Journal of Composites and Compounds 7(2025) 1-14

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Journal of Composites and Compounds

Bioactive glasses, glass ceramics, and ceramics composites: State-of-the-art review and future challenges

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A B S T R A C T

Bioactive glasses, glass ceramics, and ceramic composites represent a transformative class of materials in regenerative medicine. The purpose of this review is to analyze the status of current developments in these bioactive materials, including their biological and mechanical properties, fabrication techniques, and clinical applications. Bioactive glasses are able to bond to both hard and soft tissues, stimulate osteogenesis, and release therapeutic ions that enhance cellular responses. Glass ceramics offer enhanced mechanical strength through controlled crystallization processes. Ceramic composites, incorporating bioactive components with polymers or other materials, address challenges, enabling tailored mechanical and biological properties for specific clinical applications. Despite significant progress, future challenges include optimizing mechanical properties for load-bearing applications, improving fabrication methods for complex structures like scaffolds and coatings, and exploring new compositions with therapeutic ions for enhanced bioactivity. This review underscores the potential of bioactive glasses, glass ceramics, and composites to revolutionize tissue engineering, dentistry, and medicine while identifying key challenges for advancing their clinical utility.

A R T I C L E I N F O R M A T I O N

Article History:
Received 25 March 2025
Received in revised form 29 April 2025
Accepted 01 May 2025

Keywords:
Bioactive glasses
Glass ceramics
Ceramics composites
Biomaterials

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https://doi.org/10.61186/jcc.7.3.1

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1. Introduction

Inorganic biomaterials such as glass ceramics and bioactive glasses are engineered to provoke particular biological responses, especially a robust interaction with bone [1]. The concept of bioactive material lies between that of resorbable and inert materials. Although multiple definitions of bioactivity exist, Hench's definition is obvious: bioactivity is the ability of an implanted substance to bond with living tissue [2]. The development of these materials for human bone implants and replacements has gained increasing importance in the last five to ten years [3].Due to their remarkable qualities, including superior biocompatibility, adjustable degradation rates, osteoinductive properties, antibacterial capabilities, and pro-angiogenic effects, from 1969 to the present, bioactive glass and

glass ceramic has been used in many applications within tissue engineering, implantology, and pharmaceutics. These qualities are crucial for developing multifunctional systems [4, 5]. When artificial materials are placed into bone deficiencies, they are often encased in fibrous tissue. However, in 1971, Hench and associates found that specially made glasses termed Bioglass® in the Na_2O-CaO-SiO_2-P_2O_5 system do not produce fibrous tissue but create a strong chemical relationship upon direct contact with the surrounding bone [6]. Since bioglass was invented, various glasses, glass ceramics, and sintered ceramics have been used to adhere to live bone [7]. When bioactive glasses come into contact with biological fluids, a hydroxyapatite (HA) coating forms on their surface, linking them with bone tissue. The dissolution and biomineralization processes on the surface of bioactive glasses lead to the production of such an HA layer; this HA-forming capability of bioactive glasses is referred to as "bioactivity" [8]. Additionally, by releasing physiologically active ions during dissolution, BGs can initiate various advantageous biological reactions, including osteogenesis and angiogenesis. Additionally, it was discovered via both in vitro and in vivo investigations that dissolving the glass network creates a silica-rich gel layer, and the subsequent deposition of an apatite-like layer on the glass surface is a crucial phase for connecting glass to live tissues [9].

However, different biomaterials display diverse bonding properties, such as time dependence, strength, mechanisms, and bonding zone thickness [10]. Moreover, a bioactive material's structure, porosity, and chemical composition are essential characteristics that affect the material's behavior in vivo [11]. Moreover, glass ceramics are bioactive, forming hydroxyapatite when exposed to bodily fluid simulations, which improves their ability to integrate with bone tissue. Glass ceramics based on silicate and phosphate have been created, with compositions specifically designed to enhance mechanical and biocompatibility [12, 13]. Some glass ceramics possess antibacterial properties, alleviating concerns about infection associated with implants [14]. The materials are appropriate for bone, dental, and joint replacements due to their hardness, abrasion resistance, and low friction coefficients [15]. Melting quenching procedures and thermal treatments can create glass ceramics, which are materials containing crystal phases embedded within a matrix of glass. With the ability to develop innovative bilayered implants for complete tooth replacement, these adaptable materials exhibit promise for various dental applications, including restorative dentistry and implantology [12].

Furthermore, metal and metalloid oxides, nitrides, sulfides, and carbides are ceramics. Bioceramics, natural or synthetic materials that bond with bone, have emerged as an alternative to metallic implants [16]. Due to their favorable and compatible physico-chemical properties with specific human body components, they play a crucial role in the biomedical field. In the 18th century, bioceramic porcelain was first utilized for crown treatments. Plaster of Paris was later introduced to dentistry in the 19th century. With advancements in processing technology, the application of ceramics in medicine expanded significantly throughout the 20th century [17]. Recently, the scientific community has shown increasing interest in ceramic materials, glass ceramic materials, and bioactive glass. Fig. 1 illustrates the number of publications related to each substance based on data from the Web of Science.

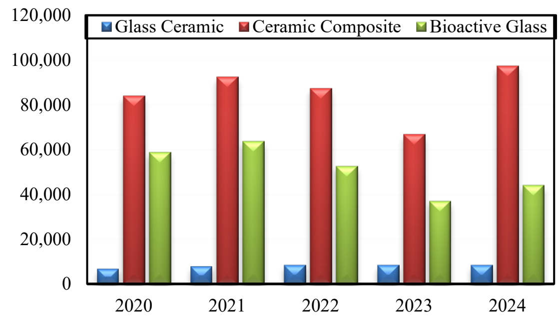

Fig. 1. The number of publications related to each material.

