Silicate-Based Bioactive Composites for Tissue Regeneration

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Y. L. Zhou, Z. G. Huan, and J. Chang

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Abstract

Silicon (Si) is an essential trace element in the human body, which has been confirmed to be necessary for bone development. Silicon participates in the biosynthesis of collagen, the basic component of connective tissue; has a beneficial effect on phosphorylation of proteins, saccharides, and nucleotides; and is also essential for the formation of cytoskeleton and other cellular structures of mechanical or supportive function. Considerable research has been focusing on

Y.L. Zhou • Z.G. Huan • J. Chang (✉)
State Key Laboratory of High Performance Ceramics and Superfine Microstructure, Shanghai Institute of Ceramics, Chinese Academy of Sciences, Shanghai, China
e-mail: jchang@mail.sic.ac.cn

I.V. Antoniac (ed.), *Handbook of Bioceramics and Biocomposites*,
DOI 10.1007/978-3-319-12460-5_15

silicate-based materials, which have shown great potential in bone-related tissue engineering and tissue regeneration applications. Among them, silicate-based bioactive composites with proper composition and structure are promising bone regeneration materials owing to their enhanced and adjustable mechanical and biological properties. In this chapter, we reviewed the current status of silicate-based bioactive composites, including inorganic–organic, inorganic/inorganic, and inorganic/metallic systems, with the focus on fabrication methods and properties for bone tissue regeneration. Although it is evident that many advances have been achieved for silicate-based bioactive composites for the purpose of tissue regeneration, great efforts are still required in their development to fulfill the requirement of practical applications, which is an interdiscipline and subjected to accumulation of materials science and engineering, chemistry, biology, and transplantation medicine. Therefore, the aim of this chapter is to provide hints for future development of silicate-based bioactive composites and design of bioactive materials for bone tissue regeneration.

Keywords

Silicate • Composites • Tissue regeneration • Scaffolds • 3D plotting • Electrospinning • Hydrogel • Membranes • Surface modification • Bioceramics • Bioactive glasses • Bone cements • Metal matrix composites • Metallic substrates

Introduction

With the rapidly aging population and increased accidents, the need for bone regeneration with defects associated with poor healing caused by various reasons such as osteoporosis, fractures, trauma, or large-sized bone tissue injury is urgent. Autogenous bone grafting is the most effective treatment in clinical practice. However, the obvious restraint of this approach is insufficient amount of donor tissue. The immunological reaction in the host recipient is the main limitation for the use of allogeneic or xenogeneic bone grafts. Synthetic materials used for bone repair include metal materials, inorganic nonmetallic materials, organic materials, and composites, which have great potential in clinical applications. Inorganic nonmetallic materials, especially bioceramics, have received significant attention in hard tissue regeneration due to their ability to support new bone formation. Among the synthetic bone replacement materials available on the market, calcium phosphates such as hydroxyapatite (HA) and tricalcium phosphate (TCP) are important bioceramics which are widely used due to their excellent bioactivity, osteoconductivity, and similarities in the composition to the bone tissue.

Bioactivity and biodegradability are two critical aspects in the design of bioceramics for clinical application. Current efforts are devoted toward the synthesis of bioceramics with the degradation rate matching new bone formation process, which means the optimized maintenance of mechanical strength of the implants during the whole process after implantation. Bioinert ceramics such as Al_2O_3 and

ZrO_2 could result in the formation of fibrous capsule along the surrounding bone after implantation which may lead to the failure of implantation. Previous studies have shown that sintered Ca–P bioceramics have poor biodegradability [1, 2]. In contrast, silicate-based bioactive inorganic materials with certain compositions have showed unique bioactivity to bond with living bone and soft tissue and adjustable biodegradability [3].

The main advantage of silicate-based inorganic materials over Ca–P-based bioceramics is dependent on the fact that silicon (Si) plays an essential role in mineralization and gene activation in bone regeneration process [4]. In the late 1960s, Hench et al. discovered that certain silicate-based glasses can induce formation of HA, the main mineral constitute of the bone, which forms a mechanically strong interfacial bond between the host tissue and the implants in physiological environment [5]. Based on these findings, subsequently a new concept of "bioactive" biomaterials was developed instead of inert biomaterials in terms of the implants [6]. Generally, bioactive materials are defined as a class of materials, which have the ability to induce specific biological activity [7], while narrowly, bioactive materials are defined as materials which can promote the interfacial bonding with tissues after implantation and enhance new tissue regeneration through a series of interfacial ion exchange reactions, and a silica-rich gel layer forms followed by the formation of the Ca–P layer on the material surface [8].

Preparation and evaluation of silicate-based biomaterials have attracted more attention in recent years. Silicate-based bioactive inorganic materials mainly fall into three categories: silica-based bioactive glasses, e.g., Bioglass®; crystalline silicate-based ceramics, including wollastonite (β-$CaSiO_3$), pseudowollastonite (α-$CaSiO_3$), diopside ($CaMgSi_2O_6$), etc. [9]; and silicate-based glass–ceramics which were introduced as bone implant materials by Kokubo et al. in 1982 [10]. It has been well accepted that the Si and Ca ions released from silicate-based inorganic materials could stimulate proliferation, osteogenic differentiation of stem cells, and angiogenesis of endothelia cells [11, 12], which makes them hold the promise as a new class of bioactive materials for bone regeneration. However, the major disadvantages of silicate-based inorganic biomaterials, similar to their phosphate-based counterparts, remain their high brittleness, low mechanical strength, and poor machinability. One of the strategies to solve the problem of the poor mechanical properties of some ceramic materials is the preparation of composite materials with other materials such as other type of ceramics, polymers, and metals in order to combine the advantage of two different types of materials. Some recent studies have demonstrated that the combination of silicates with other materials has the advantages not only in the improvement of mechanical properties but also in the controllability of the degradation rate as compared to that of each single component, and the challenge of the approach is to maintain the bioactivity of the silicates with the change of the composition and structure, while the mechanical property is improved.

In recent years, many studies have demonstrated that combining silicates with other materials is an effective way to design bioactive biomaterials with improved properties for tissue regeneration, in particular as orthopedic and dental implants or

for bone tissue engineering applications. Therefore, in this chapter, a systematic review on the recent approaches in preparation and characterization of silicate-based composite biomaterials will be introduced. From the perspective of the material constituents in the composites, silicate-based bioactive composites can be generally classified into three categories: (1) silicate-based bioactive inorganic–organic composites, (2) silicate-based bioactive inorganic/inorganic composites, and (3) silicate-based bioactive inorganic/metallic composites. Therefore, this chapter will focus on these three parts with a short summary, and an outlook in future trends will be presented.

Silicate-Based Bioactive Inorganic–Organic Composites

From materials perspective, the bone tissue is probably one of the most idealist composites in nature. It consists of the fundamental organic phase of proteins such as collagen and the reinforced inorganic nanocrystals of calcium carbonate hydroxyapatite (CHA), which is a typical model of functionally heterogeneous porous scaffolds designed for bone tissue engineering. The porosity and the interaction between the two phases play an important role in determining the mechanical properties of the bone. Inspired by the structure–strength mechanism of natural bone tissue, many researches have been focusing on the development of inorganic–organic composite biomaterials, aiming at combining the properties of traditional materials to some extent in order to achieve admirable improvement in their performance. In consequence, the actual performance of these composites depends on the nature and relative content of the constitutive inorganic and organic components, as well as the synthesis methods [13]. According to the preparation methods or the application purpose, silicate-based bioactive inorganic–organic composites mainly include electrospun fibers, membranes and coatings, scaffolds, hydrogels, and bone cements. Among the majority of these composites, the polymeric matrix would improve the mechanical properties, machinability, porosity, or other properties such as drug-loading ability, while the silicate-based bioactive inorganic particles would ensure the bone integration with the implant or as reinforcement phase to improve mechanical strength on the other hand. In some cases, silicate-based bioactive inorganic particles would serve as efficient drug reservoir if they are endowed with a mesoporous structure. In this session, these five categories of silicate-based bioactive inorganic–organic composites as mentioned above, mainly the fabrication process and properties of the hybrid materials, will be presented. As the interfacial interaction between inorganic silicate phase and polymer phase plays a critical role in determining the fabrication and the final properties of the composites, it is sometimes necessary to improve the compatibility of the two phases, such as the dispersion of one phase with the other. Therefore, in the last part of this section, the surface modification of silicate-based bioactive inorganic materials to enhance the dispersity of inorganic phase in polymer matrix is discussed.

Electrospun Fibers

Electrospinning is a new emerging technique for fabrication of nanoscale continuous fibers with applications in many biomedical and industrial fields. Electrospun fibers display morphological similarities to the natural extracellular matrix (ECM) and have great potential in tissue engineering applications. Using electrospinning techniques, composite nanofibers of most soluble or fusible polymers and a large variety of additives can be fabricated in order to obtain high-performance materials with enhanced or novel properties. Studies have shown that electrospinning is a promising method to precisely control the arrangement of inorganic nanofillers within polymer matrices, which is commonly difficult to achieve using traditional techniques. Calcium silicate hydrate (CSH) nanowire/poly(L-lactide) (PLLA) nanocomposites with tailored CSH distribution, microstructures, and mechanical properties were successfully prepared through a combined method of electrospinning and hot pressing (Fig. 1). In this process, CSH nanowires in PLLA matrix could be controlled from completely randomly oriented to uniaxially aligned and then hierarchically organized with different interlayer angles, leading to corresponding nanocomposites with improved mechanical properties and varied anisotropies [14]. The addition of CSH nanowires greatly enhanced the bending strength, hydrophilicity, and apatite-forming ability of PLLA films, as well as the attachment and proliferation of bone marrow stromal cells (BMSCs).

Electrospinning is also proved to be a useful approach to prepare composite nanofibers consisting of degradable polymers and silicate-based inorganic bioactive particles with improved mechanical strength and biological functions [15]. Poly(ε-caprolactone) (PCL) nanofibers containing bioactive glass (BG) nanoparticles and simvastatin drug were produced by electrospinning. Incorporation of BG nanoparticles in a relatively low concentration (not more than 20 %) could strengthen the polymer matrix by increasing the crystallinity of PCL nanofibers due to the nucleating properties of BG nanoparticles. The chemical and structural characteristics of the polymer affected degradation kinetics of the composite, while incorporation of the BG phase could increase the water-adsorbing capacity of the material, leading to its increased hydrolytic degradation rate. Therefore, it is possible to modify the biodegradation and drug release behaviors of the composites by solely adjusting the BG concentration. The fibrous nanocomposite demonstrated excellent bioactivity such as inducing the precipitation of bone-like apatite minerals on its surface in simulated physiological medium [16]. In a word, the biomedical materials made of nanofibers with high porosity and interconnectivity would show promising potential in tissue regeneration by providing similar structure to that of ECM and controllable drug delivery function [17].

Bioactive Composite Membranes and Coatings

Bioactive Composite Membranes

Bioactive membranes for guided tissue regeneration in the area of wound dressing, nerve conduits, bone healing, and periodontal regeneration have received

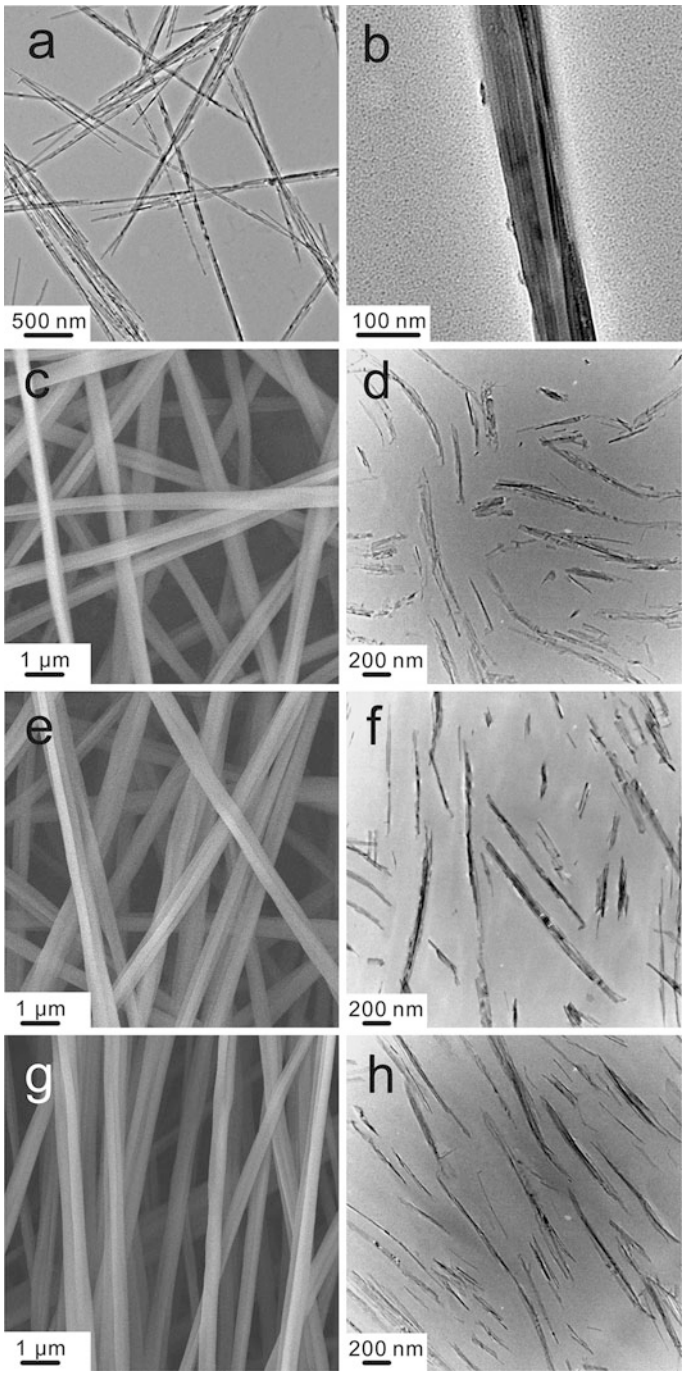

Fig. 1 (continued)

increasing interests [18]. The matrix of these membranes mainly includes natural or synthetic biodegradable polymers. To achieve desirable bioactivity, silicate-based materials have been incorporated into different kinds of polymer membranes. The chitosan/tobermorite ($Ca_5Si_6O_{16}(OH)_2 \cdot 4H_2O$) composite membrane for periodontal regeneration was prepared by solvent casting method. The incorporation of tobermorite particles improved the bioactivity of the composite membranes by inducing formation of crystalline bone-like HA on the surface of the material in simulated body fluid (SBF). The growth of MG63 human osteosarcoma cells was enhanced by up to 30 % on the surface of the composite membranes compared to the blank control [19]. Additional incorporation of growth factors into silicate-containing membranes would further enhance tissue healing process, suggesting a potential approach in tissue engineering and regenerative medicine. A hybrid membrane of collagen and nanobioactive glasses (NBG) incorporated with basic fibroblast growth factor (FGF2) was developed for guiding bone regeneration. Three membrane groups, including pure collagen, collagen–NBG hybrid, and its combination with FGF2, were implanted in rat calvarium defects for 3 weeks. The results showed that the collagen–NBG–FGF2 membranes were most effective on the defect recover than collagen–NBG and pure collagen membranes [20].

