers and scaffolds were synthesized.

2 Preparation and Properties of Different Forms of Bioactive Glasses

2.1 Synthesis of Bioglasses: From Melt Quenching to Sol–Gel Methods

Conventional route to prepare bioglasses is the well-known melt quenching method, which was similar to the preparation of glasses. Typically, stoichiometric amounts of different constituent oxides or carbonates of high purity are mixed by ball mill and the obtained powders are sintered at high temperature (1300–1500 °C) [30] depending on the varied compositions (Fig. 1). However, it is worth noting that bioglasses containing less than 10 % alkali oxide are difficult to melt due to the high viscosities, while their silica contents exceeding 60 % could fail the formation of HCA layers, thus the effective bond to host bone [9].

Despite the excellent bioactivity of bioglasses, the narrow compositions with regulatory approval as particulate synthetic bone filling/grafting materials are not suitable to be fabricated into fibers, coatings or scaffolds [31]. In order to obtain bioglasses with adjustable compositions with higher silica content, the sol–gel methods, which could be manipulated at room temperature, become a popular approach to prepare bioglasses [32]. Typical process of this chemistry-based synthesis route is as follows: the compositional precursors are mixed in a solution, and then the precursors undergo a polymer-type reaction to form a gel, in which a wet inorganic network of covalently bonded silica is generated. The gel is then dried

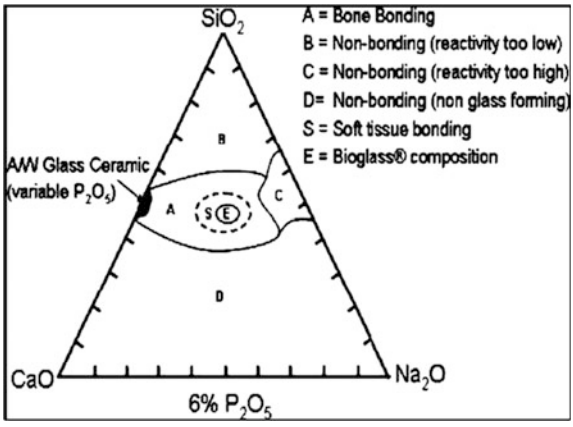

Fig. 1 Ternary compositional diagram given for 45 % SiO_2-24.5 % Na_2O-24.5 % CaO-6 % P_2O_5 (wt%) glass by Hench for bone-bonding [30]

Table 1 Compositions of several bioactive glasses [6]

Compositions (wt%)	45S5	13-93	13-93B1	13-93B3	6P53B	58S	70S30C
Na_2O	24.5	6.0	5.8	5.5	10.3	0	0
K_2O	0	12.0	11.7	11.1	2.8	0	0
MgO	0	5.0	4.9	4.6	10.2	0	0
CaO	24.5	20.0	19.5	18.5	18.0	32.6	28.6
SiO_2	45.0	53.0	34.4	0	52.7	58.2	71.4
P_2O_5	6.0	4.0	3.8	3.7	6.0	9.2	0
B_2O_3	0	0	19.9	56.6	0	0	0

and heated to 550–650 °C to become a glass [33]. Compared to the dense melt-quenching glasses with similar compositions, bioglasses prepared by this approach possess an inherent nanoporosity that can result in increased specific surface area, larger pore volume, thus the higher dissolution rates and improved cellular response. Moreover, the improved concentration of silanol groups (Si–OH) on the surface tend to induce better bioactive behaviors [34]. As the role of Na_2O in melt- quenched bioglasses is to lower the melting point and improve the process-ability, which is useless in sol–gel methods, the sol–gel glasses tend to have fewer components than the conventional ones. Various compositions of bioglasses (e.g. 58S SiO_2 58.2 wt%, CaO 32.6 wt%, P_2O_5 9.2 wt%) are shown in Table 1 [6].

In order to prepare bioglasses with mesoporous structures, surfactants including cationic surfactant (e.g. CTAB) and nonionic block copolymer (e.g. P123) are added into the precursors to act as structure-directing agents. Mesopores can be formed by calcination at a relatively low temperature (<700 °C) to remove the surfactant [35].

2.2 Fabrication of Bioglasses: From Micro to Nano

2.2.1 Bioglasses Particulates for Clinical Use

Being the second most commonly transplanted tissues in body, bone plays an essential role in health. Bone defects caused by trauma, diseases such as osteo-porosis or tumour removal, especially those large ones beyond the self-healing ability of human, can only be regenerated by grafts. With the limitation of auto-grafts and the underlying risks of allografts, the demand for bioactive bone repair materials has become an emergency [36–38]. It is exactly the original and most important application for bioglasses. First synthesized in 1969 and used in clinical trials, bioglasses were used in the form of particles or granules since they can be pressed easily into a defect. The granules have a size range of 90–710 μm. They were used to save tooth in the root or to repair bone in the jaw. Figure 2 showed a typical image of the bioglass product calle Novabone [31].

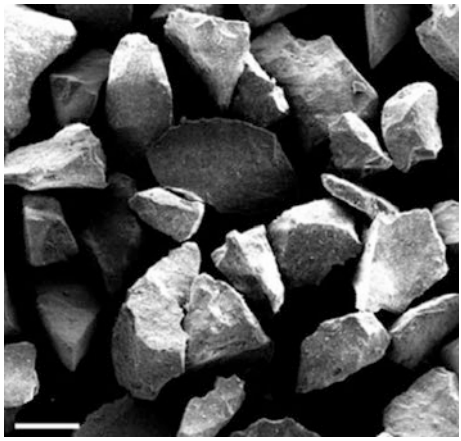

Fig. 2 SEM image of the bioglass particles for clinical use. *Scale bar* is 200 μm [31]

2.2.2 Bioglasses Scaffolds for Bone Regeneration

While the particulates of several to hundreds of micrometers were used in defect filling to help the bone/teeth repair in orthopedic/oral operations, the concept of bone regeneration put forward the use of porous scaffolds to guide bone repair, mimicking the natural bone (Fig. 3). It is proposed that the scaffolds should not only provide the mechanical support at the defect site, but also allow the cells (e.g. bone marrow stem cells) to attach, proliferate and differentiate, stimulate them to form new bone, and, offer space for the neovascularization [39, 40]. Moreover, the scaffolds should be degradable to let the new bone remodel naturally.

Scaffolds formed by bioglasses particulates undergoes a thermally bond of loose packing of particles/short fibers in a designed geometry. But the low porosity of 40–50 % and the insufficient interconnection of the porous structure occurred as the main disadvantages [6].On an early stage, fugitive phase (e.g. NaCl, starch), which could be removed by dissolution or decomposition before sintering, was introduced in the forming of scaffolds (Fig. 4). However, the problem of connectivity still remained.

Later after that polymer foam was used to serve as template for microstructure. The porosity of silicate, borosilicate and borate bioglass scaffolds was increased to the range 60–90 % by the methods [39, 40]. The solution/suspension freezing approach has also been carried out in a controlled manner to make bioglass scaffolds with oriented microstructure. Compared to the randomly oriented ones, mechanical strength of these scaffolds were significantly improved. By varying the composition and mixture of the suspensions, the pore diameter and structure could be adjusted. For instance, scaffolds of bioglass (13-93) showed pore diameters of 100–150 μm (Fig. 4d, e).

The developing technology of three dimensional (3D) printing, the rapid prototyping methods, or the solid freeform fabrication (SFF) have brought new options for scaffolds preparation [41–43]. Both the external shape and internal structure

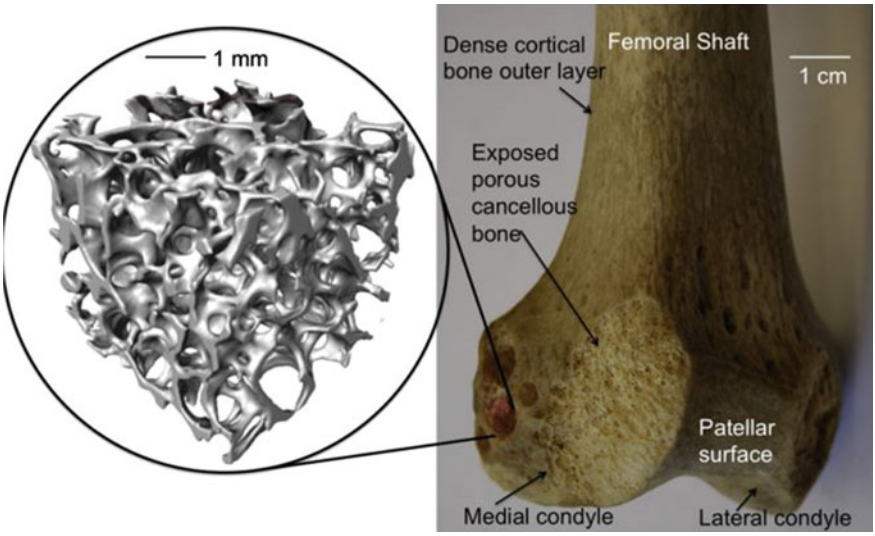

Fig. 3 Photograph of a human femur with a core-drilled piece removed. *Inset* X-ray microtomography (micro-CT) image of the cancellous bone removed from the femur proximal to the knee joint [31]

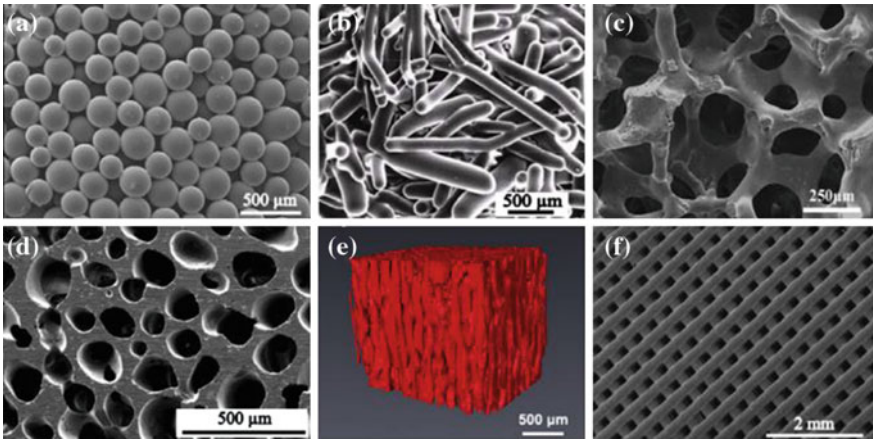

Fig. 4 Microstructures of bioglass scaffolds created by a variety of processing methods: **a** thermal bonding (sintering) of particles (microspheres); **b** thermal bonding of short fibers; **c** "trabecular" microstructure prepared by a polymer foam replication technique; **d** oriented microstructure prepared by unidirectional freezing of suspensions (plane perpendicular to the orientation direction); **e** X-ray micro-CT image of the oriented scaffold shown in (**d**); **f** grid-like microstructure prepared by robocasting. Glass composition: **a** 16CaO-21Li_2O-63B_2O_3; **b**–**e** 13-93; **f** 6P53B [31]

could be defined by controlling the pore size and distribution. A typical process of 3D printing involve the building of objects layer by layer form a computer-generated model with the assistance of proper software (e.g. CAD). Binder (e.g. polyvinylalcohol, PVA) were mixed with the sieved bioglasses powders to get the paste-like suspension for printing. A narrow-diameter syringe or nozzle was used to print the suspension onto a substrate with a robotic deposition device. The formed scaffolds were then transferred to a muffle furnace and heated slowly to remove the binder or further bond the powders. By controlling the geometric and interconnected structure of scaffolds, the mechanical properties could also be manipulated. As shown in Fig. 5, a 3-D printed MBG scaffolds under mild conditions using PVA as a binder possessed 200 times higher compressive strength than the PS-templated ones while maintaining the apatite-formation ability and drug delivery property [44].