The purpose of this review is to highlight the main obstacles that remain to be overcome, as well as to offer a comprehensive analysis of current technologies available in bioactive glasses, ceramics, glass ceramics, and composite materials. We thoroughly examine each material type, including bioactive glasses, ceramics, glass ceramics, and composites, with sections addressing composition, characteristics, synthesis techniques, applications, and future challenges. It is through the analysis of these materials that we can improve our understanding of the role they play in a wide range of applications and their unique properties and advances.

2. Properties of bioactive glasses

Several glass formulations have been developed for bioactive glass, a nanocrystalline ceramic [18]. Generally, a material that produces a specific biological action is called a bioactive material [19]. The following sections will provide further information regarding the composition, properties, synthesis methods, and applications.

2.1. Composition and properties

Bioactive materials can create an adherent interface with tissues strong enough to withstand mechanical fracture. They exhibit excellent biocompatibility, stimulate bone cell functions, and can bond chemically with bone and other tissues [20]. Additionally, these materials have great potential for use as polymer fillers and coatings. However, in the use of bioglasses in the manufacture of porous scaffolds, dental materials, or filler materials, it is crucial to consider the properties of the materials, given their granulates of varying sizes and the particles/ powders of different shapes and sizes. Developing structurally compatible bioglasses while not adversely affecting living tissues is crucial [19]. The primary criteria for a bioactive glass are that it must contain calcium and phosphorus, the key components of the mineral phase in bone tissue, while avoiding any other unnecessary or harmful substances for living organisms [2]. The silicate concentration in the glass influences the biocompatibility of bioactive glasses; a silicate concentration of 45–52% yields optimal graft–bonding ability [20].

This composition has undergone several revisions: the Food and Drug Administration (FDA) authorized and named it Bioglass. Its name is Bioglass 45S5, which is listed in Table 1. There are various biological reasons why metallic ions are introduced into bioactive glass networks. Still, they are often also used for their structural and processable effects and for imparting additional functional properties to the glass [21]. For example, to enhance the effectiveness of bioactive glasses, ions such as silver (Ag^{+}), boron (B^{3+}), cobalt (Co^{2+}), copper (Cu^{2+}), iron (Fe^{3+}), lithium (Li^{+}), niobium (Nb^{5+}), strontium (Sr^{2+}), and zinc (Zn^{2+}) are added to their structures. [22-24]. The effect of ions on bioglass bioactivity is shown in Table 2.

Table 1
Various compositions of Bioactive glass in wt.%.

Bioglass	Composition	Refs.
45S5	$45SiO_2$, 24.5CaO, $24.5Na_2O$ and $6P_2O_5$	[25-28]
S53P4	$53SiO_2$, $23Na_2O$, 20CaO and $4P_2O_5$	[29]
58S	$58SiO_2$, 33CaO and $9P_2O_5$	[29]
70S30C	$70SiO_2$, 30CaO	[30]
13-93	$53SiO_2$, $6Na_2O$, $12K_2O$, 5MgO, 20CaO, $4P_2O_5$	[31]

Table 2
The effect of ions on the bioglass bioactivity.

Ion	Effect on bioactive glass	Refs.
Zn	Antibacterial	[32-35]
B	Biodegradability	[36]
Ag	Antibacterial activity	[37-41]
	Biocompatibility	[35, 37]
Ga	Antibacterial activity	[39, 42, 43]
	Improve thermal stability	[39]
Nb	Improve mechanical properties	[44, 45]
Ti	Improving antibacterial properties	[46, 47]
Sr	Antibacterial effect	[48-50]
	Boost biological properties	[32, 34, 51, 52]
Cu	Antibacterial activity	[35, 53, 54]
	Boost biological properties	[32, 34, 51, 52]
Sm	Improve the bioactivity	[55-58]
	Improve thermal stability	[37]
	Improve the mechanical properties	[37]
	Antibacterial properties	[37]

2.2. Synthesis methods

The production process is a crucial component of the creation of bioactive materials, dramatically affecting the final production cost and quality, as well as the material created [59]. Numerous techniques, including sol-gel, melt quench, spray pyrolysis, microwave irradiation, Stöber process, flame synthesis, acid-free hydrothermal, and microemulsion, can be used to create bioglass [60]. Melt quenching operations and sol-gel techniques are the two main methods employed in the production of bioglass [27]. This section provides a basic overview of sol-gel and melt quenching methods.

2.2.1. Melt quenching process

Until the 1990s, most bioglasses were produced using melting techniques, which involved fusing oxides and additives at high temperatures, quickly quenching the melt, and grinding the glass particles into a fine powder [61]. The components are subsequently melted in electric furnaces at high temperatures (typically between 1200 °C and 1550 °C), with parameters carefully adjusted to ensure a homogeneous melt [62].

The melting process can be repeated several times to achieve incredibly high degrees of homogeneity. The following options are among the forming routes that may be employed, depending on the desired final shape: I. Forming by pulling into continuous fibers, quickly chilling in water, or casting in molds. II. The particles can sinter when the glass is heated above its glass transition temperature (Tg), generating a porous scaffold, drawing fibers from a pre-form, or facilitating particle sealing to create surface coatings [63].

After milling, the melt quench technique creates glasses with specific particle sizes. Today, more than 99 percent of bioactive glasses are produced through melting, the most common commercial process. Melt quenching also allows for modifications in compositional space and the doping of transition metals and rare earth elements [64]. The high working temperature and the evaporation of specific components, such as Na_2O and P_2O_5, pose challenges with this method [65, 66].

2.2.2. Sol-gel process

The sol-gel technique is a widely used chemical synthesis method for producing inorganic materials with unique characteristics and microstructures, such as metal oxides, glasses, and ceramics [67]. By combining the precursors and allowing them to react in a liquid environment, the sol-gel technique generates bioglass nanoparticles with better-controlled morphology and size [68, 69]. This technique provides an alternative method for creating bioactive glasses at lower temperatures [70]. For bioactive glasses, sol-gel processing offers numerous advantages over traditional melt-quenching methods, including greater homogeneity and purity, lower operating temperatures, a wider variety of bioactive structural types, improved control over composition, size, and morphology, a larger specific surface area, accelerated formation of apatite layers, faster bone regeneration, enhanced degradability, and in vivo resorption [71-73].