In order to design biodegradable membranes with asymmetric bioactivity, the composite membranes with two distinct sides were produced by combining PDLLA and Bioglass® particles in the process of solvent casting methodology that the Bioglass® particles were deposited by gravity to the bottom side. Only the inorganic-rich face promoted the deposition of bone-like apatite after immersing the composite membrane in SBF for 2 days. Interestingly, in vitro studies revealed that osteoblast-like cells seeded on both sides of the membranes present similar levels of metabolic activity and morphology after a period of 7 days [21].

Incorporation of silicate particles within membranes is an effective approach to achieve improved interaction between the material and surrounding tissues after implantation. It is obvious that the incorporation of biomolecules, embedment of physical signaling, and design of hierarchical macrostructures within the membrane would further endow the materials with further enhanced functionality, for which more investigations should be addressed.

Silicate Coatings on Polymers

Biodegradable polymers are extensively used materials in the field of biomaterials owing to their tailorable degradation rates, biocompatibility, and formability. However, higher hydrophobicity and lack of surface bioactivity often result in

Fig. 1 TEM images of (**a**) CSH nanowires and (**b**) PLLA/CSH composite nanofibers with 10 wt% nanowires. (**c**–**h**) SEM images of PLLA/CSH composite nanofibers with a 10 wt% nanowire content collected at different rotation speeds of (**c**) 100, (**e**) 1300, and (**g**) 2500 r.p.m. and (**d**, **f**, **h**) TEM images of the corresponding nanocomposites after hot pressing (**c**), (**e**), and (**g**), respectively [14]

poor tissue integration with the surrounding tissues after implantation. Coating the biodegradable polymers with hydrophilic silicate-based bioactive inorganic particles would enable improvement in the surface properties of the polymer substrate. For this purpose, BG coatings have been applied to modify the surface of polyethylene terephthalate (PET) artificial ligament grafts to enhance their osteointegration. In a rabbit extra-articular model, the BG-coated PET graft induced new bone formation between graft and host bone tissue after 12 weeks, and the average graft–bone interface width of the BG group became significantly lower than that of the control group. Furthermore, the BG coating on the ligament graft surface also stimulated expression of bone morphogenetic protein 2 (BMP-2) and vascular endothelial growth factor (VEGF) near the graft in vivo as compared to the control group after 3 weeks implantation ($p < 0.05$). This study suggests that BG coatings on PET artificial ligaments have a positive effect on osteointegration of the implants by promoting bone regeneration at the interface between PET graft and bone tunnel [22]. To further explore the biofunctionality of the silicate-based coating on biodegradable polymers, internal structure and composition gradient along the thickness based on sophisticated design could be an interesting focus in the future [23].

Composite Scaffolds

In contrast to conventional implants, bone tissue engineering (BTE) is an advanced biomedical technique that is considered as an effective approach for bone regeneration and reconstruction of lost bone tissue. In this approach, the scaffold with well-designed architecture, which performs as a temporary structural carrier for cells, and incorporated growth factors and living cells is one of the critical part of BTE. Currently, the paradigm for the development of BET is that bone substitute materials can promote the human body's own regenerative capacity in the repair process by stimulating expression of osteogenic genes, while appropriate degradability of the scaffolds is required to maintain the mechanical properties of the construct. In this regard, the scaffold should be designed as bone tissue "regeneration" rather than mere "replacement" [24].

Synthetic biodegradable polymers have been extensively investigated as scaffolds for tissue engineering applications because of good biocompatibility and processing convenience. However, poor mechanical property, lack of bioactivity, and the release of acidic degradation product limit their practical utilization. Some researches have shown that, coupled with preferable cellular response, the degradation of silicate-based bioactive inorganic materials would lead to an alkaline pH to the surroundings [25], which is in the very contrary to biodegradable polymers. Therefore, the development of composite scaffolds would enable the combination of individual advantages of polymers and silicate inorganic materials, which may increase the mechanical stability of the scaffolds and improve degradability and tissue interaction to meet the requirement of tissue engineering.

Composites with Natural Biopolymers

Natural-derived polymers such as proteins including collagen and gelatin, and polysaccharides including chitosan, are usually used as chemical components for developing biomimetic bone regenerative materials which demonstrate good biocompatibility and biodegradability. The main disadvantages of natural-derived biopolymers are their poor mechanical strength and lack of bioactivity. It is assumed that both of these problems can be addressed by reinforcing biopolymers with silicate-based inorganic phase to improve mechanical strength and bioactivity of stimulating bone tissue formation [26].

As one of the most important natural polymers, proteins are the major structural components of many tissues. Incorporation of wollastonite into collagen matrix could improve the mechanical strength and in vitro bioactivity of the composite scaffold [27]. Further investigation also shows that wollastonite nanowires can reinforce collagen scaffolds and the hybrid scaffold with interconnected pores could promote osteogenic differentiation and angiogenic factor expression of mesenchymal stem cells (MSCs) [11/10]. In another study, porous bioglass/gelatin scaffolds were implanted on rabbit's ulna, and the results showed that the nanocomposite scaffold could significantly enhance bone growth and healing of the bone defect [3].

Derived from marine crustaceans, shrimp, and crab, chitosan and its derivatives have broad potential for applications as biomaterials due to their abundant source and good biocompatibility. However, porous chitosan scaffolds lack the required strength and thus may not provide sufficient mechanical support for tissue engineering. Incorporation of wollastonite particles into a macroporous chitosan scaffolds could enhance both the mechanical strength and bioactivity such as induction of HA formation [28]. The addition of NBG in chitosan/NBG scaffolds featured macro-/microdual pore structure and facilitated rapid induction of bone mineral-like apatite in SBF. The in vitro cellular responses demonstrated that the scaffolds provided 3D matrix environment to the cells, appropriate for bone cell anchorage, spreading, migration, and growth [29].

It is obvious that the incorporation of silicate-based bioactive materials into the biopolymers can endow the latter with superior bioactivity, and reasonable combination of biopolymers with bioactive silicate inorganic particles can render the development of novel composites with desirable microstructure, mechanical strength, and osteostimulation [30].

Composites with Synthetic Polymers

Biodegradable synthetic polymers have been widely used for biomedical and pharmaceutical applications and have shown great potential in applications as tissue engineering scaffolds due to their adjustable and predictable degradation rates, mechanical strength, and machinability. Polyesters, including polylactide (PLA), polycaprolactone (PCL), poly(lactic-*co*-glycolic acid) (PLGA), polyhydroxybutyrate (PHB), etc. are currently the most promising polymers for biomedical applications. However, the release of acidic degradation by-products which lead to inflammatory responses has limited the use of these biodegradable

polyesters in tissue engineering applications. As silicate-based inorganic bioactive materials could release basic ions in aqueous solutions, it is assumed that its incorporation into the polyester matrix would counteract the acidification reaction caused by the release of the acidic degradation products of the polymers. Based on such assumption, some studies have been conducted and shown that the incorporation of silicate-based bioactive inorganic fillers, such as wollastonite and BG, could indeed effectively neutralized the pH value of the soaking media in a physiological range throughout the degradation process of PLGA. It was also found that the presence of these fillers reduced the degradation rate of the polymeric substrate to some extent [31]. In brief, incorporation of bioactive silicate particles is an effective way to compensate the pH decrease caused by the acidic degradation products of the polymer and to control the degradation behavior of scaffolds.

The addition of silicate-based inorganic particles in polymer matrix could improve the hydrophilicity and bioactivity of the composite surface. It has been found that incorporation of wollastonite into PDLLA scaffold could improve the hydrophilicity of the material and the bioactivity by inducing the formation of HA on the surface [32], and in vitro osteoblast culture experiment confirmed that the composite scaffolds could support the osteoblast proliferation [33]. Another study showed that the ionic products derived from the degradation of β-$CaSiO_3$/PDLGA composite scaffolds could enhance cell viability, alkaline phosphatase (ALP) activity, calcium mineral deposition, and mRNA expression levels of osteoblast-related genes of rat bone marrow-derived mesenchymal stem cells (rBMSCs) without addition of extra osteogenic reagents, and it was further revealed in vivo that the composite scaffold dramatically stimulated new bone formation and angiogenesis as compared with TCP and PDLGA scaffolds (Fig. 2) [34]. The addition of wollastonite into PHBV scaffolds resulted in an increase of the water absorption and weight loss as compared to that of pure PHBV scaffolds, and the presence of wollastonite within the scaffolds benefited the adhesion, proliferation, and differentiation of human bone marrow-derived stromal cells (hBMSCs). A follow-up study confirmed that the ionic products (Ca and Si) released from wollastonite might contribute to this stimulatory effect [35].

Biocompatibility, porosity, mechanical properties, and degradability are most important factors that should be kept in mind during the design of scaffolds for tissue regeneration. It is clear that the incorporation of silicate-based bioactive inorganic particles into polymer matrix provides an effective approach to obtain composite scaffolds with improved properties in these aspects.

Silicate–Polymer Composite Scaffolds for Drug Delivery

Beyond fulfilling the function of bone regeneration, BTE scaffolds have been incorporated with drugs or growth factors, aiming to achieve multifunctions such as inhibiting infections and accelerating angiogenesis. Compared to conversational drug delivery system, local drug release system into the implanting site has great advantages owing to the potential for dose reduction, controlled release pattern, and negligible side effect [36].

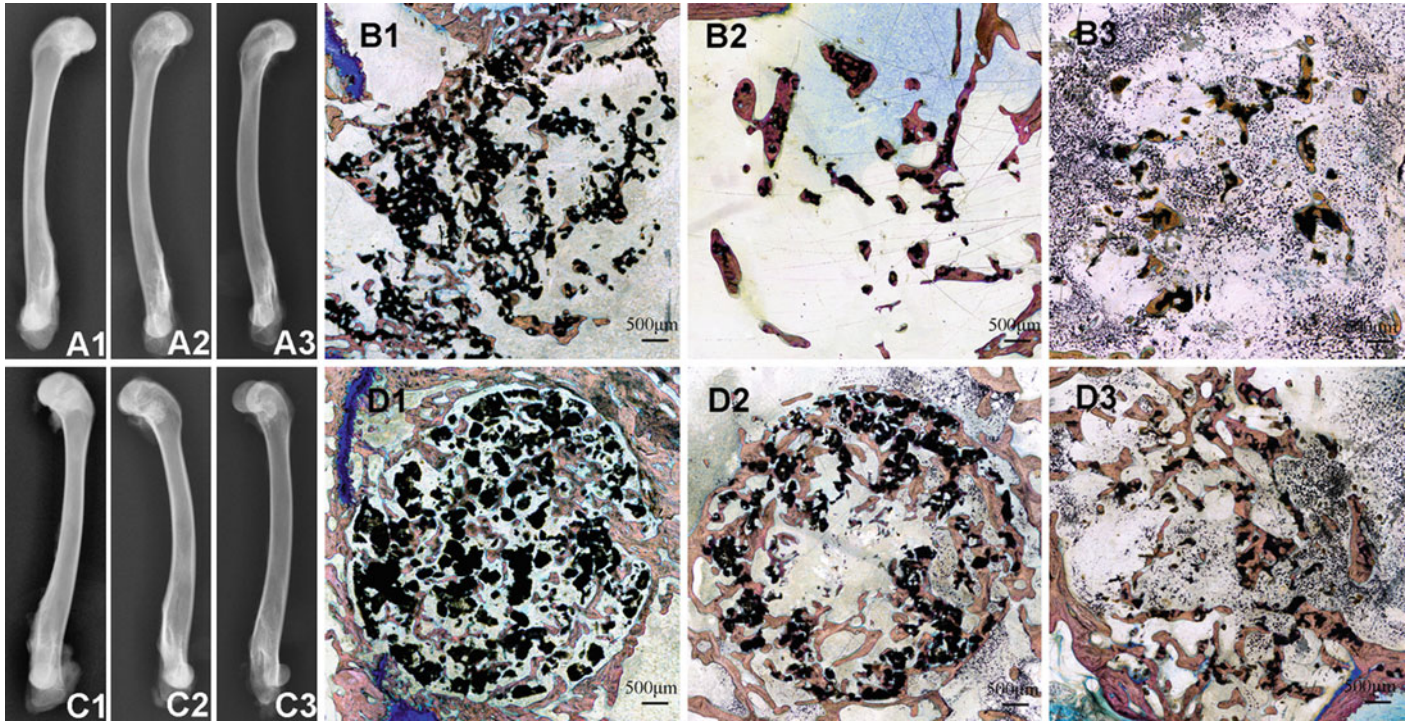

Fig. 2 Radiographs of β-TCP (A1–A3) and PDLGA/β-CS (C1–C3) after 4 (1), 12 (2), and 20 (3) weeks postoperatively. New bone formation and material degradation in β-TCP (B1–B3) and PDLGA/β-CS (D1–D3) after implantation for 4 (1), 12 (2), and 20 (3) weeks (Van Gieson's picricefuchsine staining). *Red*, *blue*, and *black* represent the newly formed bone, fibrous tissue, and residual material, respectively. Scale bar, 500 mm (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article) [34]

Silicate-based mesoporous bioactive glasses (MBG) have attracted much attention as drug delivery system owing to its highly ordered mesoporous channel structure, large surface area, and variable pore volume. It has been proved that MBG show great potential in drug delivery. Therefore, incorporation of drug-loaded MBG into a polymeric substrate appears to be an effective way to endow the scaffold with the ability of sustained and controlled drug eluting. Nanosized MBG/PLGA composite-coated $CaSiO_3$ multifunctional scaffolds were used for delivering ibuprofen with a sustained release profile to prevent infections [37].

Fabrication Techniques for Composite Scaffolds

Besides surface chemistry, factors including interconnectivity, volume, and size of the pores of scaffolds are also important parameters, which could affect functions of the scaffolds such as enhancement of tissue ingrowth in the early stage of tissue defect healing. It is generally accepted that open, interconnected, and suitable porous structure facilitates biological molecule and nutrient transportation to the inner part of the scaffolds, which is necessary to facilitate cell growth and vascularization, as well as excretion of waste products. Therefore, the development of fabrication techniques of composite scaffolds is essential for controlling the porous structure of the composites. Many conventional techniques are available for fabrication of various composite scaffolds based on the combination of biodegradable polymer and inorganic bioactive particles, including freeze-drying, solvent casting and particulate leaching, phase separation, and hot compression molding.

Freeze-drying is a common process suited to fabricate biopolymer such as collagen composite scaffolds which renders highly porous and interconnected homogenous biological constructs without damaging the structure of the biopolymer. Through the freeze-drying method, fabrication of biopolymer/silicate composite scaffolds with improved bioactivity and mechanical strength has been proved to be practical [11, 27]. In addition, freeze-drying method combined with other techniques, e.g., robocasting, was introduced to produce scaffolds with finely tuned structure of macroporous configuration, which contained well-developed micropores throughout the framework and thus have a prosperous prospect [29].