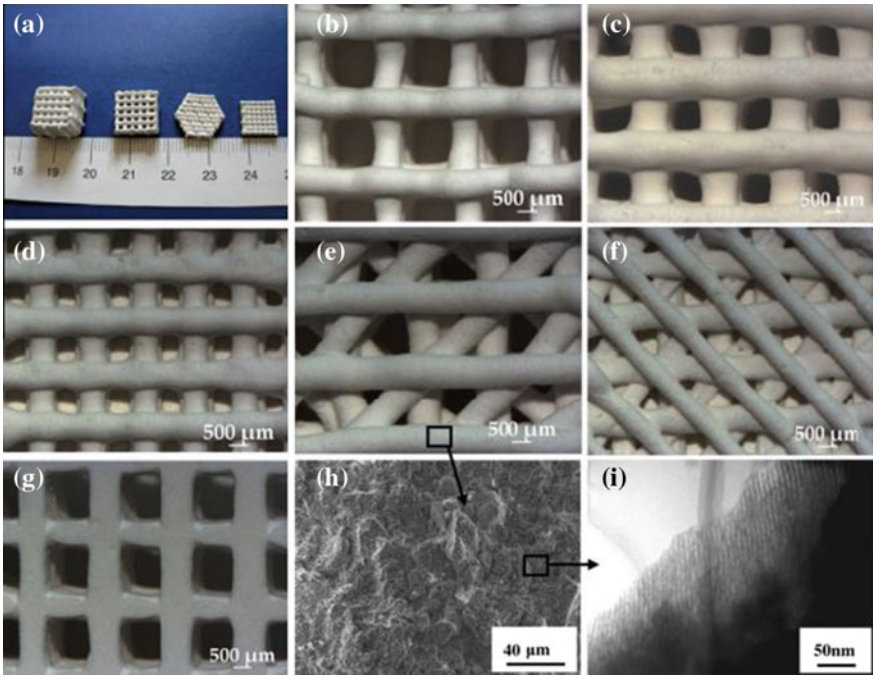

Fig. 5 Pore morphology and microstructure of MBG scaffolds. **a** MBG scaffolds produced by 3-D printing of different sizes, shapes and morphologies. **b–d** MBG scaffolds with different pore sizes varying from **b** 1307 ± 40, to **c** 1001 ± 48, to **d** 624 ± 40 µm. **d–f** MBG scaffolds with different pore morphologies. **g** Pore morphology of the bottom side of the MBG scaffolds. The pores on the bottom side remain open. **h** SEM image of the microstructure of pore walls. **i** TEM micrographs demonstrating the well-ordered mesopore channel structure of the pore walls in the scaffolds. The size of the mesopore channel is about 5 nm. The 3-D printed scaffolds obtained have controllable large pores (from several hundred micrometers to more than a millimeter) for cell seeding and tissue in-growth and nanopores (5 nm) suitable for drug loading and delivery [44]

Sol–gel process is also involved in porous scaffolds preparation. With tolerance of wider range of bioglass compositions, scaffolds as 58S (60 mol% SiO_2, 36 mol% CaO, 4 mol%. P_2O_5) could be fabricated. The whole process includes the hydrolysis, polymerization, gelation, drying and dehydration. A conventional acid-catalysed preparation of sol initiates the formation of the silica network [45, 46]. Nanoparticles of silica form and coalesce before the formation of Si–O–Si bonds between them. The gelation time could be accelerated from days to minutes by adding hydrofluoric acid (HF) in the system. Proper surfactant is then added by vigorous agitation. The surfactant-involved process produces interconnected macropores and maintain the inherent nanoporous texture [47]. To obtain ordered mesopores by this method at the same time, nonionic block copolymer (P123) and polyurethane sponges as co-template are usually applied in the system. Figure 6 shows the macroporous structure with ordered mesoporous channels on the scaffolds [48].

2.2.3 Bioglasses Coatings

Despite the excellent bioactivity and controllable biodegradability of bioglasses, the inherent brittleness of scaffolds fully constituted by bioglasses severely affected its further application. While biomaterials such as magnesium and its alloys, which possessed good mechanical properties, have the problems as high reactivity and insufficient corrosion resistance in physiological fluids [49]. It is a wise choice to coat suitable inorganic/organic materials on the surface of these implants. Distinct modification of the surface could not only break the limitations as corrosion, but also improve the biological properties and lead to better bone-to-implant interfaces [50]. Therefore, the distinguished osteoconductivity of bioglasses, especially the large surface area and pore volume of mesoporous bioglasses that could load and

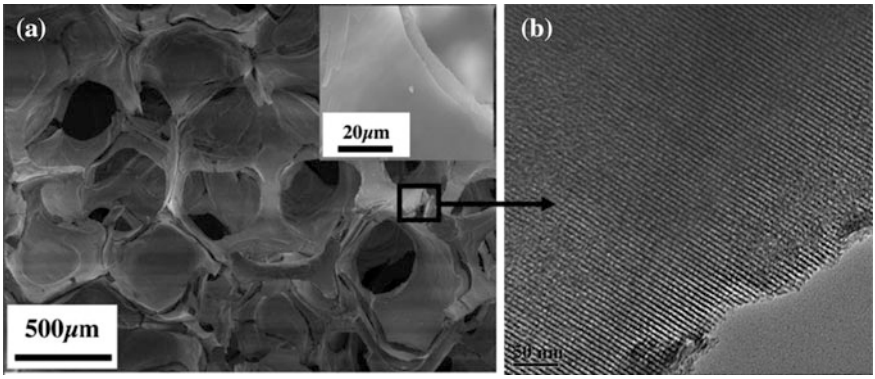

Fig. 6 SEM **a** image of macroporous structure and TEM **b** image of ordered-mesopore channels on MBG scaffolds [48]

release drugs make it an outstanding option. With the aid of heat treatment, spinning coating, electrophoretic deposition (EPD) or simply immersing in sol–gel solution of bioglasses, a coating with adjustable thickness could be acquired [51]. Typical SEM images of bioglasses coating on surface of Mg substrate is shown in Fig. 7. The thickness of both coatings were similar at around 1.5 μm while the MBG coating was observed crack free [52]. Apart from modification of metallic substrate, bioglasses are also used on the surface of glass-ceramic scaffolds [53] and Ti–6Al–4V substrate [54].

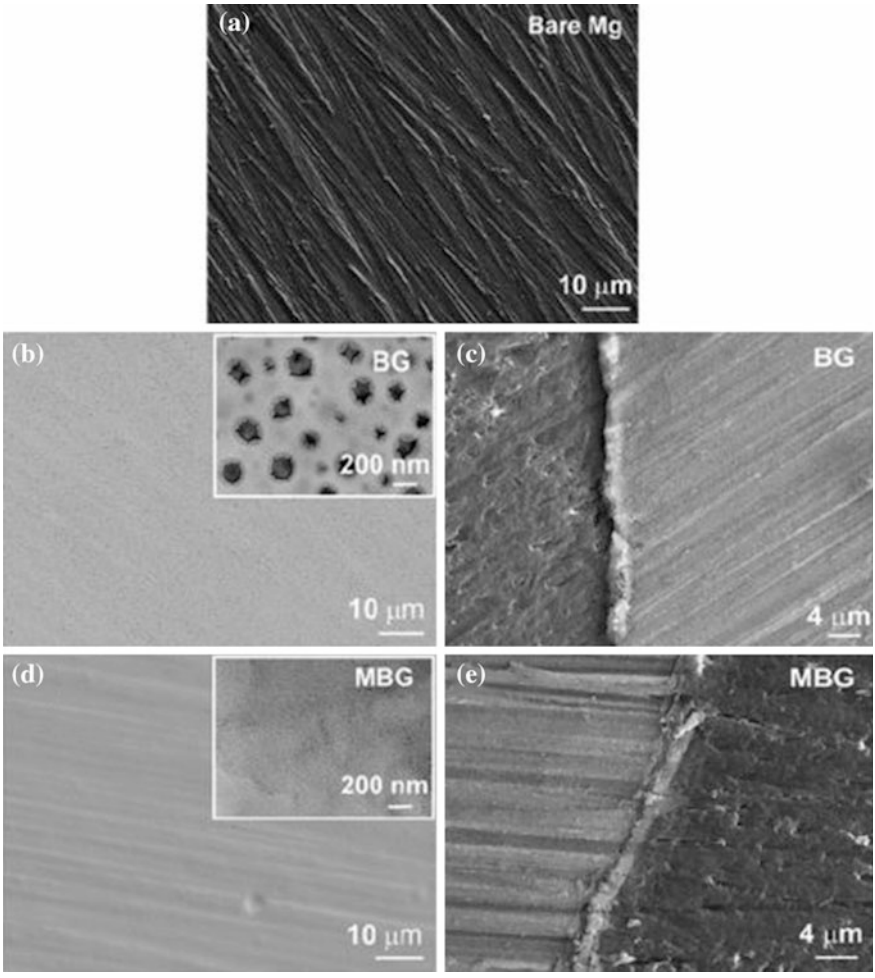

Fig. 7 Surface morphology of **a** the uncoated Mg, **b** the BG coated Mg substrate, *inset* is enlarged view of (**b**), **c** cross-section of the BG coated Mg substrate, **d** the MBG coated Mg substrate, *inset* is the enlarged view of (**d**), and **e** cross-section of the MBG coated Mg substrate [52]

2.2.4 Bioglasses Fibers

Fabricated matrix composed of fibers can mimic the three-dimensional structure of natural extracellular matrix and it is of high possibility to enhance the cellular responses [55, 56]. In the past decades, along with the development of various compositions of bioglasses by sol–gel methods, many studies on bioglasses fibers fabrication have been conducted. The most widely used technique is electrospinning, of which an electric field that sends fine streams of solution to a collector was used. In most cases, some polymer will be added and the diameter of fibers could be controlled by varying the viscosity of solution and the value of voltage. Glass fiber meshes are gained after burning out the polymer during stabilization. Fibers with a diameter from hundreds of nanometers to tens of micrometers could be obtained [57]. Figure 8 shows fibers with a highly ordered, two-dimensional hexagonal structure. Bioglass 45S5 fibers could also be produced by a novel laser spinning approach [58]. A small pool of molten bioglasses was created using a high-velocity gas jet from a supersonic nozzle. The fibers possess a rapid degradation rate in SBF

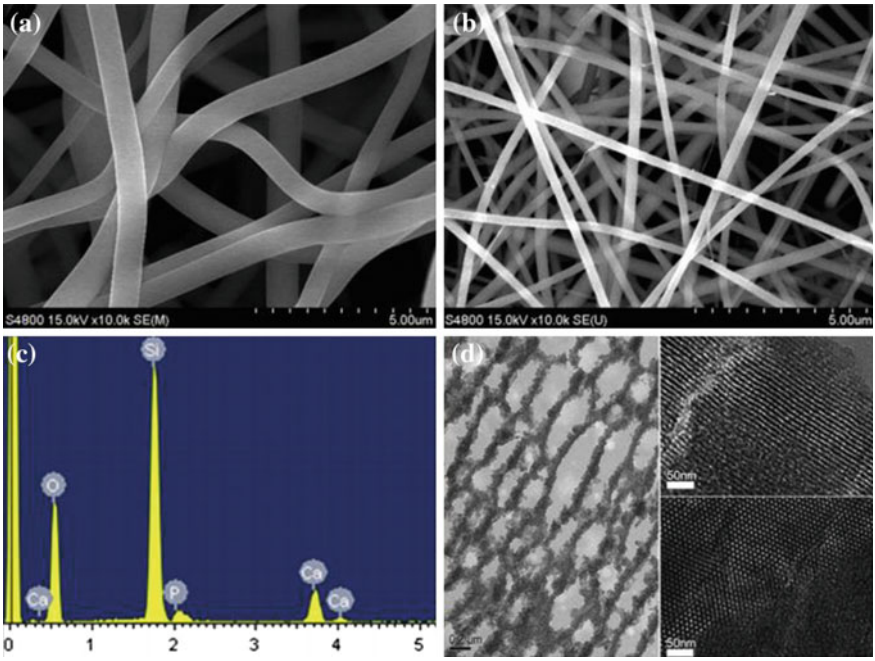

Fig. 8 SEM images of mesoporous bioactive glass nanofiber (MBGNF) matrices **a** after electrospinning and **b** after heat treatment at 600 °C. **c** SEM-EDS pattern of calcined MBGNFs and **d** TEM micrograph of ultramicrotomed MBGNFs embedded in resin. The MBGNF matrix showed characteristics typical of highly ordered, one-dimensional channels in a hexagonally packed mesostructure. *Left* nanofibrous structure. *Bottom right* highly ordered, two-dimensional hexagonal structure. *Top right* long, one-dimensional channels. *Left* magnification of 50 k, *scale bar* 0.2 mm. *Right* magnification of 250 k, *scale bar* 50 nm [57]

owning to its small diameters and highly bioactive composition. Besides the pure bioglass fibers, those composite ones with certain polymer are prepared in some recent studies. Details of them will be discussed in Sect. 2.4.

2.2.5 Bioglasses Nanoparticles

Nanostructured biomaterials are playing an important role in bone regeneration due to their unique nanostructure and functions [59, 60]. Although microparticles of bioglasses (diameter 1–1000 μm) have been investigated for many years, the preparation and application of nanoparticles (10–1000 nm) have only been looked into in the past decade [61, 62]. Nanoparticles possess specific advantages as follows: firstly, they can be directly endocytosed to affect the cellular behavior; secondly, rapid clearance by phagocytes can be avoided due to their inherent small size; thirdly, nanoparticles with porous channels can serve as drug delivery system in situ and work as therapeutic agent [63, 64]. Finally, they can be used as building blocks for bottom-up preparation of injectable gels and composite scaffolds.