For bioactive glasses, the sol-gel approach is a wet chemical process that creates materials comprising silicate, phosphate, borate, and metallic ion components [74]. The main steps in this process include material hydrolysis and condensation, followed by drying and stabilization.The operating requirements can be adjusted to control the properties of materials, such as composition and shape [75]. Tetraethyl orthosilicate (TEOS) is a common silicate precursor used for synthesizing sol-gel bioactive glasses; the preferred solvents in this procedure are ethanol and/or water [27]. Both alkaline and acidic environments can be utilized with the sol-gel process, with these varying conditions affecting the properties of the resulting materials. The solution's pH can be altered to produce bioactive glasses with different topologies. In a typical sol-gel process, TEOS first undergoes hydrolysis and condensation with the help of a catalyst to form $[SiO_4]^{4-}$ structural units [75].

Metallic ions can be added or doped to produce BGs during the initial phases of TEOS condensation or after diffusing them into a SiO_2 structure following drying and calcination procedures. Organic substances may be incorporated at any stage of the manufacturing process to enhance particle dispersion or control their shape [76]. Additionally, substantial research has been conducted recently on the sol-gel technique as a potential alternative to the melting process [77]. Fig. 2 shows the synthesis of bioactive glasses by the sol-gel method.

Fig. 2. Scheme of the sol-gel synthesis of bioactive glass powders [78].

2.3. Applications

Bioactive glass has numerous applications in the medical field, particularly in tissue engineering, dentistry, and medicine (Fig. 3). It is employed in tissue engineering as a scaffold material for bone regeneration due to its osteoconductive and osteostimulative properties, which facilitate the formation of new bone and promote vascularization.

Additionally, it is utilized for cartilage regeneration and soft tissue repair; its ability to stimulate angiogenesis is crucial for neocartilage development and wound healing. In dentistry, bioactive glass is used as a coating for dental implants, pulp capping material, mineralizing agents, and restorative materials. Moreover, it has antibacterial properties that effectively treat infections and serve as a medium for drug delivery systems. Table 3 illustrates how ions influence the uses of bioglass.

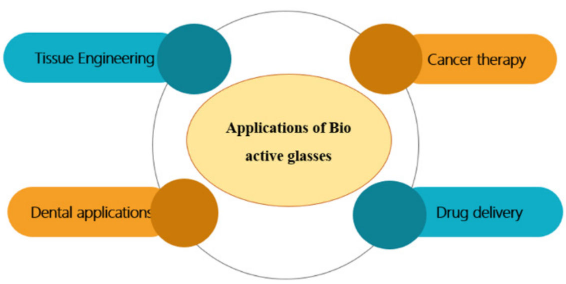

Fig. 3. Applications of bioactive glasses

Table 3
The effect of ions on bioglass applications.

Ion	Applications	Refs.
Zn	Bone regeneration	[33, 109-111]
	Wound healing	[110, 112, 113]
	Tissue engineering	[33, 34, 114]
	Drug delivery	[110]
Mg	Drug delivery	[115]
B	Tissue engineering	[116]
	Dental applications	[116-118]
Ag	Bone regeneration	[55, 119]
	Anticancer therapy	[120, 121]
	Dental applications	[122]
Ga	Bone regeneration	[24, 123]
	Anticancer therapy	[24, 124]
	Dental applications	[42, 43]
Nb	Dental applications	[45]
Ti	Bone regeneration	[47]
Sr	Dental applications	[125, 126]
Cu	Bone regeneration	[53, 127]
	Antibacterial coatings	[128]
Sm	Bone regeneration	[58, 129]

2.3.1. Tissue engineering

One class of inorganic biocompatible materials that may accelerate soft and hard tissue healing is represented by bioactive glasses, among the many biomaterials utilized in tissue engineering and regenerative medicine [79]. A monolithic tissue called Bioglass was used for the first time in the treatment of middle ear disease, as cones, which replaced the tiny bones in the middle ear. Biodegradable materials can act as temporary replacements to restore damaged tissues [80-83]. Since they promote cell growth and proliferation, they facilitate neovascularization and limit bacterial infection; These artificial biomaterials can enhance tissue repair and regeneration [84]. It has been suggested that developing bio-glass-based composites to address tissue engineering challenges results in more successful mineralization than alternative therapy forms [85, 86]. In some recent applications, bioactive glasses have also been clinically tested in contact with soft tissues, showing promising results in vitro and in vivo in enhancing angiogenesis [32].

Besides providing physical support, the ideal scaffold should also deliver growth factors and bioactive molecules that regulate the body's healing processes, along with signal transduction, proliferation, migration, and differentiation, to promote optimal bone healing and restore function [87]. Three-dimensional (3-D) pores facilitate vascularization and nourishment transfer between matrix-seeded cells and their surroundings. [88]. The scaffold must gradually degrade, and the host tissue will replace it, as it serves as a temporary substrate for cells to exist and thrive [89]. The degradation rate should align with the rate at which new tissue forms, producing benign byproducts that the body can easily absorb or eliminate. To address this challenge, most research has suggested that the scaffold's attributes are primarily dictated by the material composition, overlooking the interactive effect between architecture and composition [90].Bioactive glasses are mainly used as injectable putties, granules, or particles that are easy to press into bone deformities [32].

It is evident that bioactive materials are being used in musculoskeletal systems in order to repair intervertebral disks by cultivating annulus pulposus cells on composite films made of PLLA and Bioglass, as indicated by the increasing interest in bioactive glasses applications in medicine and dentistry [91].