Solvent casting and particulate leaching methods mainly include three steps in sequence: mixing of polymer solution with silicate-based bioactive inorganic particles and salt particles as porogens, evaporation of the solvent, and leaching of the salt out in water. Such method allows for the fabrication of porous composite scaffold with high porosity (over 80 %), interconnected pores (300–450 μm), and compressive modulus (10–14 MP). However, the main shortcoming of this technique is that it could only prepare thin scaffolds (usually several millimeters in thickness) [33].

Phase separation is usually conducted at low temperature and generally covers two procedures, namely, quenching a solution with polymer and inorganic particles to form an inorganic particle-rich phase and a polymer-rich phase and solidifying the polymer-rich phase with the removal of the polymer-poor phase to form a porous polymer network. The composite scaffolds obtained by this technique have a wide range of pore size distribution (including micro- and macropore structure), which is

beneficial for scaffolds with the desire of tiny bioactive particles or biomolecule incorporation into the struts. Through this technique, wollastonite particles were dispersed uniformly on the pore walls of chitosan/wollastonite composite scaffolds with interconnected pores varied from 60 to 200 μm [28].

Hot compression molding involves filling a mold with mixtures of polymer/inorganic particles and porogen powders and followed by heat treatment in high temperature together with intended pressure. The main virtue of this technique for preparation of biodegradable polymer/silicate bioceramics composite scaffolds is the relatively high mechanical properties of the scaffolds, whereas the disadvantages include the inefficient removing of the residual porogens and the high processing temperature that may be destructive to the chemical structure of some polymers [35].

Rapid prototyping (RP) methods are emerging techniques to design and fabricate scaffolds with complex and controlled pore size, shape, and interconnectivity directly from computer-aided design and manufacturing. Among RP techniques, 3D plotting has shown promising potential for direct fabrication of tissue engineering scaffolds with the advantage of mild processing conditions, which enables incorporation of drugs, biomolecules, and even cells during plotting. MBG/alginate hierarchical scaffolds with well-ordered nano-channels, micropores, and controllable macropores were fabricated by 3D plotting, and the structural architecture of the composite scaffolds could be optimized by control of the plotting parameters (Fig. 3). Furthermore, as a drug delivery system, the incorporation of MBG decreased the initial burst release and led to a more sustained release of dexamethasone from the composite scaffolds, and the release rate was a function of the MBG content [38]. Homogenous surface coating of MBG throughout the poly 3-hydroxybutyrate-co-3-hydroxyhexanoate (PHBHHx) scaffolds was prepared using combinational 3D printing and surface-doping protocol. These hierarchical scaffolds showed the bioactivity superior to that of scaffolds made of pure PHBHHx, and the MBG coating provided a more preferable environment for human mesenchymal stem cell (hMSC) attachment, proliferation, and osteogenic differentiation [12]. Therefore, 3D plotting could be a promising platform for the preparation of silicate/polymer composite scaffolds for BTE applications.

Injectable Composite Hydrogels

Injectable hydrogels are cross-linked polymers with hydrophilic groups which can change structure in response to salt concentration, pH, temperature, etc. and have received much attention as they can provide hydrated 3D environment that is similar to the ECM of native tissues, thus holding a great promise in tissue engineering applications. Inspired by the advances in research on silicate–polymer composite scaffolds, intended incorporation of silicate-based bioactive inorganic particles into hydrogels has been investigated, aiming at combining the advantages of the hydrogel and silicate-based bioceramics. Up to now, several polymeric hydrogel/silicate bioceramics composite systems have been developed, and their performance for

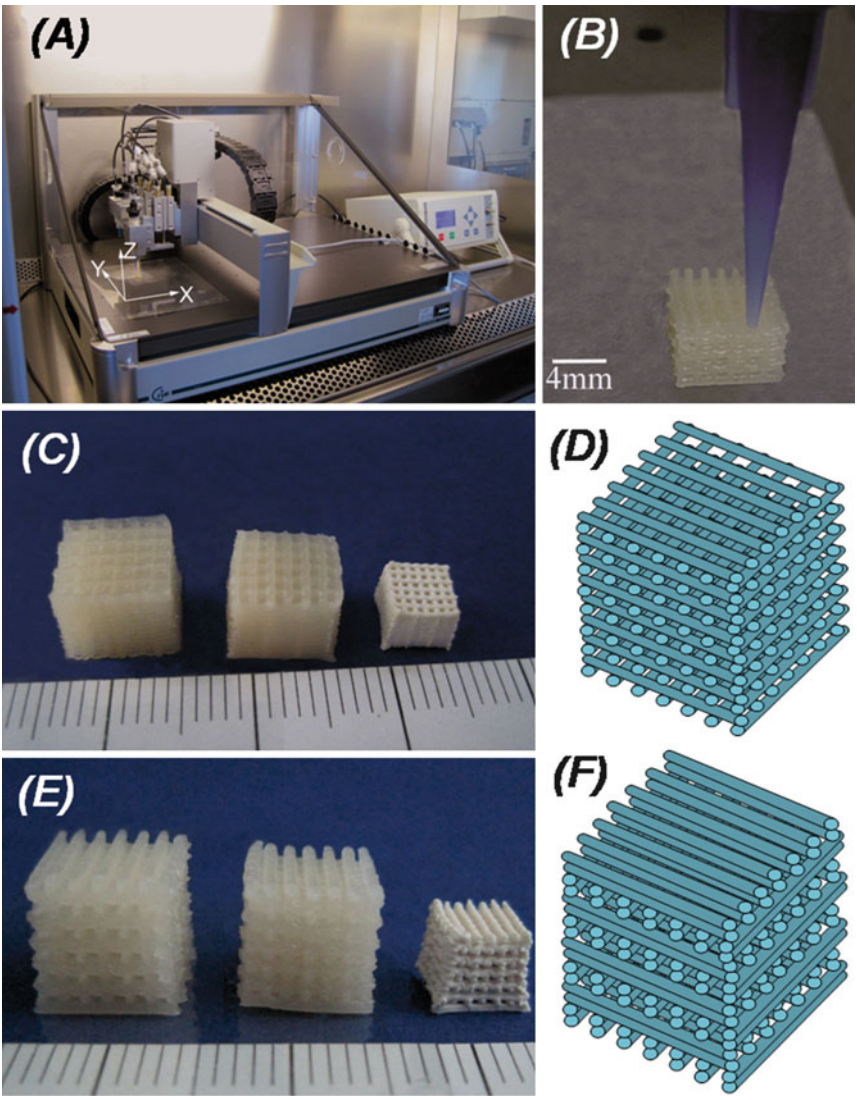

Fig. 3 Photographs of the 3D plotting system (**a**) and a scaffold during plotting (**b**); CAD models (**d**, **f**) and scaffolds (30 % MBG/alginate) (**c**, **e**) with XY pattern (**c**, **d**) and XXYY pattern (**e**, **f**). (**c**) and (**e**), scaffolds are shown in wet state after plotting and after cross-linking in 500 mM $CaCl_2$ solution and dry state, respectively (from *left* to *right*). In the design used for plotting, the cubic scaffolds had an edge length of 8 mm and a pore size of 850 μm [38]

tissue engineering has been evaluated in details. Herein, the polymeric hydrogel substrate can be generally categorized based on their source, namely, natural hydrogels and synthetic hydrogel. Among the natural hydrogels, chitosan, alginate, and their derivatives have been studied extensively. Meanwhile, for the synthetic

group, poly(vinyl alcohol)- and poly(ethylene glycol)-based hydrogels have been investigated in recent years.

Silicate/Natural Polymer Composite Hydrogels

Sodium alginate (SA) has the distinctive ability to form hydrogels via ionotropic cross-linking in the presence of divalent cations such as calcium ions (Ca^{2+}) in the room temperature. Since $CaSiO_3$ is degradable and could release Ca^{2+} in physiological environment during the degradation, $CaSiO_3$/SA composite hydrogel was prepared by self-cross-linking of alginate with Ca^{2+} in the presence of D-gluconic acid δ-lactone (GDL) and the gelling time; compressive properties and swelling behavior could be controlled by varying the amounts of $CaSiO_3$ and GDL. Here, GDL is functioning as a regulator to control the release of Ca^{2+}, which will control the injectability of the composite hydrogel. The CS/SA composite hydrogel showed bioactivity in stimulating osteogenic differentiation of rBMSCs and promotes angiogenesis of human umbilical vein endothelial cells as pure CS bioactive ceramics [39].

Alginate microspheres are considered as a promising material for drug delivery due to their excellent biocompatibility. However, their main disadvantage is the low drug loading efficiency and noncontrollable drug release. Incorporation of MBG into alginate was found to increase the loading amount of dexamethasone as compared to pure alginate microspheres, which was attributed to the large surface area and enrichment in hydroxyl groups of BG. Besides, it is interesting to note that the drug delivery ability of bioactive inorganic materials/alginate composite microspheres could be controlled by controlling the pH environment [40].

Maintenance of the pH value of the hydrogel is a vital issue for its clinical application, which allows for the incorporation of cells or bioactive agents. A novel chitosan/Bonelike® (glass based on the P_2O_5–CaO–Na_2O system) hydrogel was synthesized by using γ-glycidoxypropyltrimethoxysilane (GPTMS) in a sol–gel process which was easy to inject. The time required for gelation and the degradability of the hydrogel could be controlled by controlling the concentration of chitosan and GPTMS. Most importantly, the pH changes caused by the chitosan/Bonelike® hydrogel were small which could not cause any deleterious effect in vivo [41].

The combination of silicate-based bioceramics and natural hydrogels retains the high water content network of the hydrogel and the bioactivity of silicate-based bioceramics which show great potentials in bone regeneration and tissue engineering applications.

Silicate/Synthetic Polymer Composite Hydrogels

In comparison with natural hydrogels, the well-defined structure of synthetic hydrogels may lead to finely tunable degradation kinetic. However, the inherited low mechanical strength and lack of bioactivity of these synthetic hydrogels limit their applications. Recently, composite hydrogels with bioactive inorganic materials as reinforcement have received strong interests for biomedical applications. A series of polyvinyl alcohol (PVA)/bioglass composite hydrogels were synthesized through ultrasonic dispersion, heat high pressure, and freeze-thawed technique. Compared

with the pure PVA hydrogel, the elastic compression modulus of PVA/bioglass composite hydrogels was significantly improved by uniform distribution of bioglasses within the composites [42]. Another study has revealed that the incorporation of BG into PEG hydrogel could enhance the mechanical strength of the hydrogel, and the as formed PEGs/BG composite hydrogel possessed the ability to induce the deposition of apatite on the surface, making these hydrogel-based composites a suitable candidate as bioactive bone graft substitutes [43].

The development of advanced hydrogels with tunable physiochemical properties and desirable bioactivity remains a major challenge for tissue regeneration, for which silicate-containing hydrogels have provided promising solutions and are worthy of further investigations.

Composite Bone Cements

Polymer bone cements, which mainly consist of polymethylmethacrylate (PMMA), have been used for fixation in joint replacement surgery, filling dental cavities, and augmentation of vertebrae. Despite the desirable mechanical strength and handability, the lack of bioactivity remains the major concern over clinical applications. Currently, researches have been focusing on the incorporation of silicate-based bioactive fillers into bone cements, such as BG and bioactive glass–ceramics, in order to improve the surface bioactivity as these inorganic materials can bond to the living bone inside the body through the formation of an apatite layer on the surface. In order to provide PMMA with bioactivity, granules of a BG $50CaO \cdot 50SiO_2$ (mol %) were suspended into PMMA substrate through ultrasonic agitation in order to obtain bioactive cements. The addition of glass granules could soften the PMMA substrates. After 4 h soaking in SBF, aggregates of apatite particles appeared on the substrates. Apatite was precipitated on the whole substrate surface within 1 day. The silica gel islands on PMMA due to the silicate anions from the glass were considered to induce nucleation of the apatite particles [44]. The mechanical property and bioactivity of bioactive glass–ceramic particles (based on the $Na_2O–CaO–SiO_2–P_2O_5$ glass system) and HA into commercial PMMA bone cement were compared. The PMMA/glass–ceramic sample showed a higher flexural strength and flexural modulus than those of PMMA/HA samples. Most importantly, apatite globules were formed on the surface of PMMA/glass–ceramic composite cements, verifying their improved surface bioactivity as compared with the original PMMA cements [45].

In recent years, calcium silicate-based cements (CSCs) with high bioactivity and enhanced osteogenesis, such as Ca_3SiO_5 and Ca_2SiO_4, opened up new possibilities in the field of bone filling materials. However, the inappropriately long setting time and relatively low compressive strength of the cement made them difficult to deliver to bone defects with complex structures. One strategy to overcome these disadvantages is to combine CSCs with cohesion promoters such as chitosan. Wang et al. developed a novel rapid-setting root-canal filling and substitute materials consisting of chitosan oligosaccharide (COS) and β-Ca_2SiO_4. The incorporation of

5 wt% COS was obviously effective in shortening the setting time and enhancing the compressive strength of CSCs. In vitro experiments indicated that the hybrid cement containing 5% COS induced formation of HA in SBF after 1 day soaking [46]. Lin et al. prepared anti-washout carboxymethyl chitosan (CMCS)–Ca_3SiO_5 (C_3S) pastes. CMCS–C_3S pastes were stable in the shaking SBF after immediately mixed. The addition of CMCS could significantly enhance the cohesion of particles and at the same time restrain the penetration of liquid and thus endow the anti-washout ability. The setting times of the composite pastes increased with the increase of CMCS concentrations in the hydration liquid [47]. In a word, calcium silicate-based inorganic cement composite with biopolymer could endow better performance, like shorter setting time and better mechanical properties as compared to pure CSCs.

Surface Modification of Silicate-Based Bioactive Inorganic Materials

The interfacial interaction between bioactive inorganic particles and polymer matrix plays a significant role in determining the properties of the silicate inorganic materials/polymer hybrids. Similar to other hydrophilic inorganic particles, inorganic silicate powders tend to agglomerate in the hydrophobic polymer matrix due to their small dimensions and incompatible polarity with polymers, and the integral property of the composite would be influenced consequently. Therefore, it is critical to improve the compatibility between the silicate-based bioactive inorganic particles and the polymer components so as to obtain the uniform dispersion of silicate-based bioactive inorganic particles within the composites. For this purpose, surface modification of silicate-based bioactive inorganic materials is one of the most effective approaches to improve the compatibility of inorganic components in polymer substrates. The rationale is that the Si–OH on the surface of silicate-based bioactive particles could react with functional group of organic molecules, which would lead to a more compatible surface of the silicate particles to the polymeric substrate, which favors a more uniform dispersion and stronger interfacial strength.