Similar to the preparation of mesoporous silica nanoparticles, supramolecular chemistry and sol–gel process with proper structure-directing agents (CTAB, F127, P123, etc.) and hydrolysis catalyst (acid or alkali) were applied in the synthesis of MBG nanoparticles. Under proper synthesis conditions such as hydrothermal treatment, the template molecular self-organized to micelles which then linked with the silicate precursors, hydrolysed and assembled to form ordered mesoporous structure. High surface area and porosity were obtained after the removal of the template. MBG particles ranging from hundred nanometers to a few micrometers were prepared in the past 20 years. Via a facile hydrothermal method using CTAB and PVP as co-templates with an original molar ration of Ca/P/Si being 15/5/80, MBG nanospheres (size of 50–100 nm), which possessed typical mesoporous channels inside the particles, was successfully synthesized (Fig. 9). Excellent apatite-mineralization ability and high loading efficiency of anti-cancer drug was

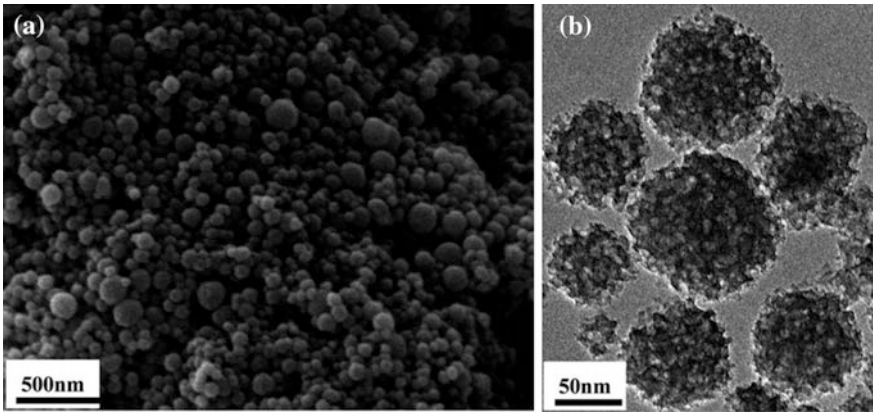

Fig. 9 SEM (**a**) and TEM (**b**) images of MBG nanoparticles [65]

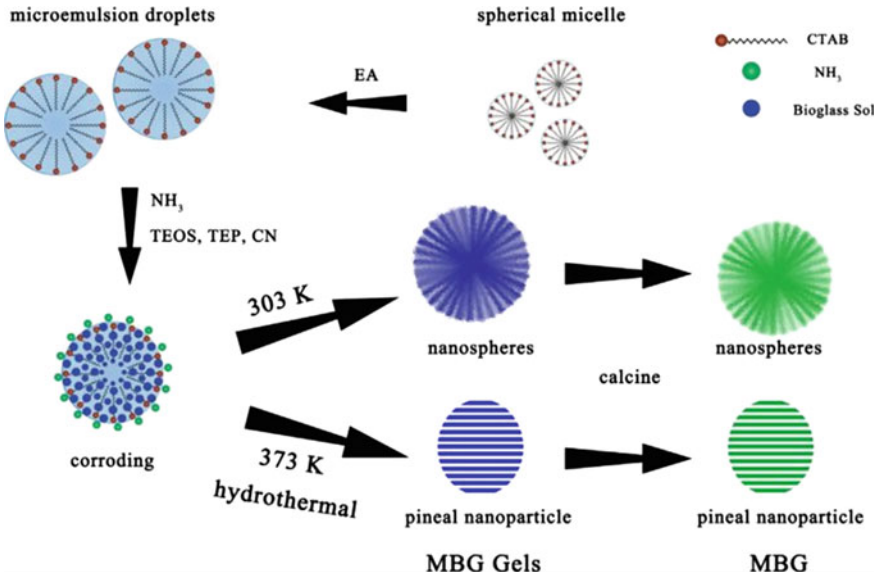

Fig. 10 Schematic illustration of the formation of MBG particles [66]

shown by the MBG nanospheres while the release behavior could be controlled by varying the pH microenvironment [65].

As illustrated in a latest report (Fig. 10), CTAB micelle self-assembled with the hydrophobic molecule ethyl acetate in water to form oil/water micro-emulsion droplets which served as template [66]. The bioglass sol then hydrolyzed and condensed at the interface by ammonia molecules. Under different temperature and pressure conditions, the size and shape of nanoparticles were obtained (Fig. 11).

2.3 Ion Substitution of Bioglasses

As mentioned above, bioglasses based on SiO_2–CaO–P_2O_5 system are beneficial for repair and replacement of bone tissue defects. The essential HCA layer on its surface forms as a result of a sequence of chemical reactions in the body fluid [7, 67]. It is proposed that three main stages are involved in the HCA formation [1, 68].

Stage 1. Rapid exchange of Na^+ and Ca^{2+} with H_3O^+ from the fluid, resulting in the hydrolysis of the silica groups and formation of silanols (Si–OH). With the consumption of H^+, the pH of the solution increased.

$$\mathrm{Si{-}O{-}Na^+ + H^+ + OH^- \rightarrow Si{-}OH^+ + Na^+(aq) + OH^-}$$

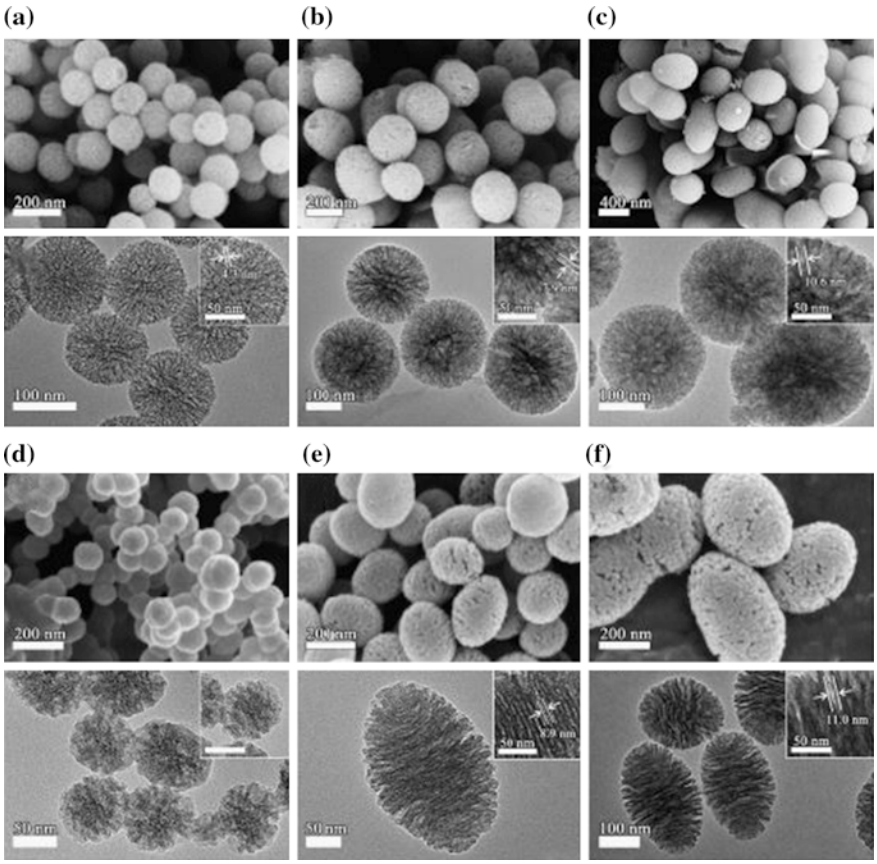

Fig. 11 Morphology of MBG particles prepared in different concentrations of the aqueous ammonia (1 mol L^{-1} for **a** and **d**, 3 mol L^{-1} for **b** and **e**, 5 mol L^{-1} for **c** and **f**), under different temperature (303 K for **a**–**c**, 373 K for **d**–**f**) [66]

Stage 2. The increasing concentration of hydroxyl in solution leads to the attack of silica glass network. The breaking Si–O–Si bonds and forming silanol groups at the interface result in the increasing Si $(OH)_4$ (dissolved silica) to the solution.

$$\mathrm{Si{-}O{-}Si} + \mathrm{H_2O} \rightarrow \mathrm{Si{-}OH} + \mathrm{HO{-}Si}$$

Stage 3. The condensation and repolymerization of the silanol groups on the surface leads to a silica-rich layer, after which Ca^{2+} and PO_4^{3+} groups migrate to the surface to form a $CaO–P_2O_5$ rich film on top. Then with the incorporation of OH^- and CO_3^{2-} anions from the solution, the $CaO–P_2O_5$ film crystallizes to make a mixed carbonated hydroxyl apatite HCA layer.

However, a major disadvantage is the high solubility of bioglasses. Resulting from the low fracture toughness, most of the released ions might be transported away from the surrounding of the implantation site by body fluid before new bone formation [46, 69, 70]. Moreover, with the advanced studies on cellular response, approaches to prevent bacterial infection with different therapeutic ions (mostly trace element of human being), the original composition of Ca, Si and P seems insufficient for the biomedical applications [71]. The trend of incorporation of various elements into bioglasses to modulate their physical, chemical and biological properties has become a hot spot in the last two decades [4].

In order to incorporate foreign ions in bioglasses, mostly by the sol–gel method, the structure-directing agent (e.g. P123) is firstly dissolved in ethanol solution and then certain ionic salts together with the basic compositions of bioglasses are all dissolved in the system. After an evaporation-induced self-assembly process and completely drying of the samples, calcination process should be conducted to remove P123 and obtain the therapeutic ion-doped bioglasses materials [72, 73]. The ion release kinetics could be modulated by tailoring the content of several precursors. Significant stimulation on anti-bacterial activity, osteogenesis, angiogenesis and cementogenesis is obtained by the ion substituted bioglasses.

Strontium (Sr) ions have been reported to inhibit osteoclast activity, therefore be beneficial for patients suffering from osteoporosis [74]. The amount of Sr in the skeleton is 0.335 % [75] of Calcium (Ca) content, its biological feature relating to the chemical correspondence to Ca. A high concentration of Sr can accumulate in bone and displace Ca in hard tissue metabolic process. 5 wt% Sr substituted sol–gel bioglasses have showed positive effect on fetal mouse calvarial bone cells [76]. Lithium (Li+) has been widely used as a long-term mood stabilizer in the treatment of bipolar and depressive disorders [77]. 5 % Li-doped MBG scaffolds with hierarchically large pores of 300–500 μm and well-ordered mesopores of 5 nm have been reported to enhance the proliferation and osteogenic/cementogenic differentiation of hPDLCs via the activation of Wnt/β-catenin signaling pathway.

Hypoxia (low oxygen pressure) plays a vital role in coupling angiogenesis with osteogenesis and the inducing of hypoxia on the defect site has been recognized as an important part for new bone tissue regeneration. Ions as copper (Cu) and cobalt (Co) incorporated in bioglasses have been proved to activate the expression of hypoxia inducing factor-1α (HIF-1α) transcription factor, which initiates the expression of a number of genes associated with neovascularization. BMSCs cultured on Cu/Co doped MBG scaffolds showed an improved HIF and VEGF expression, but it was reported the Co doped ones tend to be cytotoxic [72, 73]. Boron (B), possessing the biological effects such as stimulation of bone healing in vivo and angiogenesis in vitro, has been incorporated into bioglasses. A similar report by Haro et al. assessed the pro-angiogenic capacity of B-doped bioglass on embryonic quail chorioallantoic membrane (CAM) and found that the introduction of B significantly increase angiogenesis [12].

Bacterial infection is the main reason that cause failure of the implant in defect sites, which may results in revision surgery and prolonging time of hospitalization.

Typical bacteria including *Pseudomonas aeruginosa, Escherichia coli* and *Staphylococcu aureus* are usually found in the implant site [78]. Therefore, the anti-bacterial property is essential for biomaterials in bone regeneration. Silver (Ag), one of the most well-known precious metal, has been used to test the toxicity of food since ancient times [79]. Its ionic products, Ag ions, being doped in the network of bioglasses, could endow the materials with anti-bacterial activity. However, the addition of Ag in bioglasses structure can trigger the enhancement of quartz and metallic silver crystallization, and excessive Ag ions in bioglasses would cause toxicity to cells. It has been shown that bioglass containing 2 wt% Ag had negative effect on cell viability while that containing 0.75 and 1 wt% were safe.

Apart from these, therapeutic ions such as Zn, Fe, Mg, and Al were all applied in bioglasses composition modification [80]. The effects of these ions have been included in Table 2. Further details of ion substituted bioglasses properties will be discussed in Sect. 3.

2.4 Bioglasses Composites

In recent years, composite materials made of inorganic bioactive glasses combined with bioactive polymers have attracted much attention for bone tissue engineering application. As mentioned above, bioglasses possess excellent apatite-formation ability and osteoinduction ability. However, the inherent brittleness, generally low mechanical strength impede its clinical use. Meanwhile, another promising biomaterial, bioactive polymer (e.g. PCL, PLLA), which showed good handling characteristics for various fabrication, favorable mechanical properties, lacks sufficient bioactivity to build close bond to bone tissue [81–83]. Moreover, drug delivery capacity and controllable release profile could be obtained via the combination of these two materials [84]. Three-dimensional highly porous composite scaffolds of bioglass/PDLLA were successfully prepared by the foam replication technique (Fig. 12, W and B represented two types of foams used in scaffold preparation, 45 ppi and 60 ppi, respectively.). Highly porous structure with interconnected porosity was shown, the polymeric coating showing no negative affect on the interconnectivity. The mechanical stress test has revealed that the PDLLA-coated samples have significantly improved value compared to the non-polymer ones (Fig. 13) [85].