2.3.2. Cancer therapy

The use of bioactive glasses that contain thermosets is considered an excellent way to achieve cancer hyperthermia and bone regeneration, as well as provide the necessary thermal activity for these purposes. For instance, Wang et al [92]. created bioactive glasses doped with bismuth composed of SiO_2, Na_2O, CaO, P_2O_5, and Bi_2O_3 using the melting-quenching technique. In vitro and in vivo tests assessed the glasses' biocompatibility, apatite production, and photothermal effect. A study using nude mice demonstrated that bismuth-doped glasses could effectively kill bone tumors in vivo when exposed to near-infrared radiation. Additionally, the bioactivity of the glass remained unaffected by the presence of Bi_2O_3. Therefore, a bone tumor might be regenerated with the help of doped glass following its destruction.

2.3.3. Drug delivery

The effective treatment of various malignancies requires controlled medication delivery [93]. It has recently been discovered that mesoporous bioactive glasses are excellent platforms for targeting specific drug delivery in cancer therapy [94, 95]. It is possible to use these materials as bone fillers to repair and regenerate bone tissue when a portion of it has been removed due to bone cancer. They offer several advantages as drug carriers, including high biocompatibility, appropriate stability, and adherence to living tissues [96]. Using bioactive mesoporous glass nanospheres as drug carriers in vitro and in vivo, Sui et al. [97]assessed their biosafety. They employed 45Ca labeling and histological examination to explore mesoporous bioactive glasses' bio-distribution, clearance, cellular localization, and systemic safety. As a result of the experiments, mesoporous bioactive glass nanospheres led to no abnormalities in histopathological or biochemical parameters.

Bioactive glass nanospheres were examined by Wang et al. [98] for their biological activity and to see how much doxorubicin was released. They encapsulated doxorubicin successfully into mesoporous bioactive glass nanospheres, resulting in a 63.6 percent encapsulation efficiency. Research like that of others observed that the mesoporous structure and local pH environment could significantly impact the mesoporous bioactive glass nanospheres' drug release and encapsulation capabilities. This approach is anticipated to be crucial for various cancers and for creating novel uses for mesoporous bioactive glasses in treating Organs and tissues.

2.3.4. Dental applications

When addressing autograft issues, restoring and maintaining alveolar bone continuity during dentition is challenging [99].There has been extensive research into synthetic biomaterials like Bioglass for tissue regeneration due to their biodegradability, mechanical properties, osteogenic potential, biocompatibility, and antibacterial attributes [100]. For optimal retention in bone, or osseointegration, in implantology, there must be continuous contact between the implant surface and bone tissue [101]. Combining autograft with a mixture of Bioglass granules allows embedding titanium roots in the porous maxilla. This leads to thicker trabeculae and accelerated bone regeneration compared to autograft alone [102]. Due to its superior osteoconductive properties, slower bone resorption rate, and enhanced biocompatibility, alkali-free Bioglass is more appropriate for dental and oral maxillofacial applications [103].

A micro gap is created when restorative materials experience some degree of polymerization contraction [104]. The failure of the dental composite can be attributed to the marginal leakage between the restorative material and the tooth surface. This gap allows bacteria, fluids, and ions to enter the space between the restorative material and cavity walls [105]. Because BAG fillers seal marginal surfaces with hydroxyapatite crystal precipitates, they are potential additives that enhance biological characteristics, antimicrobial effects, hardness, acid buffering, and remineralization [106]. Especially in dental implants, improved properties can be achieved by coating BGs on a zirconia substrate [107]. The two most widely used bioactive materials in restorative dentistry are calcium silicate and calcium aluminate. Fluoride-releasing restorative materials, including glass ionomers, are among the earliest bioactive substances in restorative dentistry. Bioactive glass that contains resin-modified glass ionomer cement (GIC) has superior remineralization properties [108].

3. Properties of glass ceramics

According to a revised definition, glass-ceramics are inorganic, nonmetallic materials created by carefully allowing glasses to crystallize through various processing techniques. These materials are made from glass heated to temperatures ranging from 1300 to 1500 °C. A heat treatment is then employed to transform the glass into crystalline materials [130]. Typically, a glass-ceramic is not completely crystalline, as the microstructure usually consists of 50–95% crystalline content, with the remainder being residual glass [131, 132]. These materials exemplify a unique combination of the characteristics of glass-like materials and traditional ceramics [133]. The choice of components, cooling rate, and the presence or absence of nucleating agents used to manufacture glass ceramics determine whether the material is amorphous or crystalline [130]. Furthermore, these variables can be adjusted to create materials with the desired composition and microstructure, which may be either transparent or opaque, colored or colorless. Based on SiO_2-Al_2O_3, the most commonly used glass-ceramic materials include oxide modifiers such as LiO_2, Na_2O, K_2O, CaO, ZnO, and MgO [134].

3.1. Composition and properties

Glass-ceramic materials differ primarily in their properties based on their intrinsic properties and morphology, their residual porosity, and their amorphous phase. Glass-ceramics are versatile materials that can offer solutions the significant potential for their use in various situations, attributed to their excellent mechanical, chemical, and abrasion resistance, high hardness, variable thermal expansion based on chemical composition, and the ability to be sintered at relatively high densities (92%–98%) at temperatures typically below 1000 °C [135].

Various processing methods can create glass-ceramic, inorganic, nonmetallic materials [136]. If a glass ceramic can be twisted, milled, drilled, or threaded using metalworking tools, especially those made of hard metals, without breaking the workpiece as regular ceramics do, it is considered machinable. The crystals should comprise roughly two-thirds of the ceramic's volume, be of an ideal size, and be in mutual contact to ensure acceptable machinability. Several factors, including grain size, percentage of crystallinity, distribution of crystal phases, remaining glassy phase, intergranular bonding, and crystal orientation, influence the final properties of glass ceramics. The exceptional electrical, thermal, and biomedical qualities of fluormica glass ceramics are widely recognized. These specimens can be easily cut, drilled, and turned using standard tools [137].