Silanization of Silicate-Based Bioactive Inorganic Materials

Coupling agents can enhance the adhesive bonds of dissimilar surfaces by developing a highly cross-linked interphase region. As a typical coupling agent, silanes as bifunctional compounds can bind the filler particles to the polymer matrix which may also provide protection for leaching, and thus the mechanical properties of the composite may be retained for a longer period [48]. The 3-aminopropyltrimethoxysilane (APS) is one of the most common nontoxic silane coupling agents which was used to modify the surface of BG in order to improve the phase compatibility between poly-L-lactide (PLLA) and BG. BG particles were uniformly dispersed without agglomeration in PLLA matrix after surface modification. Furthermore, the bending strength, bending modulus, and shearing strength of PLLA/BG-APS composites were all higher than those of unmodified composites [49]. Silane coupling agent (Z-6030, γ-methacryloxypropyltrimethoxy) has also been used as coupling agents to

eliminate the weak bonding between polymethylmethacrylate (PMMA) and $CaSiO_3$ phases. The hydroxymethyl groups of Z-6030 could be substituted by hydroxyl groups that could chemically bond with –OH groups on the $CaSiO_3$ particle surface forming O–Si–O chemical bonding. The results indicated that appropriate amount of $CaSiO_3$ nanoparticles (0.6 %) modified by appropriate amount of Z-6030 (1.5 %) could improve the flexural strength and surface hardness of PMMA denture base materials [50].

Silane coupling agents improve the interfacial strength between silicate and polymer by developing a highly cross-linked interphase region, which is realized by the chemical bonding between the hydroxyalkyl groups of silane coupling agents and hydroxy groups on the surface of silicate-based bioactive inorganic particles. If the presence of silane coupling agent was inadequate, the combination between the agent and the silicate particles would not be sufficient to improve the mechanical strength or, even worse, may result in a decrease of the strength. Therefore, the proper ratio of the silane coupling agent to the silicate particles is essential for the effect and efficiency of surface modification [50].

Surface Modification with Dodecyl Alcohol

Dodecyl alcohol was used to modify silicate-based bioactive inorganic particles through esterification reaction to improve the homogeneous dispersion of inorganic particles in polymeric matrix [51]. The hydroxyl groups of dodecyl alcohol condensed with the Si–OH groups on the surface of BG particles through esterification. The modified composite films can still induce the formation of HA on their surface after immersion in SBF, and the distribution of HA was more homogeneous on the composite films. However, the disadvantage of the modification with dodecyl alcohol was the decrease in hydrophilicity, which may affect the biocompatibility of the composite materials. Fortunately, this modification is reversible, and the dodecyl alcohol can be removed after the achievement of homogenous dispersion of silicate-based inorganic particles in composite materials by hydrolytic treatment in hot water. The properties (such as tensile strength) of the composite films after treatment will not be affected. Most importantly, cells on the composite films after hydrolysis showed a high proliferation rate [52] (Fig. 4).

In summary, it is a useful way to improve the dispersivity of inorganic particle in polymer matrix by modifying the surface of silicate-based bioactive inorganic particles with nontoxic organic molecules, especially biocompatible molecules.

Silicate-Based Bioactive Inorganic/Inorganic Composites

The composite system is designated as inorganic composite systems if the components in the composites are mainly inorganic. Silicate-based bioactive inorganic composite materials are a kind of inorganic composite system which has attracted great attention in recent years owing to their enhanced properties if the constituents are optimally designed. The properties and functions of inorganic composites can be tuned by controlling the composition and fabrication methods. Basically, the silicate-based

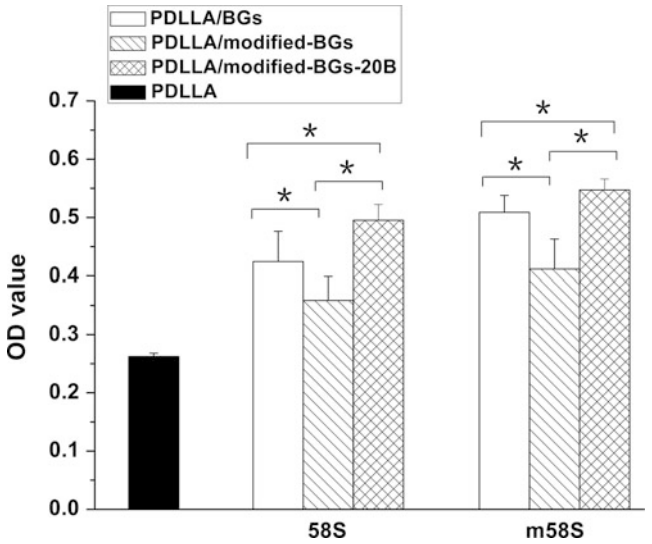

Fig. 4 The dMSC proliferation on different composite films. OD value on y-axis represented the number of living cells. *Asterisk* indicates that the difference between the two data was significant ($p < 0.05$) [52]

inorganic composite system could be generally classified into two categories, namely, the preformed silicate-based composite ceramics and the silicate-based bone cements with the ability of self-setting. At the end of this section, silicate-based bioceramic composites modified with graphene and SiC were also briefly reviewed.

Silicate-Based Composite Ceramics

Compared to bioinert metal oxide ceramics (e.g., Al_2O_3 and ZrO_2) and conventional calcium phosphate ceramics, silicate-based bioceramics with specific compositions possess distinct bioactive properties by enhancing the in vitro osteogenic and angiogenic differentiation of stem cells, which is also the main force for the development of the silicate-based bioceramics. However, the main shortcomings of silicate-based materials are intrinsic brittleness and mechanical weakness which restrict their intended medical applications. The design of composite materials thus offers an exceptional opportunity to allow well control of material properties. It is a common notion that the chemical composition is one of the most important factors that affect the properties of materials. The rational design of silicate-based composite ceramics is that their mechanical properties, degradation behavior, bone bonding, and regenerating ability could be regulated by tuning the components of the materials. Despite their successful applications, calcium phosphate ceramics and bioinert ceramics such as alumina and zirconia are still frequently investigated due to their poor biodegradability or lack of bioactivity [1, 2]. Previous studies have shown that

BG and glass–ceramic containing CaO and SiO_2 possessed good bioactivity and the CaO–SiO_2 system (like calcium silicate, CS) has been considered as the basis for the development of the third-generation tissue regeneration materials presently in development [6]. Meanwhile, silicate-based bioceramics in some certain composition show admirable biodegradability. Therefore, development of calcium phosphate–silicate and bioinert ceramic/silicate composite ceramics may offer a chance to produce novel bioceramics with improved bioactivity and biodegradability.

Calcium Phosphate–Silicate Composite Ceramics

Calcium phosphate ceramics appear to be very prominent for hard tissue replacement due to their remarkable biocompatibility and their close chemical similarity to biological apatite in human hard tissues. Although some calcium phosphate bioceramics are osteoconductive, they lack the ability to stimulate cell differentiation and bone regeneration, which impede their wider clinical applications. Low degradability and mechanical strength also severely hinder their practical use [2]. The design of calcium phosphate–silicate composite materials is one of the primary approaches to enhance bioactivity of the materials.

Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, HA) ceramic is one of the most frequently used calcium phosphate ceramics for hard tissue regeneration due to its remarkable biocompatibility, high osteoconductivity, and chemical similarity to biological apatite in human hard tissues. However, conventional HA bioceramics represent poor mechanical strength, and moreover their low degradability prevents complete bone replacement and bone remodeling. Therefore, there is urgent clinical demand for increasing the mechanical properties and degradability of the HA-based bioceramics, and one approach to solve these problems is to combine HA with a biodegradable and toughening phase. HA/CS composite bioceramics with different weight ratio were fabricated, and it was found that the mechanical properties, bioactivity, and the dissolution rate of the composites were upgraded with increasing CS content. Moreover, the proliferation rate of BMSCs on the composites was significantly higher than that of the pure HA ($P < 0.05$). These results suggest that the mechanical properties, bioactivity, degradability, and cell activity of the HA/CS composite bioceramics could be tailored by adjusting the initial HA/CS ratio, and the HA/CS composites might be promising candidates for hard tissue repair [53].

Bioresorbable β-$Ca_3(PO_4)_2$ (TCP) is another widely used calcium phosphate bioceramics. However, relatively low bone formation ability of TCP may impede its further clinical applications. Calcium silicate ($CaSiO_3$, CS) ceramics have been investigated as a new type of bioceramic for hard tissue regeneration owing to their excellent bone regeneration ability and biodegradability [54]. Liu et al. [55] investigated the in vivo effect of CS on the degradability, osteogenesis, and bioactivity of TCP by preparing porous TCP/CS composite bioceramics with different weight proportions. The results showed that the osteointegration and osteogenesis of porous TCP/CS composite bioceramics were significantly enhanced as compared with pure TCP ceramics, and the degradation rate of the composite was between those of pure TCP and CS. It was therefore assumed that a suitable combination of calcium

phosphate and calcium silicate ceramics may render greater functionality as compared to pure calcium silicate and calcium phosphate ceramics. Further experiment results proved that the TCP/CS composite scaffolds had excellent osteoconductivity and stimulated rapid bone formation compared with pure β-TCP and β-CS scaffolds in rabbit femur defects, and most importantly, they could degrade progressively at a rate matching the regeneration of new bone [56]. The introduction of CS into porous TCP bioceramics is thus an effective method to prepare bioactive bone grafting scaffolds for clinical applications.

Calcium Silicate/Bioinert Metal Oxide Composite Ceramics

Although the silicate-based bioceramics possess good bioactivity, the insufficient mechanical properties hinder the silicate-based bioceramics in clinical application, especially in those where high mechanical strength is required. On the other side, some bioinert metallic oxide ceramics such as alumina and zirconia have high mechanical strength and toughness. Appropriate incorporation of tough metallic oxide (MO_X) particles into silicate-based bioceramics is considered as a practical approach to improve mechanical properties of the materials.

Alumina (Al_2O_3) and zirconia (ZrO_2) as bioinert ceramics have been widely applied in the field of prosthodontics and orthopedics owing to their high mechanical properties, which makes them as ideal toughening fillers when improving the mechanical strength of silicate-based bioceramics is concerned. A uniform Al_2O_3 and α-calcium silicate (α-$CaSiO_3$) composite ceramic were fabricated by mechano-chemical method and then sintered at 1250 °C to produce composite ceramics with open porosity and high hardness and fracture toughness. A newly formed phase $CaAl_2O_4$ from the reaction of CS and alumina mainly contributed to the improvement of mechanical properties of the composite ceramics [57]. Besides Al_2O_3, zirconia (ZrO_2) ceramic is another bioinert ceramic that can be applied to reinforce silicate-based bioceramics. β-$CaSiO_3$/ZrO_2 nanocomposites were fabricated by spark plasma sintering (SPS) technique. The addition of ZrO_2 could inhibit the phase transition of CS and increase its phase transition temperature. A nanocrystalline ZrO_2 network structure was formed in the nanocomposites, by which the fracture toughness was significantly improved. The composites showed good in vitro bioactivity with HA layer formation on the surface of the nanocomposites in SBF [58].

Besides the MO_X-reinforced CS ceramics, different kinds of silicate-based ceramics hybrids have been developed. A series of β-$CaSiO_3$/Mg_2SiO_4 (CS/M_2S) composites with different ratios were prepared by sintering the CS/M_2S composite powder compacts at different temperature. The heat treatment induced a reaction between the CS and M_2S, and the composites obtained were a mixture of CS, M_2S, $CaMg(SiO_3)_2$, and $Ca_2MgSi_2O_7$. With the formation of these intermediate phases, the mechanical properties of CS/M_2S composites steadily increased with the increase of M_2S amount. It was also found that CS/M_2S composites retained the ability to induce apatite formation on the surface in SBF if the proportion of M_2S was reasonably selected. Furthermore, in vitro cell culture experiments indicate that the composites supported osteoblast-like cell proliferation effectively. The results

suggest that combination of CS and M_2S is a proper way to obtain Ca–Si–Mg composite ceramics with improved properties [59].

Silicate-Based Bone Cements

In order to meet the need of minimal invasive surgery in clinical applications, the concept of self-setting bone cements has been introduced to be applied as injectable or moldable bone substitutes to augment human bone tissues [60]. Inorganic bone cements like calcium phosphate cements (CPC) and plaster ($CaSO_4 \cdot 1/2H_2O$, POP) have been steadily studied as self-setting bone filling materials. However, both CPC and POP have their own problems such as lack of osteogenic activity and unsatisfactory degradability. Recently, calcium silicate-based bone cements (CSCs) have attracted attention owing to their distinguished advantages such as apatite-inducing activity and osteostimulation ability. Similar to calcium silicate bioceramics, ionic products of calcium silicate-based cements during their degradation could significantly stimulate the proliferation and osteogenic differentiation of osteoblast-like cells and dental pulp cells [61]. It is therefore clear that the single-phase bone cements need to be modified to fully meet the clinical demand. Composite CSC with other inorganic phases may be an alternative way to obtain composite cements with adorable properties for practical application. In this section, the properties of CSC and their composites with other kind of inorganic bone cements are introduced, respectively.

Calcium Phosphate–Silicate Composite Bone Cements

CPC have been extensively studied owing to their chemical similarity to the mineral phase of bone tissue and good osteoconductivity for bone reconstruction. In clinical applications, CPC can be used in the form of blocks or as a self-setting paste, which could rapidly set and provide supporting for bone regeneration. However, as soluble acidic phosphates are used as sources of phosphate ions, the setting process of some kinds of CPC (e.g., brushite cement) may cause a rapid decrease of pH in vivo immediately after implantation. This phenomenon can have an adverse impact on the biocompatibility of the material. Tricalcium silicate (Ca_3SiO_5, C_3S) is one of the main components of Portland cement. Once mixed with water, C_3S will react with water to create calcium–silicate–hydrate (C–S–H), and the polymerization and solidification of the C–S–H network contribute to the self-setting property of the material. However, this material could induce a significant increase in the surrounding pH (>10), and the setting time of the cement paste is quite long, which may make it not suitable for clinical applications. Considering the characteristics of CPC and C_3S cements, composite cements were designed and prepared by hybriding CPC, containing β-TCP and monocalcium phosphate monohydrate (MCPM), with bioactive C_3S. The results showed that the composite cements processed higher injectability by moderately prolonged setting time and mechanical strength as compared with their CPC counterparts. More importantly, the composite cements possessed an improved ability to promote osteoblastic differentiation of BMSCs,

indicating that the composites may possess a better support for bone regeneration [62].

Another calcium phosphate–silicate composite cement can be obtained by mixing $CaHPO_4 \cdot 2H_2O$ (DCPD) and C_3S with 0.75 M sodium phosphate buffers (pH = 7.0) as liquid phase. The setting times, injectability, degradability, and compressive strength are investigated and compared with that of DCPD/CaO cement system. With the weight ratio of C_3S varied from 20 % to 40 %, the workable DCPD/C_3S pastes set within 20 min, and the hydrated cement shows significantly higher compressive strength (around 34.0 MPa after 24 h) than that of the DCPD/CaO cements (approximately 10.0 MPa), and the degradability of DCPD/C_3S cement is improved. Additionally, the composite cement possesses better ability to support and stimulate cell proliferation than the DCPD/CaO cement [63].