On the other side, polymer scaffolds (e.g. PHBV) with poor hydrophilicity could be modulated via the addition of bioglasses in the system [86]. PHBV/BG scaffolds were prepared by a solvent casting-particulate leaching method (Fig. 14). Open pores with a size from 30 to 300 μm were maintained with 20 wt% of bioglasses while the compressive strength and water absorptivity of the scaffolds increased from 0.11 to 0.34 MPa, 52–91%, respectively (the water absorptivity shown in Fig. 15). Other property modification including the degradation rate and drug release kinetics by the composite of polymer/bioglasses materials has also been conducted by researchers [87]. Some of the results are displayed in Figs. 16 and 17.

Table 2 Some therapeutic ions and their biological roles

Element	Role
K	Principal cation in extracellular fluid, regulation of osmotic pressure, glycogenesis, muscle contraction of cardiac muscles
Na	Principal cation of extracellular fluid, regulates plasma volume, maintains osmotic pressure, transmission of nerve impulses, absorptive processes for bile salts and amino acids
Ca	Constituent of bones and teeth, regulation of nerves, enzyme activation, neuromuscular excitability
Mg	Component of enzyme system with thymine pyrophosphate cofactor. Constituent of bones and teeth, activator for phosphate transferring enzymes
Zn	Cofactor for many enzymes, cell replication, metabolism of vitamin A and E, tissue repair and wound healing
Sr	Helpful in calcification of bones and teeth, bone healing, bone resorption
Cr	Maintains the configuration of RNA molecule, active ingredient in glucose tolerant factor
Co	Constituent of vitamin B12, cofactor of enzymes involved in DNA biosynthesis
Cu	Essential for hematologic and neurologic systems, formation of myelin sheaths in nervous systems, constituent of many enzymes, helps in iron absorption
Fe	Required for hemoglobin, component of enzymes for cellular respiration, myelination of spinal cord, synthesis and packaging of neurotransmitters
Mn	Cofactor of hydrolase, decarboxylase, involved in glycoprotein, part of enzymes required for urea formation and pyruvate metabolism
Se	Constituent of glutathione peroxidase, part of defense system protecting organisms from harmful free radicals, oxidant with vitamin E
Al	Decreasing the bioactivity Stabilizing the glass structure Decreasing the expansion coefficient
Si	Calcification of bone, component of mucopolysaccharides, component of connective tissues, cross linking agent, helps in resiliency of connective tissues
B	Helps in both osteogenesis and angiogenesis
P	Constituent of teeth, bones, adenosine triphosphate and nucleic acids
F	Increases hardness of bones, increases enamel remineralization, prevents dental caries
S	Required for amino acid, connective tissue, skin, nails and hair
Cl	Fluid and electrolyte balance, principal anion in extracellular fluid and gastric juice
I	Component of thyroid hormones Iron Required for hemoglobin, component of enzymes for cellular respiration, myelination of spinal cord, synthesis and packaging of neurotransmitters

Apart from biodegradable organic polymers, studies on bioglass/inorganic composites have been widely reported [53, 88]. Implants manufactured using titanium, cobalt alloys and stainless steel possess high mechanical property but have sever shortcomings as limited corrosion resistance in biological fluid and lack of bioactivity. A strategy to decrease these undesired effects is the superficial modifications by bioceramics (e.g. Bioglasses, HA) via the technique of atmospheric plasma spraying or flame spraying process. Figure 18 gives the image of the section

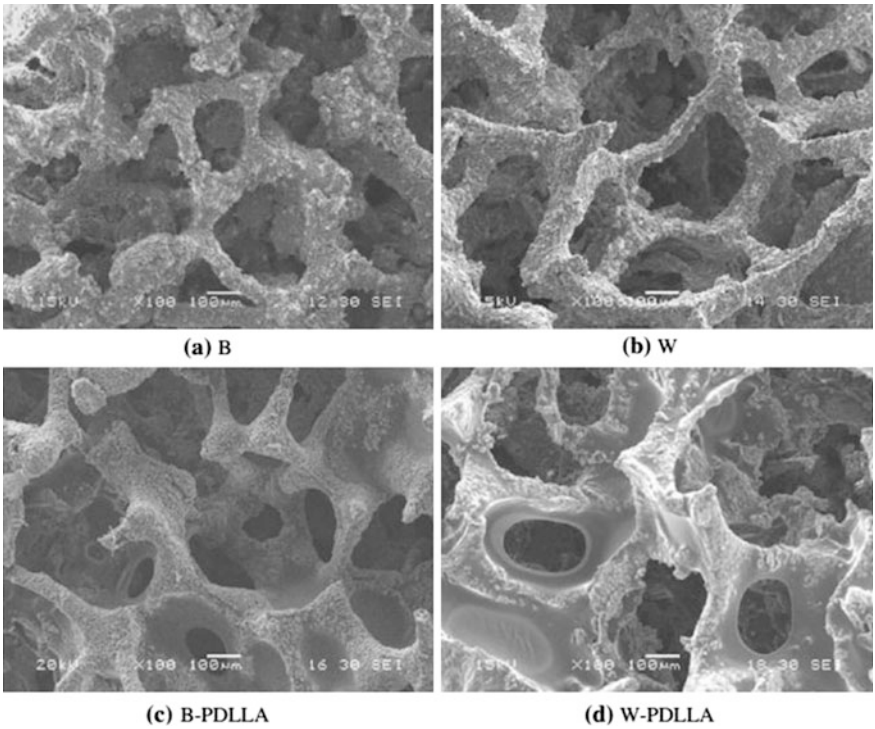

Fig. 12 SEM micrographs of B-type BioglassR-based scaffolds **a** before and **c** after PDLLA coating, and of W-type scaffolds **b** before and **d** after PDLLA coating [85]

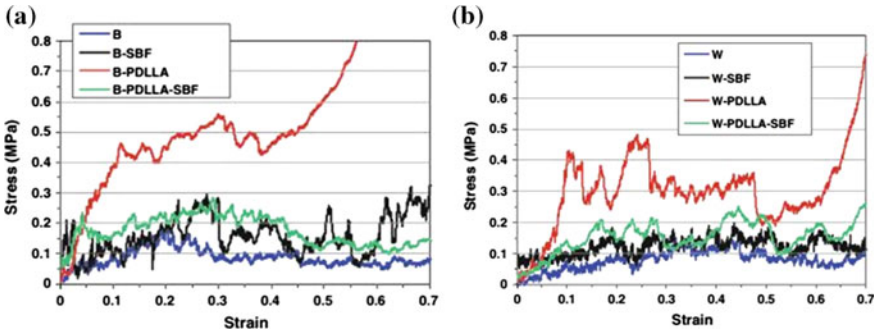

Fig. 13 Compressive stress–strain diagrams of **a** uncoated and PDLLA-coated B-type scaffolds, before and after 28 days in SBF and **b** uncoated and PDLLA-coated W-type scaffolds, before and after 28 days in SBF [85]

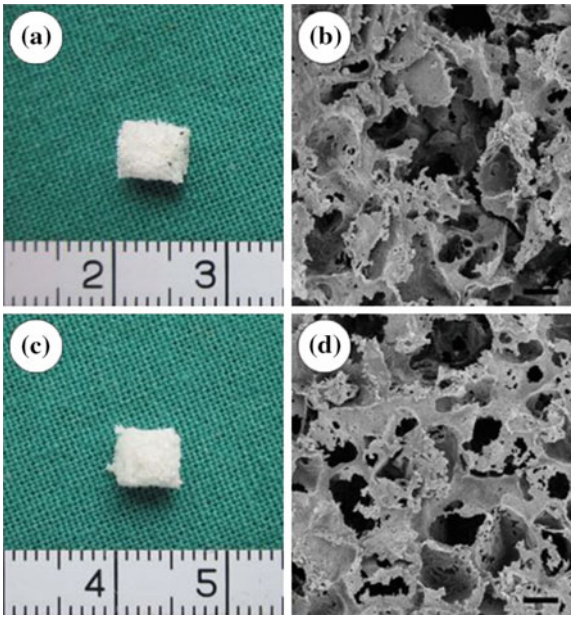

Fig. 14 Optical and SEM micrographs of the PHBV and PHBV/BG scaffolds. The PHBV and PHBV/BG scaffolds prepared using the compression molding, thermal processing and salt particulate leaching method had a regular shape, and some pores on the surface of the scaffolds can be observed. The SEM images show that the PHBV and PHBV/BG scaffolds exhibited a macroporous structure with interconnected open pores, and the pore size varied from 30 to 300 mm. *Scale bar* 100 mm [86]

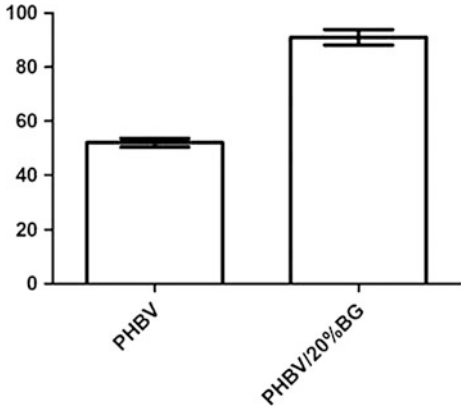

Fig. 15 Water absorptivity before and after BG addition [86]

between bioglasses and the metallic substrate [51]. Further studies have revealed that the apatite formation ability was significantly improved by the surface modification. Similar experiments were conducted on the Mg alloy surface in other reports (Fig. 19) and the water contact angle was significantly decreased, showing a greatly improved hydrophilcity (Fig. 20) [49].

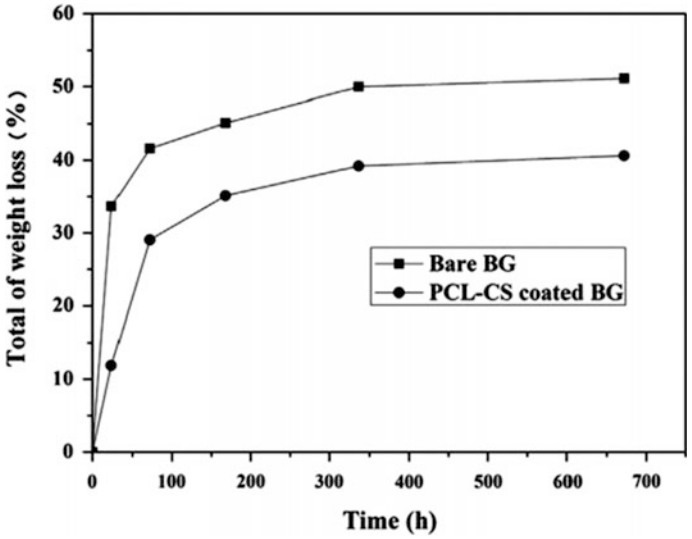

Fig. 16 Weight loss of bare (uncoated) and PCL–CS coated BG scaffolds after immersion in PBS solution for 28 days

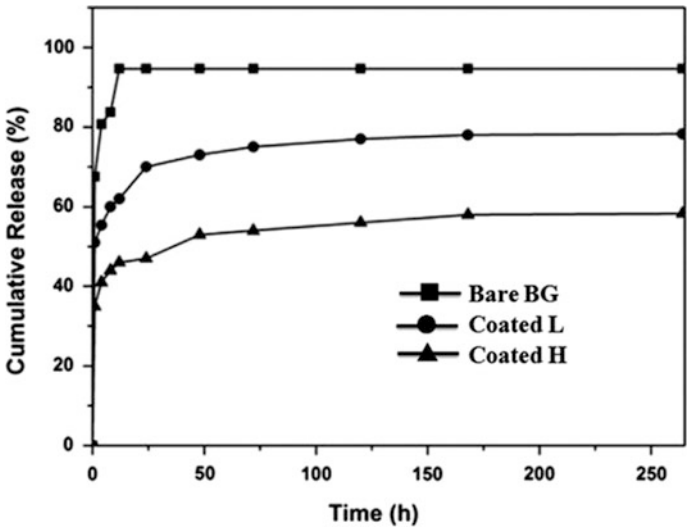

Fig. 17 In vitro vancomycin released from bare and coated BG scaffolds. Coated BG scaffolds were loaded with the drug at two different concentrations (vancomycin/solvent: 25 mg/ml (L) and 50 mg/ml (H))

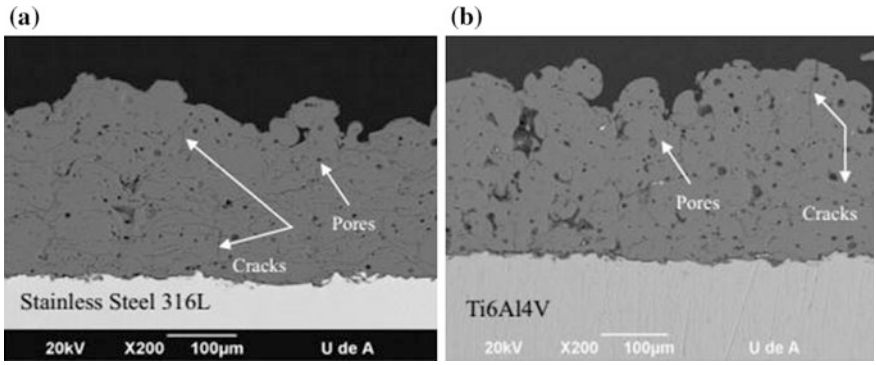

Fig. 18 SEM cross-section of different metallic surface covered with bioglassess [51]. **a** bioglasses on Stainless Steel 316L, **b** bioglasses on Ti6Al4V