3.2. Synthesis methods

Glass ceramics can be produced using various techniques, including sol-gel, powder sintering, melting, casting, and crystallization, all outlined below.

3.2.1. Melting, casting, and crystallisation method

A precursor glass is made by mixing raw glass-forming ingredients and nucleating agents and melting them at high temperatures, usually between 1300 and 1500°C. A process called annealing is used to cool molten glass slowly at room temperature after it has been cast into the desired shape. During the first stage of a controlled heat treatment, temperatures are slightly above the glass transition temperature (Tg) to promote nucleation. In the second heating stage, temperatures are increased to allow crystals to grow steadily and without stress. The final microstructure is influenced by the Dimensions, composition, and concentration of nucleating agents and shapes of the crystals. This method can manufacture complex geometries, resulting in uniformly dense compositions with precise dimensions.Although melting temperatures can be lowered by adding low-melting-temperature oxides, a high overall temperature and prolonged treatment times remain limitations of this approach [138, 139].

3.2.2. Powder sintering method

This process aims to accelerate production by simultaneously sintering and crystallizing glass particles. A raw glass blank is made by melting raw glass materials, cooling them in water, grinding them finely into powder, sieving them, and pressing them at a specific temperature. Without additional nucleating agents, bulk nucleation along the glass grain boundaries forms the final crystalline structure. This method can produce high-temperature fused glasses that are challenging to generate a molten glass phase, making it less complicated and time-consuming than the melting and casting process. However, the resulting intrinsic porosity, thus limiting the creation of geometrically complex combinations, is a significant disadvantage [138-140].

3.2.3. Sol-gel process

The sol-gel liquid-phase method is used for curing compounds with high levels of chemically active components. The compounds are then heated to produce oxides or other solid compounds. A precursor, such as an inorganic compound or metal alkoxide, is used to mix these raw materials in the liquid phase uniformly. Catalytic hydrolysis and condensation processes are subsequently conducted to create a stable, transparent sol system in the solution. Aging further causes the sol to become more polycondensed and polymerized, resulting in a gel characterized by a three-dimensional spatial network.

Drying, sintering, and hardening the gel led to the preparation of molecular and nanostructured materials. This process enables the creation of various glasses with unique compositions, such as high-silica glasses, which are challenging to produce using standard fusion quenching techniques under mild synthesis conditions. A commonly used alternative to these compounds is inorganic metal salts, such as nitrates and chlorides, and organic chelating agents that are less expensive and volatile. To produce monolithic sol-gel glass, the gel is aged and densified over a long period at high temperatures [141]. The benefits of sol-gel glasses over the conventional melted-quenching technique include improved homogeneity, higher purity levels, and reduced stoichiometric losses [142].

An additional advantage is the substantial compositional flexibility of the prepared materials and the ease of applying them over a vast substrate area [143]. The primary benefits of this technique are the nanoscale size of the glass particles, which enhances the uniformity of the final product, and lowering the temperature, which prevents the potential volatilization of the glass particles and reduces contamination. However, this method can be costly and time-consuming, and gel shrinkage is risky during sintering [138, 144].

3.3. Applications

A glass ceramic can be used in two applications: as a highly durable material for restorative dentistry and a substitute for hard tissue [145].

Using ferrimagnetic and bioactive glass ceramics as thermo-seeds for treating bone tumors is expected to be advantageous. These materials may effectively kill cancer cells when positioned near the tumors by forming an interfacial bond with bone and indirectly heating cancer cells due to their ferrimagnetic properties [146].

3.3.1. Tissue engineering

Bioceramics are utilized to restore significant bone loss resulting from diseases such as cancer, and several ceramics are currently available for treating severe bone and joint disorders or deformities [147]. These may include rings arranged in a circle around a metal pin in the center of the remaining bone [148]. New bone grows into the implants, effectively acting as a scaffold for regrowth. The Apatite-Wollastonite glass–ceramic (A–W GC) has a high level of osseointegration and important mechanical properties like flexural strength and fracture toughness. However, the system's lack of bioresorbability and inability to bulk nucleate pose additional research and design challenges. Recently developed chlorapatite glass ceramics demonstrate osseointegration and resorbability [149]. Nevertheless, further investigation is necessary to assess their in vivo activity, the relationship between structure and properties, and mechanical and microstructural characteristics.

This powerful A/W GC features a chemical composition of MgO 4.6, CaO 44.9, SiO_2 34.2, and CaF_2 0.5, which increases its compressive strength to 10800 kg cm^{-2} and bending strength to 2000 kg cm^{-2}. A/W GC was developed in 1983 for spine and hip surgeries for patients with severe lesions or abnormal bones; however, its mechanical strength is not as good as that of cortical bone [150]. Each component consists of 35%, 40%, and 25% calcium oxyfluorapatite ($CaO_{10}(PO_4)_6(O, F_2)$) and calcium silicate ($CaSiO_3$), respectively. It was developed by Kokubo et al [151]. Several glass-ceramic vertebral prostheses with radiopaque anchors that adhered well to the bones were suitable for clinical applications. In the operating room, the surgeon can choose among different prostheses based on their size [152].

Despite being significantly more bioactive, Cerabone® A/W shares properties with lithium disilicate-based glass-ceramics [153]. When biological fluids come into contact with a glass-ceramic, Ca^{2+} ions are released, imparting bioactive qualities. Among them are calcium phosphates, hydroxyapatite, and other bioactive glasses [152].

3.3.2. Cancer therapy

Magnetic glass ceramics, serving as thermo-seed materials for cancer Therapy, have recently garnered significant attention due to their acceptable bioactivity.

A variety of factors affect the heat generated by these materials when implanted around cancerous bone tissues, including the magnetic properties of the material, the amount of magnetic crystal phases present within the material, the intensity and frequency of the applied alternating magnetic field, as well as the glass-ceramic microstructure [154, 155].