These researches have demonstrated that the combination of bioactive calcium silicate with calcium phosphate cement is a possible approach to obtain bioactive self-setting composite cements with superior self-setting and biological properties for bone regeneration.

Calcium–Silicate–Aluminate Composite Bone Cements

$Ca_3Al_2O_6$ has the fastest hydration rate among the main components of Portland cement. Although not suitable as single-phase bone cement due to its arguable cytocompatibility, it is assumed that the limited presence of C_3A in C_3S, C_2S, or C_3S/C_2S (CSC) cements may accelerate the hydration process and improve the short-term compressive strength of the materials. C_3S/C_3A and C_2S/C_3A composite systems are able to form biphasic mixtures. Studies showed that the addition of C_3A into C_3S and C_2S indeed could reduce the setting time and improve the compressive strength of the substrates. Furthermore, both mixtures are bioactive and biocompatible and have a stimulatory effect on the L929 cell growth when the content of C_3A is below 10 % [64, 65]. Further study showed that the CSC/C_3A cement was notably more compatible with the human dental pulp cells compared with the commercially available Dycal® [66]. Therefore, silicate-based cements mixed with small amount of C_3A appear as a promising candidate as dental cement considering their relative short setting time, high compressive strength, good in vitro bioactivity, and biocompatibility.

Calcium Silicate/Calcium Sulfate Cements

Plaster ($CaSO_4 \cdot 1/2H_2O$, POP) has been used as bone filling material for more than a hundred years. It can react with water promptly and transform into gypsum ($CaSO_4 \cdot 2H_2O$), which is in the form of solid and hard lump. After 1 or 2 weeks of implantation, the gypsum degrades and tends to form many pores that allow the new bone tissues to grow in, and after 4–6 weeks, the gypsum degrades almost completely. An obviously too fast degradation rate and lack of bioactivity are the drawbacks of POP in its orthopedic applications. Some studies have found that the addition of POP into pure C_3S or C_2S cements could decrease the setting time and enhance the compressive strength and degradation rate [67, 68]. Most importantly, the composite paste showed activity in induction of apatite formation in SBF, and the

dissolution extracts of the paste had a stimulatory effect on cell growth in certain concentration range [69]. POP has also been composed with CSC to further improve the property, which showed that the addition of POP into CSC significantly decreased the initial and final setting time and enhanced the short-term compressive strength and degradation rate. The obtained composite cement with 30 % POP has been found to possess optimal setting time and short-term compressive strength. In addition, the prepared composite cements still maintain apatite-mineralization ability in SBF (Fig. 5), and their ionic extracts have no significant cytotoxicity to L929 cells [70].

Another study has shown that the addition of silicate bioceramics without hydration property such as calcium silicate (CS) into POP can also form bioactive bone cements. The POP/CS cements showed high surface bioactivity by introducing 23 % bioactive calcium silicate (CS) into POP, and these biphasic composites were favorable for decelerating the biodegradation rate by nearly 18.5% as compared to pure POP cements in 28 days in vitro. Further in vivo evaluation of the composite cements showed that the materials had a mild bioresorption rate of 39.6 % after 4 weeks, and enhanced new bone tissue regeneration was confirmed for the composite material as compared with pure gypsum in critical-sized femoral defects in rabbits [71].

Calcium Silicate/Calcium Carbonate Cements

In cement industry, calcium carbonates are often used as hydration accelerator and filler component within cement pastes, which reduce the setting time and promote the mechanical strength of Portland pastes. In biomedical applications, calcium carbonates of biological origin (nacre and coral) and their derivatives have been used as biocompatible and resorbable bone substitutes in the form of powders, porous ceramics, and hydraulic cements. To combine the advantages of the silicate-based cements and $CaCO_3$, $C_3S/CaCO_3$ composite cements with the weight percent of $CaCO_3$ in the range of 0, 10, 20, 30, and 40 % were synthesized. The results showed that the initial setting time was dramatically reduced from 90 to 45 min as the content of $CaCO_3$ increased from 0 % to 40 %, and the workable paste with a liquid/powder (L/P) ratio of 0.8 ml/g could be injected within 20 min. The composite cement showed higher mechanical strength (24–27 MPa) than that of the pure C_3S paste (14–16 MPa). Furthermore, the composite cement could induce apatite formation and degrade in phosphate-buffered saline. This study indicates that the $C_3S/CaCO_3$ composite paste has better hydraulic properties than pure C_3S paste and the composite cement is bioactive and degradable [72].

Calcium Silicate–Fluoride Composite Bone Cements

Fluoride plays a significant role to protect enamel against demineralization and has already provided clinical benefits on tooth and skeleton repair. Incorporating fluoride into dental resins and glass ionomer cements has already been proved to be an effective method to increase the remineralization properties of filling materials. The mechanism of the protective effect of fluoride is that it can partially substitute –OH

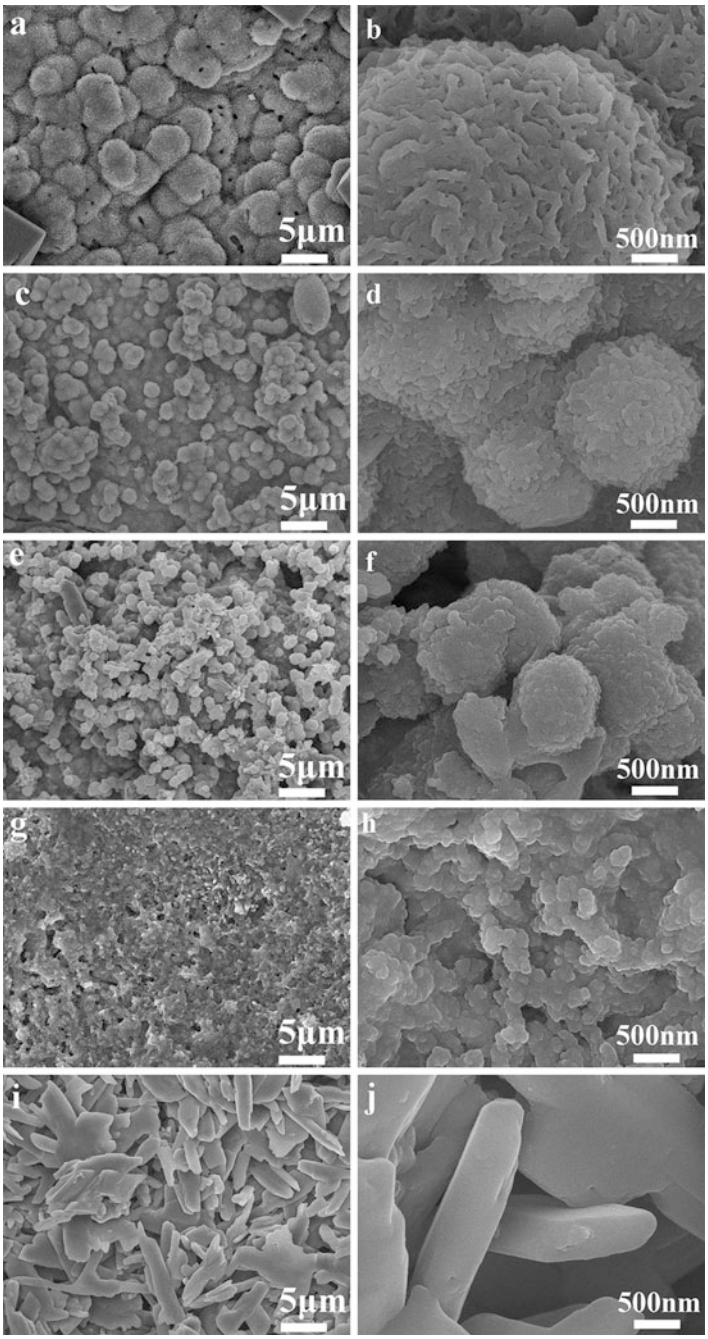

Fig 5 SEM graphs of the different samples after soaking in the SBF solution for 7 days: (**a**, **b**) CSC, (**c**, **d**) CSC+30 % POP, (**e**, **f**) CSC+50 % POP, (**g**, **h**) CSC+70 % POP, and (**i**, **j**) POP [70]

Table 1 Summary for the properties of silicate-based cements

Cements	Compressive strength after 1 day (MPa)	Compressive strength after 28 days (MPa)	Initial setting time (min)	Final setting time (min)	References
Ca_2SiO_4	0.6	~10	~300	~420	[64]
Ca_2SiO_4–C_3A (10 %)	2.20	~18	~110	~160	[64]
Ca_3SiO_5	/	14–16	~90	~180	[72]
CSC Ca_3SiO_5–Ca_2SiO_4 (20 %)	~26.4	~54.1	~100	~150	[70]
POP	~5	~10	~5	~15	[70]
CSC–POP (30 %)	~28	~35	~15	~25	[70]
Ca_2SiO_4–POP (40 %)	~5	~35	~15	~40	[67]
Ca_3SiO_5–POP (60 %)	/	~11.9 ± 0.6	~18	~35	[68]
CSC–C_3A (5 %)	~33	~54	~30	~70	[66]
Ca_3SiO_5–MPM (20 %)	/	~18	~30	~90	[62]
Ca_3SiO_5–DCPD (60 %)	~22	~35	32 ± 1.6	60 ± 3.5	[63]
Ca_3SiO_5–$CaCO_3$ (30 %)	/	24–27	~45	~95	[72]

of HA and form fluoride-substituted HA which is more stable under acid conditions. Therefore, the addition of fluoride salts into silicate-based bone cements is an effective approach to increase the cement mineralization ability. Different amounts of CaF_2 (0, 1, 2, and 3 wt%) were incorporated into C_3S cement to investigate the apatite formation ability of C_3S pastes. The initial crystalline apatite formation time of the pastes with the addition of CaF_2 is 1 day, while the C_3S pastes need 3 days to induce visible formation of the initial crystalline apatite. The thicknesses of apatite layers deposited on the surface of C_3S doped with 0, 1, 2, and 3 wt% CaF_2 were about 88, 102, 168, and 136 μm, respectively, after soaking for 7 days. The high-level bioactivity of 2 wt% CaF_2-doped C_3S was attributed to F^- released by the hydration product of C_3S cements and the formation of F-substituted apatite with a formula of $Ca_{8.94}M_{1.06}(PO_4, HPO_4)_6(OH)_{1.95}F_{0.05}$ (M represents substituted ions such as Na, K, Mg) [73]. Therefore, the self-setting CaF_2-doped C_3S with excellent bioactivity and better mechanical properties might be more useful as bioactive materials for bone tissue repair.

The physicochemical properties such as setting time and mechanical strength of the cement play an important role in successful clinical applications. Therefore, a summary of the compressive strength and the initial and final setting time of the silicate-based composite cements after hydration for 1 day and 28 days is presented in Table 1.

It is clear to see that incorporation with CPC, C_3A, CaF_2, POP, or $CaCO_3$ will result in the improvement of some properties of CSC, such as shorter setting time, better mechanical properties, and admirable biodegradability as compared to pure CSC. And most importantly, the composite cements show high bioactivity which is important for bone filler materials. However, further in vivo studies are needed to proof the suitability of the composite cements as a filler material with adequate strength or reasonable setting rate for clinical applications.

Other Types of Silicate-Based Bioactive Composites

One of the main challenges of implant technology is the development of new generation of light implant materials with enhanced mechanical properties, wear resistance, and better biological response. Graphene and silicon carbide (SiC) are two kinds of innovative materials which are very promising as base materials for medical implants.

Silicate/Graphene Composites

Graphene possesses a flat monolayer of carbon atoms in a two-dimensional (2D) honeycomb lattice with high aspect ratio layer geometry and a very high specific surface area, which has received tremendous attention in recent years due to its exceptional thermal, mechanical, and electrical properties. Graphene is currently one of the most popular research areas and has been extensively studied for biotechnology applications due to its extremely large surface area, good biocompatibility, biostability, and ease of chemical functionalization. The addition of graphene into ceramics can improve the mechanical strength of the composites, while poor mechanical performance is the main drawback of silicate-based bioceramics which limits their applications under load-bearing conditions. Calcium silicate/reduced graphene oxide (CS–rGO) composites have been synthesized using a hydrothermal approach followed by hot isostatic pressing (HIP). CS − rGO composite with 1.0 wt% rGO shows improved hardness, elastic modulus, and fracture toughness as compared to pure CS. The addition of rGO does not affect the activity to induce apatite formation on CS ceramics in SBF. Interestingly, the introduction of rGO into the CS matrix stimulated human osteoblast cell proliferation and significantly increased ALP activity of the cells as compared with pure CS ceramics [74]. The graphene has also been incorporated into nano-58S bioactive glass scaffolds using a selective laser sintering system, which improved the mechanical properties of the composite scaffolds without affecting the bioactivity of bioactive glass component in SBF. The composite scaffold showed a good cell biocompatibility by in vitro cell culture tests, in which human osteoblast-like cells (MG-63 cells) colonized and grew favorably on the surface of composite scaffolds [75].

Silicate/SiC Composites

Porous biomorphic SiC ceramics with hierarchical microcellular architecture and honeycomb-like microchannels have been considered as potential bone implants or

tissue engineering scaffolds for their sufficient biomechanical properties and intrinsic three-dimensional interconnected porous structure [76]. The combination of the excellent mechanical properties and low density of the biomorphic SiC ceramics with osteoconductive properties of the silicate-based materials opens new possibilities for the development of alternative dental and orthopedic implants with enhanced mechanical and biochemical properties that ensure optimum fixation to living tissue. Uniform and adherent BG film-coated biomorphic SiC by pulsed laser ablation using an excimer ArF laser possessed a dense apatite layer on the composite surface after 72 h immersion [77]. Moreover, in vitro cytotoxicity observation of BG-coated biomorphic SiC ceramics, using MG-63 human osteoblast-like cells, revealed that the biological response of the cells on the ceramics was similar to those on well-known implant materials like Ti_6Al_4V and bulk bioactive glass [78]. The BG-coated SiC ceramics which possess excellent bone-bonding ability are promising devices for dental and orthopedic applications.

Silicate/Metal Composites

As "the first-generation biomaterials," metallic biomaterials have been widely used in clinical applications as medical devices for replacement of hard tissues such as artificial hip joints, bone plates, and dental implants. Ti-based alloys, Co–Cr alloy, and stainless steel are the most commonly used metallic substrates in load-bearing orthopedic implants due to their reliable mechanical properties. However, for metallic substrates, there is always a concern about their corrosion resistance in physiological fluids and their bioactivity. The corrosion products of these conventional surgical alloys, e.g., toxic metallic ions and/or particles, may be potentially harmful to the human body. On the other side, metallic materials cannot bond directly with living bone tissues which means bioinert. After placed into the human body, metallic materials are frequently encapsulated by fibrous tissue, which cause loosening and premature failure [79]. Most importantly, conventional surgical alloys are nondegradable which often require second operations to remove after bone healing. Recently, degradable Mg alloys with good mechanical properties and biodegradability have attracted more attention as bone implant materials although some limitations like poor corrosion resistance, hydrogen elution during degradation, and lack of bioactivity need to be addressed before the clinical application [80]. Coatings with bioactive and osteoinductive properties have been made to improve the surface characteristics of metallic implants extensively [81]. As the silicate-based materials possess excellent bioactivity, it is not surprising that researchers have taken great efforts to combine metallic substrates and silicate bioactive materials to form composites with enhanced performance. In this part, the current status of silicate-based bioactive glass and ceramic coatings on the nondegradable and biodegradable metallic substrates are reviewed.