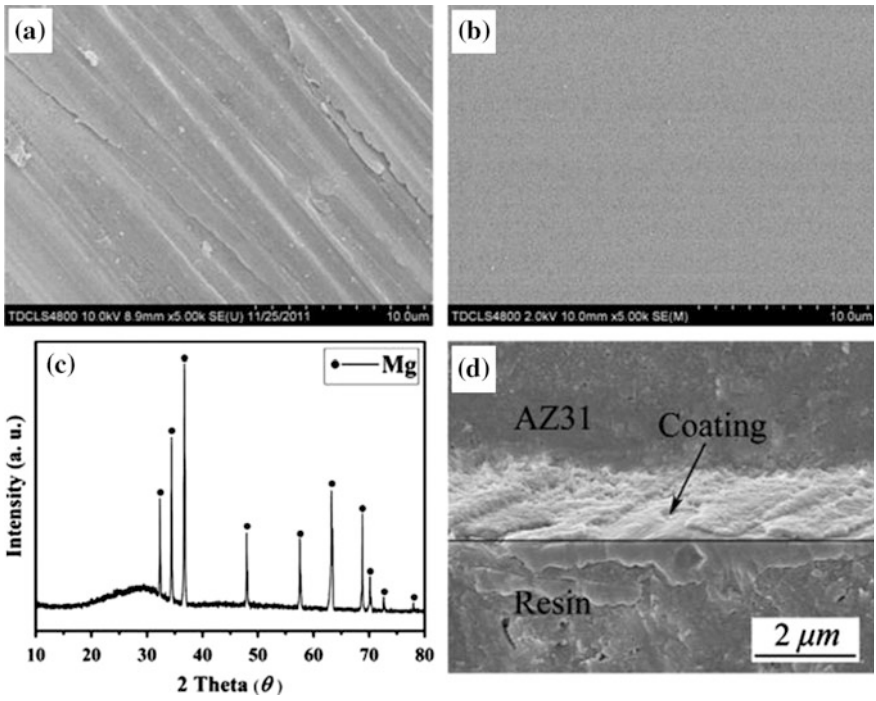

Fig. 19 Surface morphologies of AZ31 alloy without (**a**) and with (**b**) 58S MBG coatings. The XRD pattern (**c**) and cross-section micrograph (**d**) of 58S MBG coated samples [49]

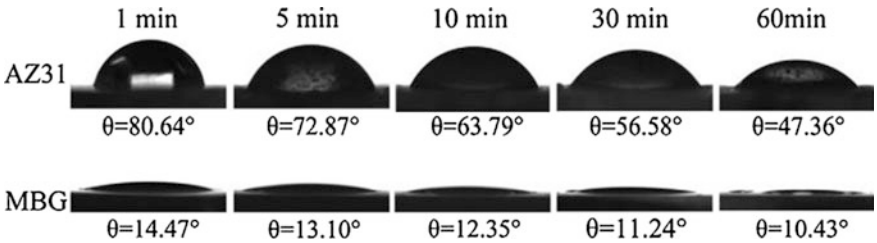

Fig. 20 Photographs of water contact angle on AZ31 alloy with and without 58S MBG coatings for different contact time [49]

3 Application Potential of Bioglasses in Tissue Engineering

3.1 Drug/Growth Factor Delivery by Bioglasses

One of the most important issues in biomedical application is the controlled release of drugs/growth factors by the drug delivery systems (DDSs) [89]. Multifunctional therapeutic effects can be maintained via the controlled release rate and enough release period of certain drug delivery [90–92]. To intensify the positive effect of bioglasses for bone tissue applications and to endow the material with anti-bacterial capacity, considerable researches have been conducted to use bioglasses as platforms to encapsulate and carry drugs, growth factors, hormones and peptides. With the development of their mesoporous forms, the drug delivery ability of bioglasses has been largely improved for the easy loading and prolonged release of various biomolecules [77]. The abundant Si–OH groups inside the MBG channels might play a key role in interacting with drugs and factors by hydrogen bond and Van der Waals force while Fickian diffusion mechanism is usually involved in the release behavior [93].

One of the approaches to load drugs in bioglasses is to add drugs into the sol–gel solution for glass preparation [26]. As the reaction of sol–gel process was usually conducted at room temperature, the activity of drugs (e.g. antibiotic Tetracyline) could be preserved. The samples were obtained after freeze-drying. The antibiotic was incorporated into the bioglass structure by the chemical connection between the phosphate group and the tetracycline acid moiety. Drug release in SBF showed that 12 % of the drug were burstly released at the first 8 h while a sustained release behavior lasted for the next 80 days of 22–25 % of the drug.

Improved drug loading and release behavior becomes possible by the application of bioglasses with mesoporous channels. Previous studies used MBG scaffolds to deliver DMOG, a small molecular drug that could induce hypoxia via counteract the effect of HIF-PH ad stabilize HIF-1α expression [94, 95]. To modulate the

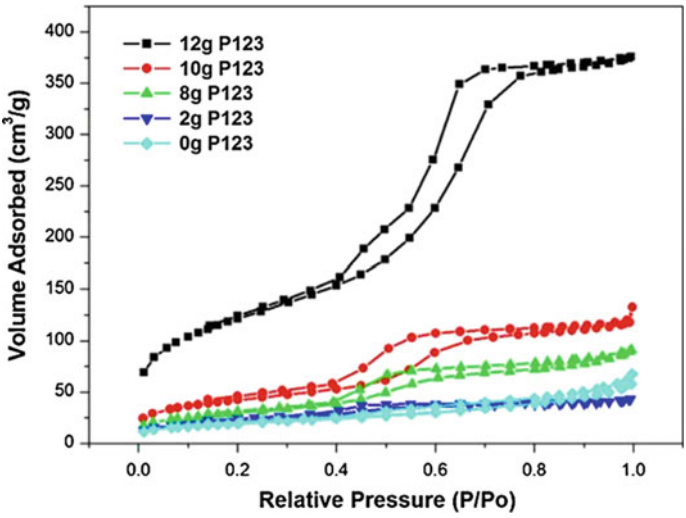

Fig. 21 Nitrogen adsorption–desorption isotherm analysis for bioactive glass scaffolds prepared using different contents of P123 template [48]

loading capacity of scaffolds, different amounts of the mesopore template P123 were added in the preparation and scaffolds with different specific surface were obtained (Fig. 21). The 12 g-P123@ MBG scaffolds showed a maximum loading efficiency of 23 % DMOG and possessed the lowest burst release kinetics of the drug (Fig. 22) [48].

Bioglass/polymer composite materials have been designed to serve as drug carriers. As reported in a recent study, osteogenic enhancer fibroblast growth factor-18 (FGF-18) loaded mesporous bioglass nanospheres were combined with FGF-2 loaded biopolymer fibers (Fig. 23). The obtained composite nanofibrous scaffolds showed increased apatite-formation ability and mechanical property. In vitro study revealed the stimulatory effect on the activity of MSCs while the in vivo study carried out on rat calvarium defects showed significantly enhanced proliferation of osteocytes, bone lining cells and vessel forming cells. PLGA scaffolds coated with MBG possessed favored BMCs proliferation and osteogeic differentiation while the MBG surface improved the BMP-2 delivery of the scaffolds [96].

3.2 Application in Bone/Teeth Regeneration

Started with the discovery of 45S5, numerous investigations have been conducted on the important properties of bioglasses on bone and tooth repair and regeneration for orthopedic and dental applications [97–99]. The outstanding osteoconduction

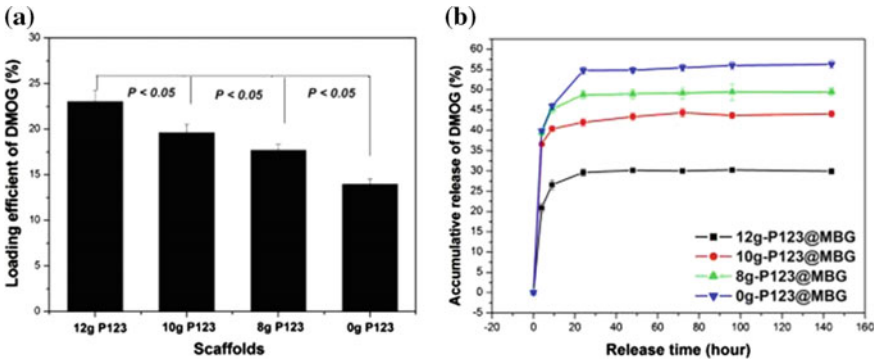

Fig. 22 **a** Drug loading and **b** release of DMOG in MBG scaffolds prepared using different contents of P123 template [48]

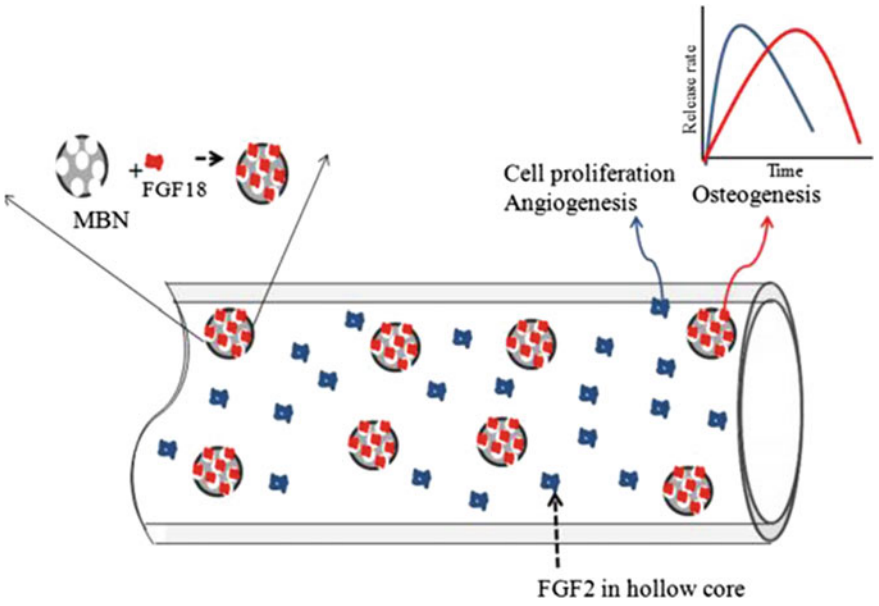

Fig. 23 Schematic design of the present study and the development of a novel therapeutic bone scaffold where FGF18 preloaded within MBG nanoparticles were incorporated within an FGF2-loaded core–shell electrospun polymeric fiber. FGF2 is released initially to stimulate cellular mitosis and possible angiogenesis, while FGF18 is released more slowly to promote osteogenesis [96]

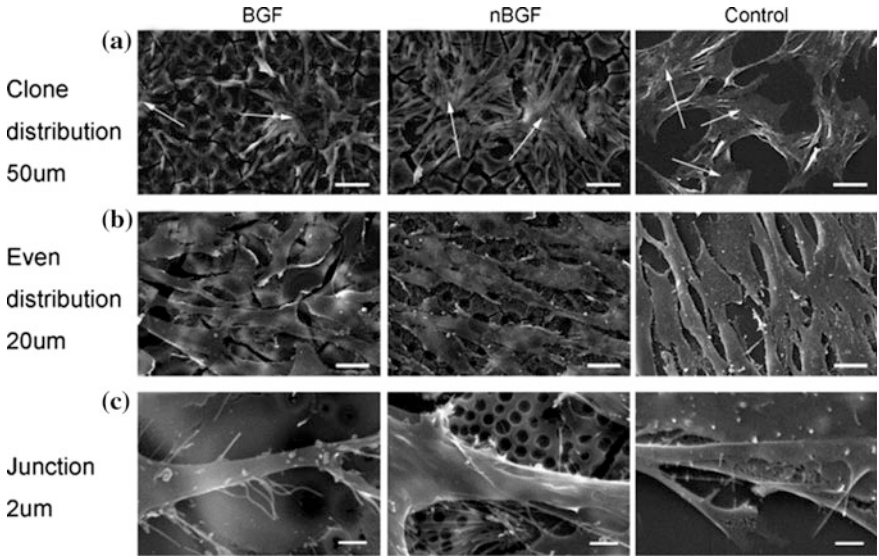

Fig. 24 SEM images of BMSCs attached on BGF (1), nBGF (2) and control glass slide (3). **a** The colony-like distribution of BMSCs after attachment for 6 h, *bar* 50 m. **b** The ordering distribution of BMSCs grew and filled the gaps between colonies after attachment for 3 days, *bar* 20 m. **c** The junctions connecting BMSCs and films. *White arrows* point to BMSCs [102]

and osteostimulation capacities of bioglasses have been studied in depth both in vitro and in vivo. Studies on the interaction between bioglasses and typical bone-related cells, mesenchymal stem cells, osteoblasts and osteoclasts have been looked into [100, 101]. The effect of dissolved ion concentrations, surface morphology on the cellular behavior (adhesion, proliferation, differentiation, gene/protein expressions) was further investigated. In previous report, nanoporous bioglasses film on commercial glass slide prepared by sol–gel method could be attached by BMSCs tightly. While the control group of commercial glass surface appeared a relatively oblate polygons of cells rather than obvious community-like structure, the cells on bioglasses and nanoporous bioglass film presented in a gyrate configuration with order, fulfilled with proliferated BMSCs (Fig. 24). It was clearly indicated that rougher surface with nanoporous structure was more beneficial in promoting the attachment of cells and therefore the combination with bone tissues [102].