Magnetic bioactive glass ceramics can form apatite upon exposure to SBF, which has commonly been used to assess their in vitro bioactivity. Glass ceramics bond with living tissues by creating an appetite layer following SBF immersion. In general, two different magnetic field intensities are utilized to evaluate the magnetic hysteresis loops of glass ceramics: high (≥10 kOe) and low (500 Oe).

The higher magnetic field value is adequate for saturation magnetization, while low-field measurements are suitable for clinical laboratory settings [156]. The calorimetric measurement of magnetic glass ceramics is often performed using a magnetic induction furnace at an operating frequency of approximately 500 Oe (~400 kHz) [155].

Li et al. [157] proposed a new scaffold for tissue engineering based on chitosan, incorporating apatite-wollastonite magnetic glass-ceramic particles to enhance osteogenic potential in bone defects. Various rabbit models were used to test the scaffold in vivo, with some implanted with free scaffolds and others with scaffolds filled with rabbit bone marrow stromal cells (BMSCs). Based on the results, the scaffolds were effective in enhancing the osteogenic potential of newly produced bone in vivo.

Magnetic bioactive glass-ceramic is a viable bone substitute biomaterial for regenerating injured hard tissues and treating malignant hyperthermia [156].

3.3.3. Dental applications

There are several inherent drawbacks associated with traditional dental restorations, which can be addressed by functional dental ceramic coatings. Coatings protect dental substrates like crowns, bridges, implants, inlays, and veneers and serve as multipurpose materials.

The main goal of these coatings is to enhance the biocompatibility, antibacterial properties, and resistance to deterioration of the restorations. Natural polymers like chitosan are often incorporated into the coatings to improve their performance further, increasing their effectiveness and durability. For instance, researchers have successfully created Fluorapatite glass-ceramics (FGC) coatings on Ti_6Al_4V substrates using dip-coating and heat treatment methods. As a result of their excellent bioactivity and defect-free, crack-free interface, these coatings are also suitable for implanting in humans [158, 159].

FGC was primarily used on overlay inlays, which are metal-based restorations, in the early 21st century. For example, Holand et al. [145] used FGC veneers on metal anterior teeth, which produced a visual match with neighboring natural teeth. As ZrO_2 has become more widely utilized in dental restorations, FGC has also become commonly used as a veneering material for ZrO_2 restorations, and to finish bridge constructions with porcelain [160, 161].

FGC veneers were found to function as zirconia veneers over the course of 30 months in the oral cavity, according to Spies et al. [162]. According to Ritzberger et al. [163], three-unit ZrO2 bridges were improved by applying FGC veneers, leading to restorations that closely resembled natural teeth and met aesthetic demands.

Zhang et al. [164] used FGC to penetrate and cover ZrO_2 surfaces to prevent ZrO_2 restorations from becoming loose, significantly strengthening the bond between ZrO_2 and natural teeth. Their research demonstrated that it enhances the durability of the adhesive bond and flexural strength, along with approximately a threefold increase in bond strength compared to the initial bond. Fluorapatite–mullite composite glass ceramics were produced and heated to high temperatures to enhance the coating's adherence to substrates. This process allowed the coating to penetrate the substrate [165].

The final coatings exhibited mechanical resistance, chemical durability, and robust bonding. The osseointegration potential was also promising, and the risk of inflammation was low [164].

4. Ceramic

Due to their favorable physico-chemical characteristics that align with specific human body components, ceramics classified as metal and metalloid oxides, nitrides, sulfides, and carbides play a significant role in the biomedical sector [166, 167].

4.1. Composition and properties

Since their inception, ceramics have been recognized as one of the most significant high-performance materials because of their exceptional mechanical strength, hardness, and the ability to resist corrosion, wear, and temperature. In contemporary industries such as mechatronics, aerospace, defense, energy, as well as chemical and biomedical fields, enabling applications for advanced ceramics with distinctive geometrical features and unique functionalities [163].

Compared to other biomaterials, bioceramics possess a distinct set of qualities. For example: (i) materials with intense intrinsic strength, such as alumina and zirconia, exhibit excellent mechanical properties, including strong resistance to wear and low friction coefficient, making them suitable for high-stress applications like dental implants and artificial joints; (ii) biocompatibility- generally speaking, bioceramics are compatible with human tissues, decrease the likelihood of adverse reactions or inflammation.

Certain bioceramics, such as hydroxyapatite and bioactive glasses, display bioactive behaviors that promote tissue regeneration and osteointegration; (iii) versatility- bioceramics can be precisely shaped, and their compositions can be modified to improve certain properties. Due to these characteristics, bioceramics can address a wide range of biomedical challenges. Research on ceramic biomaterials is advancing rapidly, uncovering new significant applications in biotechnology and medicine, particularly in load-bearing components, joint replacements, fillers, veneering materials, drug delivery systems, and biomimetic scaffolds [168, 169].

4.2. Synthesis methods

Ceramic synthesis is a versatile and essential field of materials science that produces high-performance ceramics with specific properties tailored for industrial and scientific applications through various techniques. The chosen synthesis method depends on the intended application and material requirements.

4.2.1. Sol-gel process

The sol-gel technique is a method for producing ceramic powders, among other things. It involves slowly dehydrating the hydroxide sol of a specific powder to form a gel, which is then calcined to produce a fine, uniform powder. The advantages of this process include a relatively low production cost and the ability to obtain various materials. However, the drawbacks involve challenges in managing particle size and the extent of agglomeration, which can be mitigated by either polymerizing agents that facilitate the gelling process or various capping agents that prevent grain growth. Natural polymers, mainly starch and its derivatives, are the most commonly used [170-172]. Fig. 4 shows the synthesis of ceramics by the sol-gel method.