Despite the effectiveness of these coatings in prohibiting the corrosion and improving the surface bioactivity of the metallic substrate, the main concern remains over the interface between the coating and the substrate, which in some cases is

relatively weak in terms of bonding strength and thus susceptible to mechanical loading. Therefore, the development of metal matrix composites (MMCs) may represent an alternative method to achieve the desired improvements of silicate/metal composites biomaterials, thereby avoiding complications arising in coating processes [82]. Silicate-based BG and bioceramic composite with biodegradable Mg alloys are also addressed. Metal matrix composite with silicate particles as reinforcement has been proposed as a new concept to improve the bioactivity and moderate the degradability which will be presented in the last part.

Silicate-Based Bioactive Coatings on Nondegradable Metallic Substrates

Metals normally cannot bond to living tissue in a natural manner; therefore, the rationale behind the deposition of ceramic coatings on bioinert metallic substrates is that the coating would endow the substrate with considerable surface bioactivity, thus leading to improved bone–implant integration [82]. Most of the previous studies have been focused on Ca–P ceramic coatings owing to their chemical similarity to the inorganic constitution of human bones. However, the interface between the Ca–P coating and the metallic substrate frequently suffers from inadequate bonding strength due to the mismatch between the thermal expansion coefficients of the two components [83]. In addition, the Ca–P coatings that have been developed in most of the currently available technologies present the characteristic of high crystallinity, which resulted in inferior bioactivity. In comparison, silicate-based ceramics possess similar thermal expansion coefficient to that of typical biomedical metals, e.g., titanium and its alloys, and superior bioactivity as compared with their Ca–P counterparts, which makes them an ideal bioactive coatings, and have attracted much attention in recent years [84]. In this part, the progresses in the development of bioactive coatings consisted of silicate-based bioceramics, such as wollastonite ($CaSiO_3$), dicalcium silicate (Ca_2SiO_4), bredigite ($Ca_7MgSi_4O_{16}$), and akermanite ($Ca_2MgSi_2O_7$), will be introduced, and the fabrication approaches will also be briefly reviewed.

$CaO–SiO_2$ Coatings

Wollastonite coatings were prepared on Ti–6Al–4V substrate by plasma spraying technique, which exhibited high bonding strength as the thermal expansion coefficient of wollastonite is close to that of the Ti–6Al–4V substrates [85]. Biological evaluation revealed that, after 1 month of implantation in the muscle, a bone-like apatite layer was formed on the surface of the wollastonite coating. When implanted in the cortical bone, bone tissue could extend and grow along the wollastonite coating. The coating bonded directly to the bone without any gaps or fibrous tissue formation, indicating its good biocompatibility and bone–implant integration. The results suggest that deposition of wollastonite on the surface of Ti–6Al–4V is an effective way to enhance bioactivity of the metal substrates through the formation of bone-like apatite layer which was very important for implant bonding to the bone tissue.

C_2S coating on titanium alloys has also been fabricated though plasma spraying, and a dense HAp layer could form on the surface after incubation in SBF solution for 2 days [86]. The results indicated that the plasma-sprayed C_2S coatings possess excellent bioactivity. In order to expedite the bonding strength between the coating and the substrate, C_2S-based composite coatings reinforced with titanium were fabricated via atmospheric plasma spraying on Ti–6Al–4V alloy substrates. The cross-sectional pictures of the coatings showed that the composite coatings had a typical lamellar structure with alternating C_2S and Ti phases. The incorporation of Ti could effectively inhibit the propagation of the cracks in the coatings and increase the bonding strength of the composite coatings with an increase in Ti content, while the Ti-reinforced C_2S coatings still showed good bioactivity [87].

CaO–SiO_2–MgO Coatings

It has been reported that Mg ions in certain concentration could stimulate adhesion and proliferation of osteoblastic cells, and CaO–SiO_2–MgO ceramics have shown good bioactivity by stimulating bone regeneration [88]. On these bases, plasma spraying akermanite ($Ca_2MgSi_2O_7$), diopside ($CaMgSi_2O_6$), and bredigite ($Ca_7MgSi_4O_{16}$) as new silicate coatings on titanium alloys have been studied.

Akermanite possesses a relatively moderate degradability, and its ionic products could significantly stimulate proliferation and osteogenic differentiation of stem cells. Recently, akermanite coatings have been prepared on Ti–6Al–4V through plasma spraying technique. The bonding strength between the akermanite coatings and Ti–6Al–4V substrates is around 38.7–42.2 MPa, which is higher than that of plasma-sprayed HA coatings. The akermanite coatings revealed distinct apatite-mineralization ability in SBF and supported the attachment and proliferation of rabbit bone marrow mesenchymal stem cells (BMSCs). It is also noted that the proliferation rate of BMSCs on akermanite coatings is obviously higher than that on HA coatings [83]. The findings suggest that the akermanite coatings may be a promising candidate for orthopedic and dental applications.

Similar to akermanite, another two kinds of Mg-containing silicate ceramics, diopside ($CaMgSi_2O_6$) and bredigite ($Ca_7MgSi_4O_{16}$), have also the ability to induce apatite formation and stimulate bone formation, while their degradation rates differ from that of the former [9, 89]. Diopside coatings were sprayed onto Ti–6Al–4V substrates using an atmospheric plasma spraying system [90]. The bonding strength of the diopside coating to the metallic substrate is approximately 32.5 MPa, which is higher than that of HA coatings. In addition, the diopside coating shows a Young's modulus of 38.56 GPa, which is close to the cortical bone. With similar fabrication method, the plasma-sprayed bredigite coating on Ti–6Al–4V substrate reveals an even higher bonding strength to titanium alloy substrate up to 49.8 MPa [91] and supports the attachment and proliferation of rabbit bone marrow stem cells. It is found that the proliferation rate of cells on bredigite ceramic coating is significantly higher than that on the HA coating. The released SiO_4^{4-} and Mg^{2+} ions from bredigite coating as well as the deposited nano-apatite layer on the coating surface might contribute to the improvement of cell proliferation. These results suggest that

diopside and bredigite coating may be potential candidates for modifying surface properties of metal orthopedic implants.

$CaO–SiO_2–MgO–SrO$ Coatings

Concerning the importance of strontium (Sr) in stimulating the growth and mineralization of the bone, $Sr_2MgSi_2O_7$ (SMS) ceramics have been developed recently, which showed good activity in supporting BMSC growth and enhancing the ALP activity and bone-related gene expression of BMSCs as compared to β-TCP [92]. Coatings composed of $Sr_2MgSi_2O_7$ (SMS) ceramic have been prepared on Ti–6Al–4V by plasma spraying method [93]. The coatings have higher bonding strength (~37 MPa) than conventional hydroxyapatite (HA) coatings (mostly in the range of 15–25 MPa). Furthermore, a study has shown that the SMS coating could inhibit both the inflammatory reaction and the osteoclastic activities. Meanwhile, the coating depressed the expression of osteoclastogenesis-related genes (RANKL and MCSF) in BMSCs with the involvement of macrophages, while OPG expression was enhanced as compared to HA coatings, indicating its ability to downregulate osteoclastogenesis. All these results suggested that the SMS coating possesses multifunctional effects, including reduced inflammatory reaction, downregulated osteoclastic activities, and maintained osteogenesis.

Ideal coating materials for orthopedic implants should be able to induce osteointegration, which requires several important parameters, such as good bonding strength, limited inflammatory reaction, and balanced osteoclastogenesis and osteogenesis, to gain well-functioning coated implants with long-term life span after implantation. In some terms, silicate bioceramic coatings on nondegradable metallic substrates have shown great promise. However, more in vitro and in particular in vivo investigations are required to confirm the feasibility of this type of new coatings for clinical applications.

Silicate Bioceramics Composite with Biodegradable Metallic Substrates

Degradability of magnesium alloys, which is unique from other metals used as biomedical implants, allows the gradual resorption of the implants and thus avoids the need for the second surgery to remove the implants after bone healing. However, its inappropriately too fast degradation rate and lack of bioactivity of the material have hindered its potential clinical applications. In order to improve the performance of Mg alloys, bearing of silicate-based coatings on the surface of Mg alloys and fabrication of Mg-based metal matrix composites containing silicates have been proved to be efficient. In this part, both the two approaches are introduced, respectively [94].

Silicate Bioactive Coatings on Biodegradable Mg Alloy Substrates

Tailoring of the surface of Mg alloy substrates with suitable inorganic or organic coatings may reduce the corrosion rate. Coating biodegradable Mg alloy substrates with silicate-based bioactive coatings may provide the composite with biocompatibility and osteoconductivity. Silicate-based mesoporous bioactive glass (MBG) coatings have

been fabricated on pure Mg substrate uniformly using a sol–gel dip-coating method [95]. The MBG-coated Mg displays a significantly lower biodegradation rate in SBF in comparison with uncoated Mg samples, namely, the weight loss of the MBG-coated samples lost 10 % of its original weight, while the uncoated Mg showed a weight loss of 57 %. In another study, nanostructured diopside ($CaMgSi_2O_6$) has been coated on AZ91 Mg alloy using a combined micro-arc oxidation (MAO) and electrophoretic deposition (EPD) method, aiming at decreasing the corrosion rate and improving the surface bioactivity and cytocompatibility of Mg alloys [96]. The results demonstrated that the diopside coating could not only slow down the corrosion rate but also improve the surface bioactivity and cytocompatibility of AZ91 Mg alloy.

Metal Matrix Composites

Although coatings are efficient in improving surface properties of magnesium, it is always difficult to obtain a coating with high bonding strength to the substrate as the coating process has to be conducted in a relatively low temperature due to the high thermal reactivity of magnesium and its alloys. The delamination of coatings from the magnesium substrates has been frequently observed which may lead to a sudden increase in corrosion rate in the long term after implantation [97]. An alternative approach to improve the performance of Mg and its alloys might be the application of metal matrix composite (MMC) based on magnesium alloys, which could avoid complications arising from coating technologies. The advantage to use MMCs as biomaterials is the adjustable mechanical properties (Young's modulus, tensile strength) as well as the adjustable corrosion properties by choosing the appropriate composites [98].

Recently, biodegradable MMCs with ZK30 magnesium alloy (containing 3 wt% zinc and 0.5 wt% zirconium) as the matrix and 45S5 BG as the reinforcement component have developed the powder metallurgy (P/M) method [99]. BG particles were found to be homogeneously distributed in the composites with their chemical composition and morphology retained (Fig. 6). Immersion tests showed that the ZK30-BG composites possessed improved corrosion resistance and lower hydrogen evolution rates when compared with the ZK30 alloy, which was attributed to the accelerated Ca–P deposition on the surface of the composites, induced by the presence of BG within the composites. The cytotoxicity tests and ALP assay showed that the ZK30-BG composites not only were cytocompatible but also possessed superior abilities to stimulate cell proliferation and to promote osteoblastic differentiation of rBMSC as compared with the ZK30 alloy.

Summary

Silicate bioactive glasses and ceramics have shown excellent bioactivity in tissue regeneration. However, common drawbacks of silicate-based bioactive materials are brittleness and uncontrollable degradability, while silicate-based biocomposites offer an optimal way for solving these problems from the materials science perspective. Silicate-based bioactive composites with proper composition and structure are one of the most promising bone regeneration materials owing to their bioactivity,

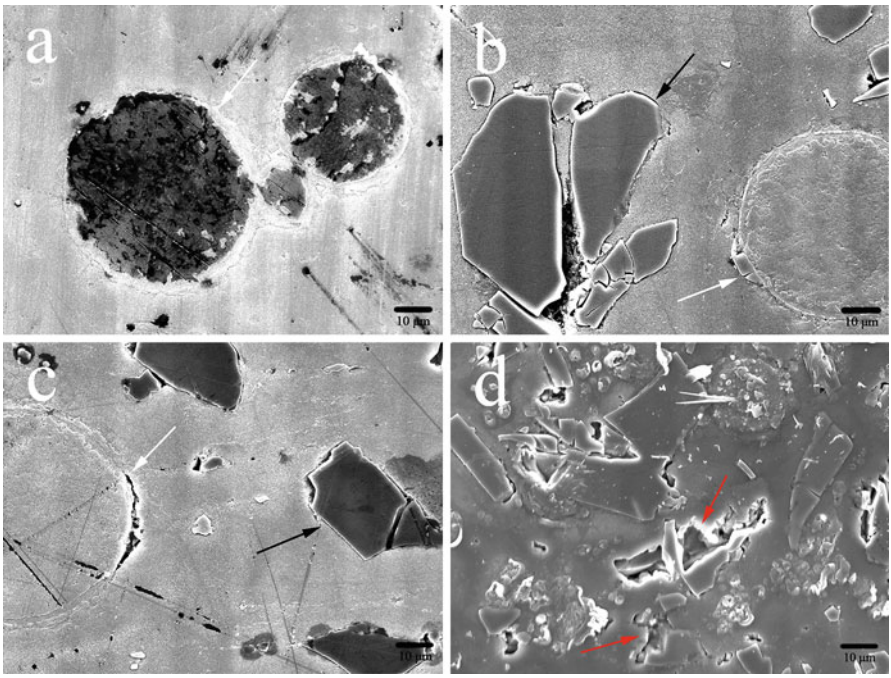

Fig. 6 SEM micrographs of the extruded (**a**) ZK30, (**b**) ZK30-5 % BG, (**c**) ZK30-10 % BG, and (**d**) ZK30-15 % BG rods on the transverse section. The red arrows point to the micropores present in the ZK30-15 %BG composite. The *white* and *black arrows* point out ZK30 and BG particles, respectively [99]

degradability, and success in stimulating new bone growth by the action of their dissolution products on cells. The synthetic silicate-based composites reviewed in this chapter consist of silicate-based inorganic–organic composites, silicate-based inorganic/inorganic composites, and silicate-based inorganic/metallic composites.