The apatite formation ability, which is essential for the close bond to host bone or teeth, has been widely examined in many previous studies on bioglasses. Nanofibers (diameter: 240–470 nm according to the ratio of water/TEOS) of bioglass 70S were fabricated by electrospinning [103]. After immersion in SBF solution, cauliflower-like structure could be seen on the fiber surface, the porous lamella-like mineral deposition being a typical feature of bone-like apatite formed (Fig. 25). The SADE pattern also showed obvious diffraction rings, suggesting the polucrystalline nature of apatite coverage wrapping the amorphous bioglass fibers.

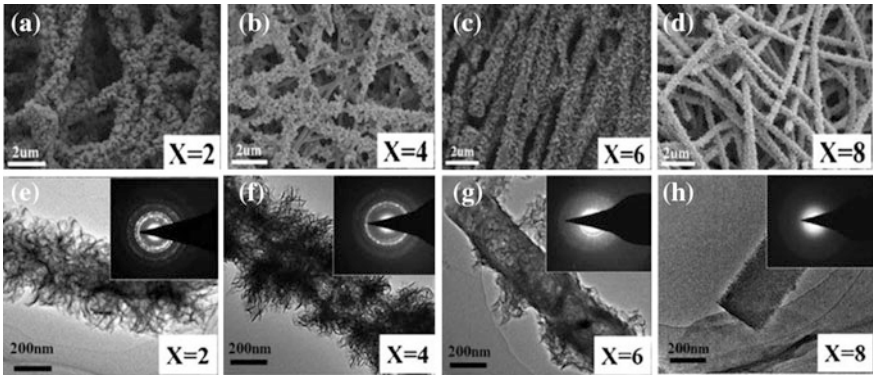

Fig. 25 **a–d** SEM images and **e–h** TEM images of BG fibers prepared with different X ratio after soaking in SBF for 30 h. The *insets* show SAED patterns of the corresponding samples [103]

Porous scaffolds made of 13-93 bioglass implanted in a non-healing rodent calvaria defect model for up to 12 weeks have successfully induced the apatite formation in the defect site. Analysis by von-Kossa and hematocylin and eosin (H&E) staining method revealed the large amount of newly formed bones [104].

As mentioned in Sect. 2.3, the biological property of ion-substituted bioglasses has also attracted much attention. For instance, Sr-incorporated MBG scaffolds was prepared in order to combine the therapeutic effects of Sr ions on osteoporosis with the bioactivity of MBG to regenerate osteoporotic-related fractures [105]. Experiments on critical sized femur defects created in ovariectomised rats showed a stimulatory effect of Sr ions on osteogenesis (Fig. 26).

3.3 Application in Soft Tissue Engineering

Not surprisingly, given the inorganic nature and mechanical rigidity of bioglasses, more attention has been paid on the application in hard tissue engineering. Yet, noticing that quite a lot of characteristics that is key to hard tissue regeneration are also important for soft tissue engineering, lots of studies on the application potential of bioglasses in this area have emerged in recent years [106].

Neovascularization, a key role in both new bone and soft tissue (e.g. wound healing) regeneration process, has been one of the most hotspot in biological researches. Suitable transport of nutrient and growth factors, as well as removal of waste products from the new tissue formation site are largely depended on the formed blood vessels [107]. To be more specific, strategies to improve the angiogenic stimulation of biomaterials should be taken into consideration. Years ago, fibroblasts cultured on 45S5 has be found to have a significantly increased secretion

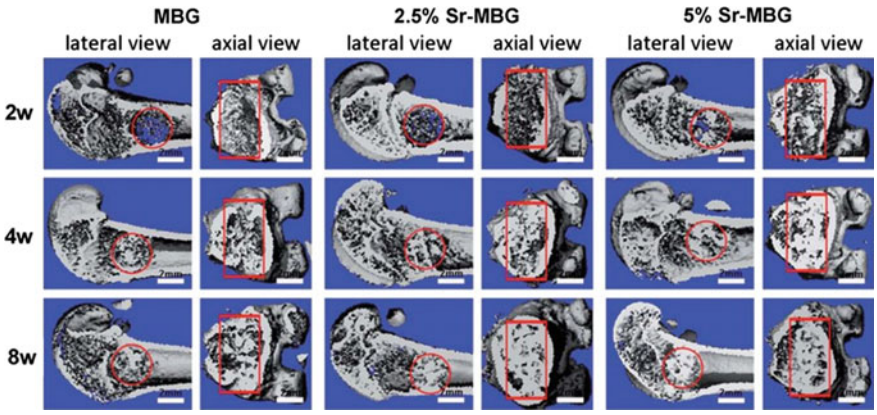

Fig. 26 3D reconstruction of longitudinal section and cross-section images by micro-CT at 2, 4 and 8 weeks post-operation of the critical femoral defect. The *circle* and *rectangle* describe the boundary of the defects. Only a little new bone was present in defects at 2 weeks, while abundant new bone regenerated at 4 and 8 weeks which depicted visible difference among the three groups. *Scale bar* 2 mm

of both VEGF and bFGF, which were representative markers for angiogenesis [108]. Besides, ion-doped bioglass (e.g. Cu) has been applied to accelerate the new vessel formation. In a previous report, Cu-doped (3 wt% in CuO) bioglass scaffolds were implanted in the rat calvarial defect for 8 weeks. Analysis by micro-CT tests have shown that a much higher number density of blood vessels on the defects were obtained in the group of BG-3Cu scaffolds compared to that of the pure BG scaffolds and blank control.

Bioactive glass microspheres have been applied as hemostatic agents for wound healing. It is proposed that the increased Ca ions, as well as the surface area of the bioglass, may accelerate the blood coagulation [109, 110]. A following study using mesoporous silver-exchanged silica spheres enriched with Ca (diameter 600 μm to 1.2 mm) showed that the additional ions into the silica network increased the degradability, therefore increased the blood clotting rates. With the aim of improving the healing of full thickness skin wounds, both 58S nanoscale bioactive glass (NBG-58S) by sol–gel method and melt-derived 45S5 bioglass powders were applied to the superficial injuries in healthy and diabetic rats [111]. Wound healing was compared by calculating the healed area as a percentage of the total wound every 2 days up to 16 days (Fig. 27). The sol–gel derived glasses led to quicker and more effective wound healing than the melt-derived glasses, which was attributed to the larger surface area and surface nanoscale topography of the sol–gel bioglasses. Importantly, both the groups showed better healing than the control group, which indicated the potential of bioglasses for soft tissue engineering.

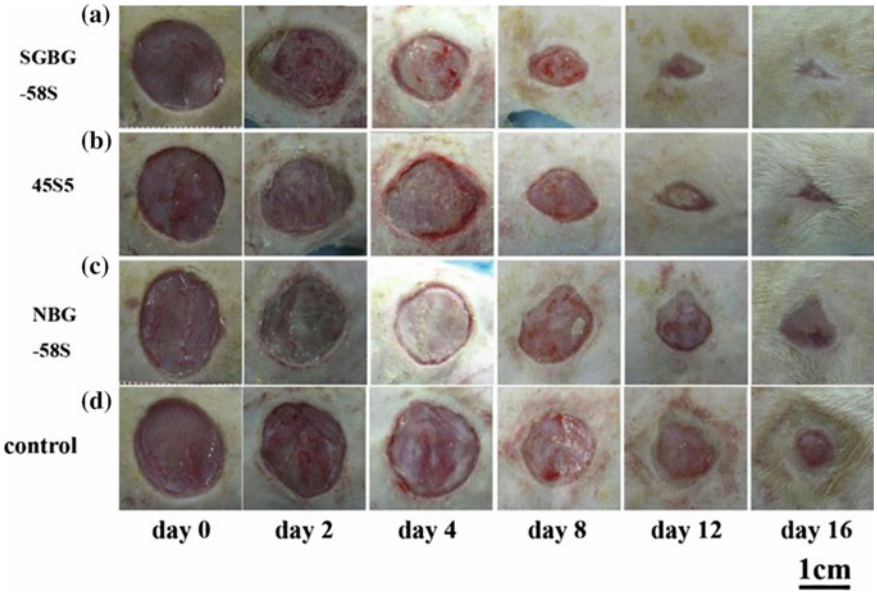

Fig. 27 BG treated and untreated wounds from days 0–16 according to Lin et al. Wounds were treated with different types of BGs, as indicated. It can be seen that SGBG-58S led to the fastest healing rates [111]

4 Conclusion and Perspective

Since the discovery of melt-derived 45S5 Bioglass by Larry Hench in 1970s, great progress has been achieved in the preparation of bioactive glasses in the past 40 years. Apart from the tunable compositions, both on the adjustment of the orginal calcium, silicate, sodium and phosphate contents and the incorporation of foreign ions including copper, zinc, strontium, sliver, etc., as well as mesoporous structure has been successfully introduced to bioglasses. With the modification of sol–gel methods and other developed fabrication techniques, different forms of micro-powders, bulks, scaffolds, films, fibers and nanoparticles of bioglasses could be obtained with specific morphology and surface characteristics. Moreover, their combination with other bioceramics, bioactive polymers and alloys in various forms has provided vast choice to satisfy the multi-requirements for potential application. As the outstanding biological property being the stimulatory effect on osteoblastic differentiation of stem cells without addition of osteogenic induction, bioglasses have been widely studied in bone tissue engineering. In the past several years, their positive effect on soft tissue regeneration (e.g. wound healing) has emerged and growing attentions have be attracted. Studies on cellular effect of bioglasses on different types of cells concerning the stem cells, osteoblasts, endothelial cells and even immune cells (skeleton system is closely connected with immune system)

have been pushed forward and there are still much left to be done. Several products have been put into clinical use while many of the newly synthesized samples are undergoing fundamental researches in laboratory by biomaterial scientists. Bioglasses, being the promising candidate for bone/soft tissue regeneration application, are facing with both great chances and challenges.

There are several important issues that suggested to be the potential directions for the study of bioglasses. First, more trials need to be conducted on the preparation of bioglasses with nanoscale architecture, including chemistry-based methods to the synthesis of nanoparticles and the construction of meso/nanoporous structures on both surface and inside the main body. For one thing, cell adhesion and new tissue growth stimulation could be achieved by nanostructured materials. For another, the incorporation of nanoscale particles into two or three dimensional coatings or scaffolds may show improvements of properties such as mechanical strength and surface roughness, being crucial to following effects on its biological properties. Second, the better delivery of drugs/growth factors, as well as the dissolution of therapeutic ions (both original and substituted) should be further studied. The possible synergistic mechanism of ions and biomolecules on the multifunctional properties, together with the release kinetics should be focused on, of which some relevant co-culture of different cells, more appropriate animal models may be involved. Last but not least, researches in the fabrication of both pure bioglasses materials and their hybrids with proper polymers, metals, other inorganic materials via additive manufacturing technologies need to move beyond current progress. By combining certain chemical process with the advanced techniques, bioglasses in various forms with optimized properties for clinical trials will not be far.