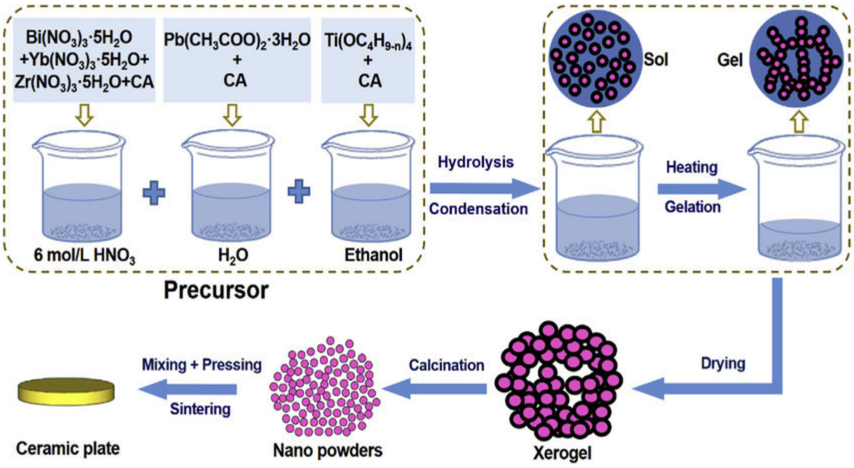

Fig. 4. Scheme of the sol-gel synthesis of ceramics [173].

4.2.2. Combustion process

One of the most effective and economical methods for producing ceramic powders is combustion synthesis, also known as self-propagating high-temperature synthesis, due to its straightforward experimental approach, comparatively quick process, and, most importantly, high-purity products. This process involves an elevated reaction temperature and a specific heating and cooling rate, which help to control the powders' microstructure. Typically, combustion synthesis starts with an oxidant precursor (usually metal nitrate) reacting with a fuel (an organic derivative) that serves as a reducing reagent. The energy generated by the reaction powers a subsequent step, igniting the reagents to produce a ceramic powder. The end products comprise nitrogen, carbon dioxide, water vapor, and metal oxide or its spinel. In this context, the fuel-to-oxidant ratio and the type of combustion fuel are the most crucial factors. When selecting a fuel, we should consider its enthalpy of combustion; a lower value for this parameter reduces the exothermicity of the combustion process and decreases the temperature at which the chosen powder is produced. While hydrazide-type compounds were used in the past, urea, carbon, and polysaccharides, starch, most commonly used, are now favored due to their nontoxicity [174, 175].

4.3. Applications

The remarkable qualities of ceramic materials, including their high strength, durability, heat resistance, and chemical stability, make them widely used across various industries. In the biomedical field, ceramics are utilized for drug delivery, implants, dental applications, and bone-tissue engineering because of their biocompatibility and regenerative potential (Fig. 5).

4.3.1. Drug delivery

In particular, biomedical applications, especially drug delivery, metal oxide-based nanoparticles, such as zinc oxides and Zn-containing composites, are considered viable platforms. Drug delivery refers to the administration of drugs using an appropriate vehicle to ensure effective treatment with minimal side effects [176]. CaP-based hybrid nanoceramics can be designed to deliver anticancer drugs with fluorescence tracers and achieve fluorescence imaging (FLI)-guided therapy. CaP nanocarriers integrated with fluorescence tracers can function as optical reporters, allowing for real-time drug delivery and release monitoring, and assessing the therapeutic effects of delivered drugs in vivo. Fluorescence agents include organic fluorescent dyes, quantum dots, fluorescent macromolecules, rare earth oxides, and metals [177].

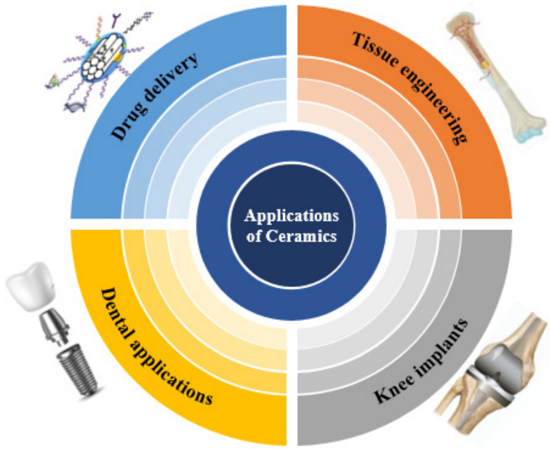

Fig. 5. Bio applications of ceramics.

Due to CO^{2-}radical impurities, Singh et al [178]. Reported a novel HAp-based nanocarrier with self-fluorescence imaging capability. Hydrothermal methods prepared the HAp nanorods, and the self-fluorescent HAp nanorods (fHAp) enabled imaging capabilities and showed great potential for theranostics applications. These results indicate that hybrid fHAp@mSi nanocarriers have significant potential for effective loading of therapeutic molecules, drug delivery within intracellular compartments, and the ability to perform in situ imaging. Peng et al. [179] used silane chemistry to coat Fe_3O_4 nanoparticles with zwitterionic polymer membranes, enhancing the nanoparticles' stability, a crucial factor in medication delivery for cancer treatment, where prolonged blood circulation is necessary.

4.3.2. Tissue engineering

Considering their capacity for autologous recellularization, the preservation of native arterial architecture, and the elimination of cell-based antigens, decellularized vascular grafts have recently been examined in tissue engineering for their potential use in cardiac medicine [180, 181].Marinval et al. [180] and Iijima et al. [181] have developed coatings for decellularized vascular grafts to reduce the risk of thrombosis and degeneration. Marinval et al. [180] manually coated a valve scaffold with three layers of a fucoidan/vascular endothelial growth factor (VEGF) polyelectrolyte multilayer film (PEM) to enhance re-endothelization and decrease thrombogenicity and calcification of decellularized porcine heart valves. The coating demonstrated the desired increase in antithrombotic activity without elevating calcification, and the modified scaffold also displayed improved re-endothelization and potential for stem cell repopulation. To polymerize the coating as a gel inside the lumen, Iijima et al. [181] coated the internal surfaces of aortic grafts (Wistar rats) with a hydrogel-VEGF mixture. In vivo, results showed that the coating stimulated medial recellularization and significantly increased endothelium formation compared to the uncoated graft control group. Understanding the need for bioactive composite scaffolds with favorable mechanical properties, Luo et al. [182] utilized in-situ mineralization and 3D printing to create alginate/gelatin scaffolds featuring a uniform nanoapatite coating; the phosphate ion concentration could regulate the coating thickness. The coated scaffold exhibited superior mechanical properties (two-fold higher Young's modulus) compared to uncoated scaffolds, and it also enhanced the proliferation and osteogenic differentiation of rat bone marrow cells.