Generally, the field of tissue regeneration has undergone tremendous progress in the last several decades. Worthy attempts have been made by applying hybrids of silicate-based inorganic materials with either natural or synthesized polymers to prepare tissue engineering scaffolds with proper pore structure, bioactivity, biodegradability, acceptable mechanical properties, and stimulation of new bone formation and angiogenesis. Compared to conventional composite processing methods, 3D plotting is more adoptable to obtain scaffolds with tailored porosity and pore structure which can accurate control the morphology of the scaffolds for predictable properties. Electrospinning is another simple technique to manipulate the microstructure of bioactive inorganic–organic nanocomposites for controllable mechanical strength and biological properties. Bioactive membranes, hydrogels, and bone cements made of silicate-based bioactive inorganic materials and natural polymers show favorable bioactivity, biocompatibility, and bioresorbability which have huge potential for guided tissue regeneration. The combination of efficient drug delivery

and bioactive silicate-based biocomposites to achieve large drug load and controlled drug delivery provides more options to treat tissue defects clinically. Due to their small dimensions and incompatible polarity with polymers, inorganic particles tend to agglomerate in the polymer matrix. Nontoxic organic molecules, especially biocompatible molecules, are useful to modify the surface of silicate-based inorganic particles for the improvement of the dispersivity in polymer matrix. As for silicate-based inorganic composites, the composite ceramic or cement systems are mainly designed to strengthen mechanical strength, regulate degradability, or improve self-setting properties. Silicate-based inorganic biomaterials could also composite with advanced materials, like graphene, to improve the mechanical strength. For metallic substrates, there is always a concern about their corrosion resistance in physiological fluids and their bioactivity. Coating silicate-based bioceramics on alloy substrates could endow the composites with favorable bioactivity. Metal matrix composites (Mg alloy/Bioglass®) showed corrosion resistance, bioactivity, and promotion of cell proliferation and differentiation which develop a new research area for silicate-based inorganic composites used in tissue regeneration.

Up to now, most of the materials assessments for silicate-based bioactive composites are conducted in vitro to evaluate the biomaterials' performance in the materials perspective, like the mechanical properties, the ability to form apatite in vitro, the self-setting properties, etc. While biomaterials are expected to perform in the body's internal environment in clinical perspective which is quite different from those exhibited in experimental condition. The internal environment is complicated and changeable, for example, bone tissue structure and mechanical strength vary by distinct and fluctuating loading conditions and different parts in the body. All of these requirements call for careful designing of biomaterials with composition, surface morphology, and physical and chemical properties. Perhaps one of the largest challenges for the application of biomaterials is the rational design of silicate-based bioactive composites based on the systematic evaluation of desired biological, chemical, and physical requirements [100].

Bone is the optimal composites and the hierarchical structure of the bone in macro-, micro-, and nanolength scale plays an important role in the mechanical properties of bone. Therefore, composites with finely tailored structure in various length scales are the main trend for the synthesized silicate-based biocomposites. 3D plotting has shown promising potential to overcome some of the limitations of the conventional methods and got some progress in the application of tissue engineering. New processing techniques, including 3D plotting, should be studied and developed for the development of scaffolds with improved mechanical properties without influencing the porosity and interconnectivity.

The general mechanism on the bioactivity of $CaO–SiO_2$-based coatings on metallic substrates involved the dissolution of the coatings, which rendered the release of calcium ions and the formation of silica-rich layer that were necessary for the formation of an apatite layer. However, the dissolution process may result in the mechanical deterioration of the coatings. Fractures have thus been reported to occur within the coating and/or at the coating–substrate interface after implantation. Therefore, it is essential to improve the stability of the coatings, as well as its

bonding strength to the metallic substrate, for which coating techniques play an important role. Many techniques have been investigated to obtain silicate-based coatings, but none of them have been used in industrial practice and clinical application. More research works are needed to develop practical coating techniques to obtain silicate-based bioactive coatings with high stability and bonding strength.

References

1. Kemal S, Sander CGL, Joop GCW, Li YB, John AJ (2012) Effect of calcium carbonate on hardening, physicochemical properties, and in vitro degradation of injectable calcium phosphate cements. J Biomed Mater Res A 100A:712–719. doi:10.1002/jbm.a.34009
2. Hu JZ, Zhou YC, Huang LH, Liu J, Lu HB (2014) Effect of nano-hydroxyapatite coating on the osteoinductivity of porous biphasic calcium phosphate ceramics. BMC Musculoskelet Disord 15:114–124. doi:10.1186/1471-2474-15-114
3. Hafezi F, Hosseinnejad F, Fooladi AIA, Mafi MS, Amiri A, Nourani RM (2012) Transplantation of nano-bioglass/gelatin scaffold in a non-autogenous setting for bone regeneration in a rabbit ulna. J Mater Sci Mater Med 23:2783–2792. doi:10.1007/s10856-012-4722-3
4. Hench LL (2009) Genetic design of bioactive glass. J Eur Ceram Soc 29:1257–1265. doi:10.1016/j.jeurceramsoc.2008.08.002
5. Hench LL, Paschall HA (1973) Direct chemical bond of bioactive glass-ceramic materials to bone and muscle. J Biomed Mater Res 7:25–42. doi:10.1002/jbm.820070304
6. Saravanapavan P, Jones JR, Verrier S, Beilby R, Shirtliff VJ, Hench LL, Polak JM (2004) Binary CaO-SiO_2 gel glasses for biomedical applications. Bio-Med Mater Eng 14:467–486
7. Rahaman NM, Day ED, Bal SB, Fu Q, Jung BS, Bonewald FL, Tomsia PA (2011) Bioactive glass in tissue engineering. Acta Biomater 7:2355–2373. doi:10.1016/j.actbio.2011.03.016
8. Hench LL (1998) Bioceramics. J Am Ceram Soc 81:1705–1728. doi:10.1111/j.1151-2916.1998.tb02540.x
9. Wu CT, Chang J (2013) A review of bioactive silicate ceramics. Biomed Mater 8:032001–032012. doi:10.1088/1748-6041/8/3/032001
10. Kokubo T, Kushitani H, Sakka S, Kitsugi T, Yamamuro T (1990) Solutions able to reproduce *in vivo* surface-structure changes in bioactive glass-ceramic A-W3. J Biomed Mater Res 24:721–734. doi:10.1002/jbm.820240607
11. Zhang Q, Nakamoto T, Chen SW, Kawazoe NK, Lin KL, Chang J, Chen GP (2014) Collagen/wollastonite nanowire hybrid scaffolds promoting osteogenic differentiation and angiogenic factor expression of mesenchymal stem cells. J Nanosci Nanotech 14:3221–3227. doi:10.1166/jnn.2014.8607
12. Yang SB, Wang J, Tang LJ, Ao HA, Tan HL, Tang TT, Liu CS (2014) Mesoporous bioactive glass doped-poly (3-hydroxybutyrate-co-3-hydroxyhexanoate) composite scaffolds with 3-dimensionally hierarchical pore networks for bone regeneration. Colloids Surf B Biointerfaces 116:72–80. doi:10.1016/j.colsurfb.2013.12.052
13. Vallet-Regí M, Arcos D (2008) Nanostructured hybrid materials for bone implants fabrication. In: Bio-inorganic hybrid nanomaterials. Wiley, Weinheim, pp 367–399
14. Dou YD, Wu CT, Chang J (2012) Preparation, mechanical property and cytocompatibility of poly(L–lactic acid)/calcium silicate nanocomposites with controllable distribution of calcium silicate nanowires. Acta Biomaterialia 8:4139–4150. doi:10.1016/j.actbio.2012.07.009
15. Allo AB, Rizkalla SA, Mequanint K (2010) Synthesis and electrospinning of ε-polycaprolactone-bioactive glass hybrid biomaterials via a sol–gel process. Langmuir 26:18340–18348. doi:10.1021/la102845k
16. Kouhi M, Morshed M, Varshosaz J, Fathi HM (2013) Poly(ε-caprolactone) incorporated bioactive glass nanoparticles and simvastatin nanocomposite nanofibers: preparation,

characterization and in vitro drug release for bone regeneration applications. Chem Eng J 228:1057–1065. doi:10.1016/j.cej.2013.05.091
17. Shin SH, Purevdorj O, Castano O, Planell AJ, Kim HW (2012) A short review: recent advances in electrospinning for bone tissue regeneration. J Tissue Eng 3:1–12. doi:10.1177/2041731412443530
18. Tirri T, Rich J, Wolke J, Seppa J, Yli-Urpo A, Narhi OT (2008) Bioactive glass induced in vitro apatite formation on composite GBR membranes. J Mater Sci Mater Med 19:2919–2923. doi:10.1007/s10856-007-3308-y
19. Hurt AP, Getti G, Coleman NJ (2014) Bioactivity and biocompatibility of a chitosan-tobermorite composite membrane for guided tissue regeneration. Int J Bio Macro 64:11–16. doi:10.1016/j.ijbiomac.2013.11.020
20. Hong KS, Kim EC, Bang SH, Chung CH, Lee YI, Hyun KJ, Lee HH, Jang JH, Kim TI, Kim HW (2009) Bone regeneration by bioactive hybrid membrane containing FGF2 within rat calvarium. J Biomed Mater Res A 94A:1187–1194. doi:10.1002/jbm.a.32799
21. Caridade GS, Merino GE, Martins VG, Luz MG, Alves MN, Mano FJ (2012) Membranes of poly($_{DL}$–lactic acid)/Bioglass® with asymmetric bioactivity for biomedical applications. J Bioact Compat Pol 27:429–440. doi:10.1177/0883911512448753
22. Li H, Chen SY, Wu Y, Jiang J, Ge YS, Gao K, Zhang PY, Wu LX (2012) Enhancement of the osteointegration of a polyethylene terephthalate artificial ligament graft in a bone tunnel using 58S bioglass. Int Orthop (SICOT) 36:191–197. doi:10.1007/s00264-011-1275-x
23. Kim JJ, Won JE, Shin US, Kim HW (2011) Improvement of bioactive glass nanofiber by a capillary-driven infiltration coating with degradable polymers. J Am Ceram Soc 94:2812–2815. doi:10.1111/j.1551-2916.2011.04735.x
24. Salinas AJ, Esbrit P, Vallet-Regi M (2013) A tissue engineering approach based on the use of bioceramics for bone repair. Biomater Sci 1:40–51. doi:10.1039/c2bm00071g
25. Zhao L, Lin KL, Zhang ML, Xiong CD, Bao YH, Pang XB, Chang J (2011) The influences of poly(lactic-co-glycolic acid) (PLGA) coating on the biodegradability, bioactivity, and biocompatibility of calcium silicate bioceramics. J Mater Sci 46:4986–4993. doi:10.1007/s10853-011-5416-9
26. Pielichowska K, Blazewicz S (2010) Bioactive polymer/hydroxyapatite (nano)composites for bone tissue regeneration. In: Abe A, Dusek K, Kobayashi S (eds) Biopolymers: lignin, proteins, bioactive nanocomposites. Springer, Berlin, pp 97–207
27. Li XK, Chang J (2005) Preparation and characterization of bioactive collagen/wollastonite composite scaffolds. J Mater Sci-Mater Med 16:361–365. doi:10.1007/s10856-005-0636-7
28. Zhao L, Chang J (2004) Preparation and characterization of macroporous chitosan/wollastonite composite scaffolds for tissue engineering. J Mater Sci-Mater Med 15:625–629. doi:10.1023/B:JMSM.0000026103.44687.d0
29. Dorj B, Park JH, Kim HW (2012) Robocasting chitosan/nanobioactive glass dual-pore structured scaffolds for bone engineering. Mater Lett 73:119–122. doi:10.1016/j.matlet.2011.12.107
30. Li JH, Baker AB, Mou XN, Ren N, Qiu JC, Boughton IR, Liu H (2014) Biopolymer/calcium phosphate scaffolds for bone tissue engineering. Adv Healthcare Mater 3:469–484. doi:10.1002/adhm.201300562
31. Li HY, Chang J (2005) pH-compensation effect of bioactive inorganic fillers on the degradation of PLGA. Comp Sci Technol 65:2226–2232. doi:10.1016/j.compscitech.2005.04.051
32. Li HY, Chang J (2004) Preparation and characterization of bioactive and biodegradable Wollastonite/poly(D, L-lactic acid) composite scaffolds. J Mater Sci-Mater Med 15:1089–1095. doi:10.1023/B:JMSM.0000046390.09540.c2
33. Xu L, Xiong CZ, Yang DG, Zhang FL, Chang J, Xiong CD (2008) Preparation and in vitro degradation of novel bioactive polylactide/wollastonite scaffolds. J Appl Polym Sci 114:3396–3406. doi:10.1002/app.28475
34. Wang C, Lin KL, Chang J, Sun J (2013) Osteogenesis and angiogenesis induced by porous beta-$CaSiO_3$/PDLGA composite scaffold via activation of AMPK/ERK1/2 and PI3K/Akt pathways. Biomaterials 34:64–77. doi:10.1016/j.biomaterials.2012.09.021

35. Li HY, Chang J (2005) In vitro degradation of porous degradable and bioactive PHBV/wollastonite composite scaffolds. Polym Degrad Stab 87:301–307. doi:10.1016/j.polymdegradstab.2004.09.001
36. Zhao L, Wu CT, Lin KL, Chang J (2012) The effect of poly(lactic-co-glycolic acid) (PLGA) coating on the mechanical, biodegradable, bioactive properties and drug release of porous calcium silicate scaffolds. BioMed Mater Eng 22:289–300. doi:10.3233/BME-2012-0719
37. Shi MC, Zhai D, Zhao L, Wu CT, Chang J (2014) Nanosized mesoporous bioactive glass/poly(lactic-co-glycolic acid) composite-coated casio$_3$ scaffolds with multifunctional properties for bone tissue engineering. BioMed Res Int 2014:323046–323057. doi:10.1155/2014/323046
38. Luo YX, Wu CT, Lode A, Gelinsky M (2013) Hierarchical mesoporous bioactive glass/alginate composite scaffolds fabricated by three-dimensional plotting for bone tissue engineering. Biofabrication 5:015005–015017. doi:10.1088/1758-5082/5/1/015005
39. Han Y, Zeng QY, Li HY, Chang J (2013) The calcium silicate/alginate composite: preparation and evaluation of its behavior as bioactive injectable hydrogels. Acta Biomaterialia 9:9107–9117. doi:10.1016/j.actbio.2013.06.022
40. Wu CT, Zhu YF, Chang J, Zhang YF, Xiao Y (2010) Bioactive inorganic-materials/alginate composite microspheres with controllable drug-delivery ability. J Biomed Mater Res 94B:32–43. doi:10.1002/jbm.b.31621
41. Shirosaki Y, Botelho CM, Lopes MA, Santos JD (2009) Synthesis and characterization of chitosan-silicate hydrogel as resorbable vehicle for bonelike® bone graft. J Nanosci Nanotechnol 9:3714–3719. doi:10.1166/jnn.2009.NS56
42. Xu H, Wang YJ, Zheng YD, Chen XF, Ren L, Wu G, Huang XS (2007) Preparation and characterization of bioglass/polyvinyl alcohol composite hydrogel. Biomed Mater 2:62–66. doi:10.1088/1748-6041/2/2/002
43. Killion JA, Kehoe S, Geever LM, Devine DM, Sheehan E, Boyd D, Higginbotham CL (2013) Hydrogel/bioactive glass composites for bone regeneration applications: synthesis and characterization. Mater Sci Eng C Mater Biol Appl 33:4203–4212. doi:10.1016/j.msec.2013.06.013
44. Tsuru K, Hayakawa S, Ohtsuki C, Osaka A (1998) Ultrasonic implantation of calcium metasilicate glass particles into PMMA. J Mater Sci Mater Med 9:479–484. doi:10.1023/A:1008875502451
45. Hamizah AS, Mariatti M, Othman R, Kawashita M, Hayati ARN (2012) Mechanical and thermal properties of polymethylmethacrylate bone cement composites incorporated with hydroxyapatite and glass-ceramic fillers. J Appl Poylm Sci 125:E661–E669. doi:10.1002/app.35295
46. Wang DG, Zhang Y, Hong GZ (2014) Novel fast-setting chitosan/β-dicalcium silicate bone cements with high compressive strength and bioactivity. Ceram Int 40:9799–9808. doi:10.1016/j.ceramint.2014.02.069
47. Lin Q, Lan XH, Li B, Yu YH, Ni YR, Lu CH, Xu ZZ (2010) Anti-washout carboxymethyl chitosan modified tricalcium silicate bone cement: preparation, mechanical properties and in vitro bioactivity. J Mater Sci Mater Med 21:3065–3076. doi:10.1007/s10856-010-4160-z
48. Oral O, Lassila LV, Kumbuloglu O, Vallittua PK (2014) Bioactive glass particulate filler composite: effect of coupling of fillers and filler loading on some physical properties. Dent Mater 30:570–577. doi:10.1016/j.dental.2014.02.017
49. Zhou ZH, Liu L, Liu QQ, Yi QF, Zeng WN, Zhao YM (2012) Effect of surface modification of bioactive glass on properties of poly-l-lactide composite materials. J Macro Sci B Phys 51:1637–1646. doi:10.1080/00222348.2012.672295
50. Qian C, Zhang XY, Zhu BS, Lin KL, Chang J, Zhang XJ (2010) The effect of $CaSiO_3$ nanoparticles reinforced denture poly-methyl methacrylate. Adv Comp Lett 20:13–20
51. Gao Y, Chang J (2009) Surface modification of bioactive glasses and preparation of PDLLA/bioactive glass composite films. J Biomater Appl 24:119–138. doi:10.1177/0885328208094265
52. Zhou YL, Gao Y, Chang J (2010) Effects of hydrolysis on dodecyl alcohol-modified bioactive glasses and PDLLA/modified bioactive glass composite films. J Mater Sci 45:6411–6416. doi:10.1007/s10853-010-4724-9