References

1. Hench, L.L.: Bioceramics—from concept to clinic. Am. Ceram. Soc. Bull. **72**, 93–98 (1993)
2. Hench, L.L., Splinter, R.J., Allen, W.C., Greenlee, T.K.: Bonding mechanisms at the interface of ceramic prosthetic materials. J. Biomed. Mater. Res. **5**, 117–141 (1971)
3. Hench, L.L., Polak, J.M.: Third-generation biomedical materials. Science **295**, 1014–1017 (2002)
4. Kaur, G., Pandey, O.P., Singh, K., Homa, D., Scott, B., Pickrell, G.: A review of bioactive glasses: their structure, properties, fabrication and apatite formation. J. Biomed. Mater. Res. Part A **102**, 254–274 (2014)
5. Hench, L., Hench, J.W., Greenspan, D.: Bioglass: a short history and bibliography. J. Australas. Ceram. Soc. **40**, 1–42 (2004)
6. Rahaman, M.N., Day, D.E., Bal, B.S., Fu, Q., Jung, S.B., Bonewald, L.F., Tomsia, A.P.: Bioactive glass in tissue engineering. Acta Biomater. **7**, 2355–2373 (2011)
7. Pantano, C.G., Clark, A.E., Hench, L.L.: Multilayer corrosion films on bioglass surfaces. J. Am. Ceram. Soc. **57**, 412–413 (1974)
8. Wu, C.T., Chang, J.: Silicate bioceramics for bone tissue regeneration. J. Inorg. Mater. **28**, 29–39 (2013)

9. Brink, M.: The influence of alkali and alkaline earths on the working range for bioactive glasses. J. Biomed. Mater. Res. **36**, 109–117 (1997)
10. Liang, W., Rahaman, M.N., Day, D.E., Marion, N.W., Riley, G.C., Mao, J.J.: Bioactive borate glass scaffold for bone tissue engineering. J. Non-Cryst. Solids **354**, 1690–1696 (2008)
11. Fu, H., Fu, Q., Zhou, N., Huang, W., Rahaman, M.N., Wang, D., Liu, X.: In vitro evaluation of borate-based bioactive glass scaffolds prepared by a polymer foam replication method. Mater. Sci. Eng. C Mater. Biol. Appl. **29**, 2275–2281 (2009)
12. Haro Durand, L.A., Vargas, G.E., Romero, N.M., Vera-Mesones, R., Porto-Lopez, J.M., Boccaccini, A.R., Zago, M.P., Baldi, A., Gorustovich, A.: Angiogenic effects of ionic dissolution products released from a boron-doped 45S5 bioactive glass. J. Mater. Chem. B **3**, 1142–1148 (2015)
13. Zhao, S., Wang, H., Zhang, Y., Huang, W., Rahaman, M.N., Liu, Z., Wang, D., Zhang, C.: Copper-doped borosilicate bioactive glass scaffolds with improved angiogenic and osteogenic capacity for repairing osseous defects. Acta Biomater. **14**, 185–196 (2015)
14. Gao, H.S., Tan, T.N., Wang, D.H.: Dissolution mechanism and release kinetics of phosphate controlled release glasses in aqueous medium. J. Control. Release **96**, 29–36 (2004)
15. Brink, M., Turunen, T., Happonen, R.P., YliUrpo, A.: Compositional dependence of bioactivity of glasses in the system Na_2O–K_2O–MgO–CaO–B_2O_3–P_2O_5–SiO_2. J. Biomed. Mater. Res. **37**, 114–121 (1997)
16. Lin, S., Ionescu, C., Pike, K.J., Smith, M.E., Jones, J.R.: Nanostructure evolution and calcium distribution in sol–gel derived bioactive glass. J. Mater. Chem. **19**, 1276–1282 (2009)
17. Vedel, E., Arstila, H., Ylanen, H., Hupa, L., Hupa, M.: Predicting physical and chemical properties of bioactive glasses from chemical composition. Part 1: viscosity characteristics. Glass Technol. Eur. J. Glass Sci. Technol. Part A **49**, 251–259 (2008)
18. O'Donnell, M.D.: Predicting bioactive glass properties from the molecular chemical composition: glass transition temperature. Acta Biomater. **7**, 2264–2269 (2011)
19. Zhao, D.Y., Feng, J.L., Huo, Q.S., Melosh, N., Fredrickson, G.H., Chmelka, B.F., Stucky, G.D.: Triblock copolymer syntheses of mesoporous silica with periodic 50 to 300 angstrom pores. Science **279**, 548–552 (1998)
20. Mamaeva, V., Sahlgren, C., Linden, M.: Mesoporous silica nanoparticles in medicine—recent advances. Adv. Drug Deliv. Rev. **65**, 689–702 (2013)
21. Slowing, I., Viveroescoto, J., Wu, C., Lin, V.: Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. Adv. Drug Deliv. Rev. **60**, 1278–1288 (2008)
22. Henstock, J.R., Canham, L.T., Anderson, S.I.: Silicon: the evolution of its use in biomaterials. Acta Biomater. **11**, 17–26 (2015)
23. Groh, D., Doehler, F., Brauer, D.S.: Bioactive glasses with improved processing. Part 1. Thermal properties, ion release and apatite formation. Acta Biomater. **10**, 4465–4473 (2014)
24. Beck Jr., G.R., Ha, S.-W., Camalier, C.E., Yamaguchi, M., Li, Y., Lee, J.-K., Weitzmann, M.N.: Bioactive silica-based nanoparticles stimulate bone-forming osteoblasts, suppress bone-resorbing osteoclasts, and enhance bone mineral density in vivo. Nanomed. Nanotechnol. Biol. Med. **8**, 793–803 (2012)
25. Vallet-Regi, M., Colilla, M., Izquierdo-Barba, I.: Bioactive mesoporous silicas as controlled delivery systems: application in bone tissue regeneration. J. Biomed. Nanotechnol. **4**, 1–15 (2008)
26. Hum, J., Boccaccini, A.: Bioactive glasses as carriers for bioactive molecules and therapeutic drugs: a review. J. Mater. Sci. Mater. Med. **23**, 2317–2333 (2012)
27. Vallet-Regi, M., Ramila, A., Del Real, R., Pérez-Pariente, J.: A new property of MCM-41: drug delivery system. Chem. Mater. **13**, 308–311 (2001)
28. Vallet-Regi, M., Izquierdo-Barba, I., Colilla, M.: Structure and functionalization of mesoporous bioceramics for bone tissue regeneration and local drug delivery. Philos. Trans. R. Soc. A Math. Phys. Eng. Sci. **370**, 1400–1421 (2012)

29. Yan, X., Yu, C., Zhou, X., Tang, J., Zhao, D.: Highly ordered mesoporous bioactive glasses with superior in vitro bone-forming bioactivities. Angew. Chem. Int. Ed. **43**, 5980–5984 (2004)
30. Hench, L.L.: The story of bioglass (R). J. Mater. Sci. Mater. Med. **17**, 967–978 (2006)
31. Jones, J.R.: Review of bioactive glass: from Hench to hybrids. Acta Biomater. **9**, 4457–4486 (2013)
32. Sepulveda, P., Jones, J.R., Hench, L.L.: Characterization of melt-derived 45S5 and sol–gel-derived 58S bioactive glasses. J. Biomed. Mater. Res. **58**, 734–740 (2001)
33. Siqueira, R.L., Peitl, O., Zanotto, E.D.: Gel-derived SiO_2–CaO–Na_2O–P_2O_5 bioactive powders: synthesis and in vitro bioactivity. Mater. Sci. Eng. C Mater. Biol. Appl. **31**, 983–991 (2011)
34. Letaief, N., Lucas-Girot, A., Oudadesse, H., Dorbez-Sridi, R.: New 92S6 mesoporous glass: influence of surfactant carbon chain length on the structure, pore morphology and bioactivity. Mater. Res. Bull. **60**, 882–889 (2014)
35. Yan, X.X., Yu, C.Z., Zhou, X.F., Tang, J.W., Zhao, D.Y.: Highly ordered mesoporous bioactive glasses with superior in vitro bone-forming bioactivities. Angew. Chem. Int. Ed. **43**, 5980–5984 (2004)
36. Lovelace, T.B., Mellonig, J.T., Meffert, R.M., Jones, A.A., Nummikoski, P.V., Cochran, D. L.: Clinical evaluation of bioactive glass in the treatment of periodontal osseous defects in humans. J. Periodontol. **69**, 1027–1035 (1998)
37. Mengel, R., Soffner, M., Flores-De-Jacoby, L.: Bioabsorbable membrane and bioactive glass in the treatment of intrabony defects in patients with generalized aggressive periodontitis: Results of a 12-month clinical and radiological study. J. Periodontol. **74**, 899–908 (2003)
38. Low, S.B., King, C.J., Krieger, J.: An evaluation of bioactive ceramic in the treatment of periodontal osseous defects. Int. J. Periodontics Restor. Dent. **17**, 358–367 (1997)
39. Schopper, C., Ziya-Ghazvini, F., Goriwoda, W., Moser, D., Wanschitz, F., Spassova, E., Lagogiannis, G., Auterith, A., Ewers, R.: HA/TCP compounding of a porous CaP biomaterial improves bone formation and scaffold degradation—a long-term histological study. J. Biomed. Mater. Res. Part B Appl. Biomater. **74B**, 458–467 (2005)
40. Peters, F., Reif, D.: Functional materials for bone regeneration from beta-tricalcium phosphate. Materialwiss. Werkstofftech. **35**, 203–207 (2004)
41. Leong, K.F., Cheah, C.M., Chua, C.K.: Solid freeform fabrication of three-dimensional scaffolds for engineering replacement tissues and organs. Biomaterials **24**, 2363–2378 (2003)
42. Sachlos, E., Czernuszka, J.T.: Making tissue engineering scaffolds work. Review: the application of solid freeform fabrication technology to the production of tissue engineering scaffolds. Eur. Cells Mater. **5**, 29–39 (2003). (discussion 39–40)
43. Liu, C.Z., Czernuszka, J.T.: Development of biodegradable scaffolds for tissue engineering: a perspective on emerging technology. Mater. Sci. Technol. **23**, 379–391 (2007)
44. Wu, C., Luo, Y., Cuniberti, G., Xiao, Y., Gelinsky, M.: Three-dimensional printing of hierarchical and tough mesoporous bioactive glass scaffolds with a controllable pore architecture, excellent mechanical strength and mineralization ability. Acta Biomater. **7**, 2644–2650 (2011)
45. Sepulveda, P., Jones, J.R., Hench, L.L.: Bioactive sol–gel foams for tissue repair. J. Biomed. Mater. Res. **59**, 340–348 (2002)
46. Jones, J.R., Lin, S., Yue, S., Lee, P.D., Hanna, J.V., Smith, M.E., Newport, R.J.: Bioactive glass scaffolds for bone regeneration and their hierarchical characterisation. Proc. Inst. Mech. Eng. Part H J. Eng. Med. **224**, 1373–1387 (2010)
47. Yun, H.-S., Kim, S.-E., Hyun, Y.-T., Heo, S.-J., Shin, J.-W.: Hierarchically mesoporous–macroporous bioactive glasses scaffolds for bone tissue regeneration. J. Biomed. Mater. Res. Part B Appl. Biomater. **87B**, 374–380 (2008)
48. Wu, C., Zhou, Y., Chang, J., Xiao, Y.: Delivery of dimethyloxallyl glycine in mesoporous bioactive glass scaffolds to improve angiogenesis and osteogenesis of human bone marrow stromal cells. Acta Biomater. **9**, 9159–9168 (2013)

49. Huang, K., Cai, S., Xu, G., Ren, M., Wang, X., Zhang, R., Niu, S., Zhao, H.: Sol–gel derived mesoporous 58S bioactive glass coatings on AZ31 magnesium alloy and in vitro degradation behavior. Surf. Coat. Technol. **240**, 137–144 (2014)
50. Li, H., Chen, S., Wu, Y., Jiang, J., Ge, Y., Gao, K., Zhang, P., Wu, L.: Enhancement of the osseointegration of a polyethylene terephthalate artificial ligament graft in a bone tunnel using 58S bioglass. Int. Orthop. **36**, 191–197 (2012)
51. Monsalve, M., Lopez, E., Ageorges, H., Vargas, F.: Bioactivity and mechanical properties of bioactive glass coatings fabricated by flame spraying. Surf. Coat. Technol. **268**, 142–146 (2015)
52. Wang, X., Wen, C.: Corrosion protection of mesoporous bioactive glass coating on biodegradable magnesium. Appl. Surf. Sci. **303**, 196–204 (2014)
53. Fiorilli, S., Baino, F., Cauda, V., Crepaldi, M., Vitale-Brovarone, C., Demarchi, D., Onida, B.: Electrophoretic deposition of mesoporous bioactive glass on glass-ceramic foam scaffolds for bone tissue engineering. J. Mater. Sci. Mater. Med. **26**, 1–2 (2015)
54. Tan, F., Naciri, M., Al-Rubeai, M.: Osteoconductivity and growth factor production by MG63 osteoblastic cells on bioglass-coated orthopedic implants. Biotechnol. Bioeng. **108**, 454–464 (2011)
55. Xu, C.Y., Inai, R., Kotaki, M., Ramakrishna, S.: Electrospun nanofiber fabrication as synthetic extracellular matrix and its potential for vascular tissue engineering. Tissue Eng. **10**, 1160–1168 (2004)
56. Clupper, D.C., Gough, J.E., Hall, M.M., Clare, A.G., LaCourse, W.C., Hench, L.L.: In vitro bioactivity of S520 glass fibers and initial assessment of osteoblast attachment. J. Biomed. Mater. Res., Part A **67A**, 285–294 (2003)
57. Hsu, F.-Y., Weng, R.-C., Lin, H.-M., Lin, Y.-H., Lu, M.-R., Yu, J.-L., Hsu, H.-W.: A biomimetic extracellular matrix composed of mesoporous bioactive glass as a bone graft material. Microporous Mesoporous Mater. **212**, 56–65 (2015)
58. Quintero, F., Pou, J., Comesana, R., Lusquinos, F., Riveiro, A., Mann, A.B., Hill, R.G., Wu, Z.Y., Jones, J.R.: Laser spinning of bioactive glass nanofibers. Adv. Funct. Mater. **19**, 3084–3090 (2009)
59. Walmsley, G.G., McArdle, A., Tevlin, R., Momeni, A., Atashroo, D., Hu, M.S., Feroze, A. H., Wong, V.W., Lorenz, P.H., Longaker, M.T., Wan, D.C.: Nanotechnology in bone tissue engineering. Nanomed. Nanotechnol. Biol. Med. **11**, 1253–1263 (2015)
60. Tran, N., Webster, T.J.: Nanotechnology for bone materials. Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. **1**, 336–351 (2009)
61. Yousefi, A.-M., Oudadesse, H., Akbarzadeh, R., Wers, E., Lucas-Girot, A.: Physical and biological characteristics of nanohydroxyapatite and bioactive glasses used for bone tissue engineering. Nanotechnol. Rev. **3**, 527–552 (2014)
62. Yang, Q., Sui, G., Shi, Y.Z., Duan, S., Bao, J.Q., Cai, Q., Yang, X.P.: Osteocompatibility characterization of polyacrylonitrile carbon nanofibers containing bioactive glass nanoparticles. Carbon **56**, 288–295 (2013)
63. Wang, H., Leeuwenburgh, S.C.G., Li, Y., Jansen, J.A.: The use of micro- and nanospheres as functional components for bone tissue regeneration. Tissue Eng. Part B Rev. **18**, 24–39 (2012)
64. Yang, L., Webster, T.J.: Nanotechnology controlled drug delivery for treating bone diseases. Expert Opin. Drug Deliv. **6**, 851–864 (2009)
65. Wu, C., Fan, W., Chang, J.: Functional mesoporous bioactive glass nanospheres: synthesis, high loading efficiency, controllable delivery of doxorubicin and inhibitory effect on bone cancer cells. J. Mater. Chem. B **1**, 2710 (2013)
66. Liang, Q., Hu, Q., Miao, G., Yuan, B., Chen, X.: A facile synthesis of novel mesoporous bioactive glass nanoparticles with various morphologies and tunable mesostructure by sacrificial liquid template method. Mater. Lett. **148**, 45–49 (2015)
67. Wu, C., Chang, J.: A review of bioactive silicate ceramics. Biomed. Mater. **8**, 032001 (2013)
68. Clark, A.E., Pantano, C.G., Hench, L.L.: Auger spectroscopic analysis of bioglass corrosion films. J. Am. Ceram. Soc. **59**, 37–39 (1976)

69. Kasemo, B., Gold, J.: Implant surfaces and interface processes. Adv. Dent. Res. **13**, 8–20 (1999)
70. Jiang, P., Lin, H., Xing, R., Jiang, J., Qu, F.: Synthesis of multifunctional macroporous-mesoporous TiO_2-bioglasses for bone tissue engineering. J. Sol-Gel. Sci. Technol. **61**, 421–428 (2012)
71. Lin, K., Liu, P., Wei, L., Zou, Z., Zhang, W., Qian, Y., Shen, Y., Chang, J.: Strontium substituted hydroxyapatite porous microspheres: surfactant-free hydrothermal synthesis, enhanced biological response and sustained drug release. Chem. Eng. J. **222**, 49–59 (2013)
72. Wu, C., Zhou, Y., Xu, M., Han, P., Chen, L., Chang, J., Xiao, Y.: Copper-containing mesoporous bioactive glass scaffolds with multifunctional properties of angiogenesis capacity, osteostimulation and antibacterial activity. Biomaterials **34**, 422–433 (2013)
73. Wu, C., Zhou, Y., Fan, W., Han, P., Chang, J., Yuen, J., Zhang, M., Xiao, Y.: Hypoxia-mimicking mesoporous bioactive glass scaffolds with controllable cobalt ion release for bone tissue engineering. Biomaterials **33**, 2076–2085 (2012)
74. Zhao, S., Zhang, J., Zhu, M., Zhang, Y., Liu, Z., Tao, C., Zhu, Y., Zhang, C.: Three-dimensional printed strontium-containing mesoporous bioactive glass scaffolds for repairing rat critical-sized calvarial defects. Acta Biomater. **12**, 270–280 (2015)
75. Nielsen, S.P.: The biological role of strontium. Bone **35**, 583–588 (2004)
76. Isaac, J., Nohra, J., Lao, J., Jallot, E., Nedelec, J.-M., Berdal, A., Sautier, J.-M.: Effects of strontium-doped bioactive glass on the differentiation of cultured osteogenic cells. Eur. Cells Mater. **21**, 130–143 (2011)
77. Wu, C., Chang, J.: Multifunctional mesoporous bioactive glasses for effective delivery of therapeutic ions and drug/growth factors. J. Control. Release **193**, 282–295 (2014)
78. Choe, H., Narayanan, A.S., Gandhi, D.A., Weinberg, A., Marcus, R.E., Lee, Z., Bonomo, R. A., Greenfield, E.M.: Immunomodulatory peptide IDR-1018 decreases implant infection and preserves osseointegration. Clin. Orthop. Relat. Res. **473**, 2898–2907 (2015)
79. Balamurugan, A., Balossier, G., Laurent-Maquin, D., Pina, S., Rebelo, A.H.S., Faure, J., Ferreira, J.M.F.: An in vitro biological and anti-bacterial study on a sol–gel derived silver-incorporated bioglass system. Dent. Mater. **24**, 1343–1351 (2008)
80. Rabiee, S.M., Nazparvar, N., Azizian, M., Vashaee, D., Tayebi, L.: Effect of ion substitution on properties of bioactive glasses: a review. Ceram. Int. **41**, 7241–7251 (2015)
81. Yao, Q., Nooeaid, P., Detsch, R., Roether, J.A., Dong, Y., Goudouri, O.-M., Schubert, D. W., Boccaccini, A.R.: Bioglass®/chitosan-polycaprolactone bilayered composite scaffolds intended for osteochondral tissue engineering. J. Biomed. Mater. Res. Part A (2014). doi:10.1002/jbm.a.35125
82. Helen, W., Gough, J.E.: Cell viability, proliferation and extracellular matrix production of human annulus fibrosus cells cultured within PDLLA/Bioglass® composite foam scaffolds in vitro. Acta Biomater. **4**, 230–243 (2008)
83. Zeimaran, E., Pourshahrestani, S., Djordjevic, I., Pingguan-Murphy, B., Kadri, N.A., Towler, M.R.: Bioactive glass reinforced elastomer composites for skeletal regeneration: a review. Mater. Sci. Eng. C **53**, 175–188 (2015)
84. Moritz, M., Geszke-Moritz, M.: Mesoporous materials as multifunctional tools in biosciences: principles and applications. Mat. Sci. Eng. C Mater. Biol. Appl. **49**, 114–151 (2015)
85. Bretcanu, O., Boccaccini, A.R., Salih, V.: Poly-dl-lactic acid coated Bioglass® scaffolds: toughening effects and osteosarcoma cell proliferation. J. Mater. Sci. **47**, 5661–5672 (2012)
86. Wu, J., Xue, K., Li, H., Sun, J., Liu, K.: Improvement of PHBV scaffolds with bioglass for cartilage tissue engineering. PLoS ONE **8**, e71563 (2013)
87. Yao, Q., Nooeaid, P., Roether, J.A., Dong, Y., Zhang, Q., Boccaccini, A.R.: Bioglass®—based scaffolds incorporating polycaprolactone and chitosan coatings for controlled vancomycin delivery. Ceram. Int. **39**, 7517–7522 (2013)
88. Bellucci, D., Sola, A., Anesi, A., Salvatori, R., Chiarini, L., Cannillo, V.: Bioactive glass/hydroxyapatite composites: mechanical properties and biological evaluation. Mater. Sci. Eng. C **51**, 196–205 (2015)

89. Chen, Y., Chen, H., Shi, J.: In vivo bio-safety evaluations and diagnostic/therapeutic applications of chemically designed mesoporous silica nanoparticles. Adv. Mater. **25**, 3144–3176 (2013)
90. Zhao, Y.N., Trewyn, B.G., Slowing, I.I., Lin, V.S.Y.: Mesoporous silica nanoparticle-based double drug delivery system for glucose-responsive controlled release of insulin and cyclic AMP. J. Am. Chem. Soc. **131**, 8398–8400 (2009)
91. Slowing, I.I., Vivero-Escoto, J.L., Wu, C.W., Lin, V.S.Y.: Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. Adv. Drug Deliv. Rev. **60**, 1278–1288 (2008)
92. Neumann, A., Christel, A., Kasper, C., Behrens, P.: BMP2-loaded nanoporous silica nanoparticles promote osteogenic differentiation of human mesenchymal stem cells. RSC Adv. **3**, 24222 (2013)
93. Zhu, Y., Kaskel, S.: Comparison of the in vitro bioactivity and drug release property of mesoporous bioactive glasses (MBGs) and bioactive glasses (BGs) scaffolds. Microporous Mesoporous Mater. **118**, 176–182 (2009)
94. Ding, H., Gao, Y.-S., Wang, Y., Hu, C., Sun, Y., Zhang, C.: Dimethyloxaloylglycine increases the bone healing capacity of adipose-derived stem cells by promoting osteogenic differentiation and angiogenic potential. Stem Cells Dev. **23**, 990–1000 (2014)
95. Weidemann, A., Johnson, R.S.: Biology of HIF-1 alpha. Cell Death Differ. **15**, 621–627 (2008)
96. Kang, M.S., Kim, J.-H., Singh, R.K., Jang, J.-H., Kim, H.-W.: Therapeutic-designed electrospun bone scaffolds: mesoporous bioactive nanocarriers in hollow fiber composites to sequentially deliver dual growth factors. Acta Biomater. **16**, 103–116 (2015)
97. Izquierdo-Barba, I., Colilla, M., Vallet-Regí, M.: Nanostructured mesoporous silicas for bone tissue regeneration. J. Nanomater. **2008**, 1–14 (2008)
98. Matsuura, N., Gorelikov, I., Williams, R., Wan, K., Zhu, S., Booth, J., Burns, P., Hynynen, K., Rowlands, J.A.: Nanoparticle-tagged perfluorocarbon droplets for medical imaging. In: Shastri, V.P., Lendlein, A., Liu, L., Mikos, A., Mitragotri, S. (eds.) Advances in Material Design for Regenerative Medicine, Drug Delivery and Targeting/Imaging, pp 87–92 (2009)
99. Kim, Y.-T., Caldwell, J.-M., Bellamkonda, R.V.: Nanoparticle-mediated local delivery of methylprednisolone after spinal cord injury. Biomaterials **30**, 2582–2590 (2009)
100. Cejudo-Guillen, M., Ramiro-Gutierrez, M.L., Labrador-Garrido, A., Diaz-Cuenca, A., Pozo, D.: Nanoporous silica microparticle interaction with toll-like receptor agonists in macrophages. Acta Biomater. **8**, 4295–4303 (2012)
101. Tautzenberger, A., Kovtun, A.: Ignatius Nanoparticles and their potential for application in bone. Int. J. Nanomed. **7**, 4545 (2012). doi:10.2147/ijn.s34127
102. Ma, Z., Ji, H., Hu, X., Teng, Y., Zhao, G., Mo, L., Zhao, X., Chen, W., Qiu, J., Zhang, M.: Investigation of bioactivity and cell effects of nano-porous sol–gel derived bioactive glass film. Appl. Surf. Sci. **284**, 738–744 (2013)
103. Li, Y., Li, B., Xu, G., Ahmad, Z., Ren, Z., Dong, Y., Li, X., Weng, W., Han, G.: A feasible approach toward bioactive glass nanofibers with tunable protein release kinetics for bone scaffolds. Colloids Surf., B **122**, 785–791 (2014)
104. Bi, L., Jung, S., Day, D., Neidig, K., Dusevich, V., Eick, D., Bonewald, L.: Evaluation of bone regeneration, angiogenesis, and hydroxyapatite conversion in critical-sized rat calvarial defects implanted with bioactive glass scaffolds. J. Biomed. Mater. Res. Part A **100**, 3267–3275 (2012)
105. Zhang, Y., Wei, L., Chang, J., Miron, R.J., Shi, B., Yi, S., Wu, C.: Strontium-incorporated mesoporous bioactive glass scaffolds stimulating in vitro proliferation and differentiation of bone marrow stromal cells and in vivo regeneration of osteoporotic bone defects. J. Mater. Chem. B **1**, 5711 (2013)
106. Miguez-Pacheco, V., Hench, L.L., Boccaccini, A.R.: Bioactive glasses beyond bone and teeth: emerging applications in contact with soft tissues. Acta Biomater. **13**, 1–15 (2015)
107. Suzuki, O., Bishop, A.T., Sunagawa, T., Katsube, K., Friedrich, P.F.: VEGF-promoted surgical angiogenesis in necrotic bone. Microsurgery **24**, 85–91 (2004)

108. Day, R.M.: Bioactive glass stimulates the secretion of angiogenic growth factors and angiogenesis in vitro. Tissue Eng. **11**, 768–777 (2005)
109. Peltola, T., Jokinen, M., Rahiala, H., Levanen, E., Rosenholm, J.B., Kangasniemi, I., Yli-Urpo, A.: Calcium phosphate formation on porous sol–gel-derived SiO_2 and CaO–P_2O_5–SiO_2 substrates in vitro. J. Biomed. Mater. Res. **44**, 12–21 (1999)
110. Dai, C., Yuan, Y., Liu, C., Wei, J., Hong, H., Li, X., Pan, X.: Degradable, antibacterial silver exchanged mesoporous silica spheres for hemorrhage control. Biomaterials **30**, 5364–5375 (2009)
111. Lin, C., Mao, C., Zhang, J., Li, Y., Chen, X.: Healing effect of bioactive glass ointment on full-thickness skin wounds. Biomed. Mater. **7**, 045017 (2012)