53. Lin KL, Zhang ML, Zhai WY, Qu HY, Chang J (2011) Fabrication and characterization of hydroxyapatite/wollastonite composite bioceramics with controllable properties for hard tissue repair. J Am Ceram Soc 94:206–212. doi:10.1111/j.1551-2916.2010.04046.x
54. Xu S, Lin KL, Wang Z, Chang J, Wang L, Lu J, Ning CQ (2008) Reconstruction of calvarial defect of rabbits using porous calcium silicate bioactive ceramics. Biomaterials 29:2588–2596. doi:10.1016/j.biomaterials.2008.03.013
55. Liu S, Jin FC, Lin KL, Lu JX, Sun J, Chang J, Dai KR, Fan CY (2013) The effect of calcium silicate on in vitro physiochemical properties and in vivo osteogenesis, degradability and bioactivity of porous β-tricalcium phosphate bioceramics. Biomed Mater 8:025008. doi:10.1088/1748-6041/8/2/025008
56. Wang C, Xue Y, Lin KL, Lu JX, Chang J, Sun J (2012) The enhancement of bone regeneration by a combination of osteoconductivity and osteostimulation using β-$CaSiO_3$/β-$Ca_3(PO_4)_2$ composite bioceramics. Acta Biomater 8:350–360. doi:10.1016/j.actbio.2011.08.019
57. Shirazi FS, Mehrali M, Oshkour AA, Metselaar HSC, Kadri NA, AbuOsman NA (2014) Mechanical and physical properties of calcium silicate/alumina composite for biomedical engineering applications. J Mech Behav Biomed Mater 30:168–175. doi:10.1016/j.jmbbm.2013.10.024
58. Long LH, Zhang FM, Chen L, Chen LD, Chang J (2008) Preparation and properties of β-$CaSiO_3$/ZrO_2 (3Y) nanocomposites. J Eur Ceram Soc 28:2883–2887. doi:10.1016/j.jeurceramsoc.2008.05.006
59. Ni SY, Chang J, Chou L (2008) In vitro studies of novel CaO–SiO_2–MgO system composite bioceramics. J Mater Sci Mater Med 19:359–367. doi:10.1007/s10856-007-3186-3
60. Dorozhkin SV (2009) Calcium orthophosphates in nature, biology and medicine. Materials 2:399–498. doi:10.3390/ma2020399
61. Zhao WY, Wang JY, Zhai WY, Wang Z, Chang J (2005) The self-setting properties and in vitro bioactivity of tricalcium silicate. Biomaterials 26:6113–6121. doi:10.1016/j.biomaterials.2005.04.025
62. Huan ZG, Chang J (2007) Novel tricalcium silicate/monocalcium phosphate monohydrate composite bone cement. J Biomed Mater Res B Appl Biomater 82B:352–359. doi:10.1002/jbm.b.30740
63. Huan ZG, Chang J (2009) Calcium–phosphate–silicate composite bone cement: self-setting properties and in vitro bioactivity. J Mater Sci Mater Med 20:833–841. doi:10.1007/s10856-008-3641-9
64. Liu WN, Chang J (2012) Setting properties and biocompatibility of dicalcium silicate with varying additions of tricalcium aluminate. J Biomater Appl 27:171–178. doi:10.1177/0885328211398507
65. Liu WN, Chang J, Zhu YQ, Zhang ML (2011) Effect of tricalcium aluminate on the properties of tricalcium silicate–tricalcium aluminate mixtures: setting time, mechanical strength and biocompatibility. Int Endod J 44:41–50. doi:10.1111/j.1365-2591.2010.01793.x
66. Liu WN, Peng WW, Zhu YQ, Chang J (2012) Physicochemical properties and in vitro biocompatibility of a hydraulic calcium silicate/tricalcium aluminate cement for endodontic use. J Biomed Mater Res B Appl Biomater 100B:1257–1263. doi:10.1002/jbm.b.32690
67. Huan ZG, Chang J, Huang XH (2008) Self-setting properties and in vitro bioactivity of Ca_2SiO_4/$CaSO_4$ dot 1/2H_2O composite bone cement. J Biomed Mater Res B 87B:387–394. doi:10.1002/jbm.b.31116
68. Huan ZG, Chang J (2007) Self-setting properties and in vitro bioactivity of calcium sulfate hemihydrate–tricalcium silicate composite bone cements. Acta Biomater 3:952–960. doi:10.1016/j.actbio.2007.05.003
69. Zhao WY, Chang J, Zhai WY (2007) Self-setting properties and *in vitro* bioactivity of Ca_3SiO_5/$CaSO_4$ dot 1/2H_2O composite cement. J Biomed Mater Res A 85A:336–344. doi:10.1002/jbm.a.31523
70. Liu WJ, Wu CT, Liu WN, Chang J (2013) The effect of plaster ($CaSO_4$ dot 1/2H_2O) on the compressive strength, self-setting property, and in vitro bioactivity of silicate-based bone cement. J Biomed Mater Res Part B101B:279–286. doi:10.1002/jbm.b.32837

71. Lin M, Zhang L, Wang JC, Chen XY, Yang XY, Cui WG, Zhang W, Yang GJ, Liu M, Zhao Y (2014) Novel highly bioactive and biodegradable gypsum/calcium silicate composite bone cements: from physicochemical characteristics to in vivo aspects. J Mater Chem B 2:2030–2038. doi:10.1039/c3tb21786h
72. Huan ZG, Chang J (2008) Study on physicochemical properties and *in vitro* bioactivity of tricalcium silicate–calcium carbonate composite bone cement. J Mater Sci Mater Med 19:2913–2918. doi:10.1007/s10856-008-3423-4
73. Lin Q, Li YB, Lan XH, Lu CH, Chen YX, Xu ZZ (2009) The apatite formation ability of CaF_2 doping tricalcium silicates in simulated body fluid. Biomed Mater 4:045005. doi:10.1088/1748-6041/4/4/045005
74. Mehrali M, Moghaddam E, Shirazi SFS, Baradaran S, Mehrali M, Latibari ST, Metselaar HSC, Kadri NA, Zandi K, Abu Osman NA (2014) Synthesis, mechanical properties, and in vitro biocompatibility with osteoblasts of calcium silicate-reduced graphene oxide composites. ACS Appl Mater Interface 6:3947–3962. doi:10.1021/am500845x
75. Gao CD, Liu TT, Shuai CJ, Peng SP (2014) Enhancement mechanisms of graphene in nano-58S bioactive glass scaffold: mechanical and biological performance. Sci Rep 4:4712. doi:10.1038/srep04712
76. Qian J, Kang YH, Wei ZL, Zhang W (2009) Fabrication and characterization of biomorphic 45S5 bioglass scaffold from sugarcane. Mater Sci Eng C 29:1361–1364. doi:10.1016/j.msec.2008.11.004
77. Gonzaleza P, Serraa J, Listea S, Chiussia S, Leona B, Perez-Amora M, Martnez-Fernandezb J, Arellano-Lopezb RA, Varela-Feria MF (2009) New biomorphic SiC ceramics coated with bioactive glass for biomedical applications. Biomaterials 24:4827–4832. doi:10.1016/S0142-9612(03)00405-8
78. DeCarlos A, Borrajo JP, Serra J, Gonzalez P, Leon B (2006) Behaviour of MG-63 osteoblast-like cells on wood-based biomorphic SiC ceramics coated with bioactive glass. J Mater Sci Mater Med 17:523–529. doi:10.1007/s10856-006-8935-1
79. Mitsuo N (2008) Metallic biomaterials. J Artif Organs 11:105–110. doi:10.1007/s10047-008-0422-7
80. Staiger MP, Pietak AM, Huadmai J, Dias G (2006) Magnesium and its alloys as orthopedic biomaterials: a review. Biomaterials 27:1728–1734. doi:10.1016/j.biomaterials.2005.10.003
81. Razavi M, Fathi M, Savabi O, Beni BH, Vashaee D, Tayebi L (2014) Surface microstructure and in vitro analysis of nanostructured akermanite ($Ca_2MgSi_2O_7$) coating on biodegradable magnesium alloy for biomedical applications. Colloid Surf B Biointerfaces 117:432–440. doi:10.1016/j.colsurfb.2013.12.011
82. Sola A, Bellucci D, Cannillo V, Cattini A (2011) Bioactive glass coatings: a review. Surf Eng 27:560–572. doi:10.1179/1743294410Y.0000000008
83. Yi DL, Wu CT, Ma XB, Ji H, Zheng XB, Chang J (2012) Preparation and *in vitro* evaluation of plasma-sprayed bioactive akermanite coatings. Biomed Mater 7:065004. doi:10.1088/1748-6041/7/6/065004
84. Nihat CK, Aligul B, Ahmet YO, Muhammed HA (2009) Hydroxyapatite/bioactive glass films produced by a sol–gel method: *in vitro* behavior. Adv Eng Mater 11:B194–B199. doi:10.1002/adem.200900034
85. Xue WC, Liu XY, Zheng XB, Ding CX (2005) *In vivo* evaluation of plasma-sprayed wollastonite coating. Biomaterials 26:3455–3460. doi:10.1016/j.biomaterials.2004.09.027
86. Liu XY, Tao SY, Ding CX (2002) Bioactivity of plasma sprayed dicalcium silicate coatings. Biomaterials 23:963–968. doi:10.1016/S0142-9612(01)00210-1
87. Xie YT, Liu XY, Zheng XB, Ding CX (2005) Bioconductivity of plasma sprayed dicalcium silicate/titanium composite coatings on Ti–6Al–4V alloy. Surf Coat Technol 199:105–111. doi:10.1016/j.surfcoat.2004.11.034
88. Xia LG, Zhang ZY, Chen L, Zhang WJ, Zeng DL, Zhang XL, Chang J, Jiang XQ (2011) Proliferation and osteogenic differentiation of human periodontal ligament cells on akermanite and beta-TCP bioceramics. Eur Cell Mater 22:68–83

89. Wu CT, Ramaswamy Y, Zreiqat H (2010) Porous diopside ($CaMgSi_2O_6$) scaffold: a promising bioactive material for bone tissue engineering. Acta Biomatrialia 6:2237–2245. doi:10.1016/j.actbio.2009.12.022
90. Xue WC, Liu XY, Zheng XB, Ding CX (2004) Plasma-sprayed diopside coatings for biomedical applications. Surf Coat Technol 185:340–345. doi:10.1016/j.surfcoat.2003.12.018
91. Yi DL, Wu CT, Ma XB, Ji H, Zheng XB, Chang J (2014) Bioactive bredigite coating with improved bonding strength, rapid apatite mineralization and excellent cytocompatibility. J Biomater Appl 28:1343–1353. doi:10.1177/0885328213508165
92. Zhang ML, Wu CT, Lin KL, Fan W, Chen L, Xiao Y, Chang J (2012) Biological responses of human bone marrow mesenchymal stem cells to Sr-M-Si (M = Zn, Mg) silicate bioceramics. J Biomed Mater Res A 100A:2979–2990. doi:10.1002/jbm.a.34246
93. Wu CT, Chen ZT, Yi DH, Chang J, Xiao Y (2014) Multidirectional effects of Sr-, Mg-, and Si-containing bioceramic coatings with high bonding strength on inflammation, osteoclastogenesis, and osteogenesis. ACS Appl Mater Interfaces 6:4264–4276. doi:10.1021/am4060035
94. Rojaee R, Fathi M, Raeissi K, Taherian M (2013) Electrophoretic deposition of bioactive glass nanopowders on magnesium based alloy for biomedical applications. Ceram Int 40:7879–7888, 10.1016/j.ceramint.2013.12.135
95. Wang XJ, Wen C (2014) Corrosion protection of mesoporous bioactive glass coating on biodegradable magnesium. Appl Surf Sci 303:196–204. doi:10.1016/j.apsusc.2014.02.147
96. Razavi M, Fathi M, Savabi O, Vashaee D, Tayebi L (2014) *In vitro* study of nanostructured diopside coating on Mg alloy orthopedic implants. Mater Sci Eng Mater Biolog Appl 41:168–177. doi:10.1016/j.msec.2014.04.039
97. Hornberger H, Virtanen S, Boccaccini RA (2012) Biomedical coatings on magnesium alloys – a review. Acta Biomater 8:2442–2455. doi:10.1016/j.actbio.2012.04.012
98. Foltz JV, Blackmon CM (1998) Matrix composites. Adv Mater & Process 154:19–23
99. Huan ZG, Leeflang S, Zhou J, Zhai WY, Chang J, Duszczyk J (2012) *In vitro* degradation behavior and bioactivity of magnesium-Bioglass composites for orthopedic applications. J Biomed Mater Res B Appl Biomater 100B:437–446. doi:10.1002/jbm.b.31968
100. Dorozhkin SV (2013) Calcium orthophosphate-based bioceramics. Materials 6:3840–3942. doi:10.3390/ma6093840