4.3.3. Knee implants

Medical devices known as knee implants consist of various components designed to replicate the joint's surface, made up of broken bone and cartilage. The lower part of the femur, the upper part of the tibia, and the back surface of the patella can all be replaced. Metals are typically used in this type of surgery [183]. The abnormal hinge-like action of these metal knee implants can increase strain on the knee's supporting muscles and ligaments, leading to various knee issues. Therefore, similar to the case with THA, using additional materials, such as bioinert ceramics, is necessary. To assess clinical and radiological outcomes and the long-term durability of the ceramic tri-condylar implant over 15 years, Nakamura et al [184] developed a ceramic tri-condylar implant with an alumina ceramic femoral component. However, Meier et al. [185] demonstrated the potential of the metal-free BPK-S ceramic complete knee replacement system, which is a safe and effective clinical alternative to metal implants.

4.3.4. Dental applications

The compatibility of ceramic materials with living tissues is a key characteristic of their use in dentistry. Examples of bioceramics that have been researched for dental applications in recent decades include alumina, zirconia, SiAlON, bioglasses, and hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) [186-188]. Numerous researchers have studied the use of a combination of polylactides and bio-ceramics in bone surgery in recent years. These materials are utilized in sinus lift operations and bone augmentation surgeries before implant insertion [189, 190]. Using autogenous, homogenous, and xenogenous bone grafts and their undesirable side effects can be reduced by porous three-dimensional structures (scaffolds) made from bioabsorbable ceramics like hydroxyapatite or tricalcium phosphate [191]. Because zirconia is bioactive, biocompatible, and has good mechanical and aesthetic qualities that improve the quality of dental implants, HAp incorporated into zirconia provides high stability and protection over an extended period, aiding in the integration of dental implants.

These composites are promising new bone restorative materials with characteristics similar to human bone, and various HAp coatings can modify the surface of zirconia composites. Because of these materials' advantages in dental implant applications can be considered alternatives to titanium and its alloys, two of their conventional counterparts [192]. Ceramics are often used in dentistry due to their easily achievable shape, color, and customized mechanical properties. Crystalline mineral salts are dispersed throughout a vitreous silicate matrix that constitutes dental porcelain. Smaller quantities of metal oxides, used as dyes to replicate the color of natural teeth and to increase the coefficient of thermal expansion while lowering the melting temperature, are incorporated into the ceramic's composition [193, 194]. Dental porcelain is applied in veneering, the fabrication of prosthetic teeth, indirect cosmetic restorations such as facades and inlays/overlays, and the construction of fixed frameworks like metal-ceramic rims and bridges [195, 196]. Glass-matrix ceramics are derived from a ternary material system comprising clay/kaolin, quartz (silica), and natural feldspar (a mixture of potassium and sodium aluminosilicate). Potassium feldspar ($K_2A_{12}Si_6O_{16}$) that develops into leucite crystals (the crystalline phase) can enhance a restoration's inherent strength. These bioceramic materials are utilized as aesthetic monolithic tooth-covering and veneering materials in ceramic substrates and metal alloys [197]. The creation of ceramic structures utilizing 3D scaffolding as substitutes for dental bone has garnered significant attention in regenerative dentistry. In this context, a study byMihai M.C. Fabricky et al. [198] explores the development of two scaffold-like structures derived from various commercial dental ceramics using the foam replication technique. Fig. 6 illustrates an overview of these newly developed ceramic scaffold structures.

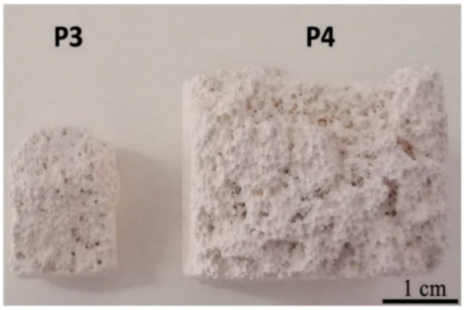

Fig. 6. General summary of ceramic scaffolds P3 and P4 [198].

5. Future challenges

The inherent brittleness of bioactive glasses and bioceramics limits their use as structural materials. Innovative solutions are necessary to tackle this issue, such as developing hybrid composites or utilizing polymers to improve mechanical properties while maintaining bioactivity. Thermal treatments often lead to the crystallization of bioactive glasses, which can diminish or inhibit their bioactivity. It is essential to create methods to prevent or control crystallization for applications like coatings and porous scaffolds [199].

Scaling up manufacturing from laboratory research to industrial applications remains challenging due to issues with cost-effectiveness, repeatability, and regulatory barriers. The widespread acceptance of bioactive glass-based products relies on developing standardized manufacturing processes [200]. Green synthesis techniques are increasingly essential for bioactive glasses to reduce the negative environmental impacts of production. Developing eco-friendly processes without compromising material properties is becoming increasingly important [201].

Additionally, investigations into bone regeneration in the past ten years have shown that inadequate or delayed vascularization presents a significant barrier to transforming regenerative medical devices into clinical products. Promoting blood vessel infiltration into the scaffolds is essential for vascularized bone to function and remain viable long-term. Viable cells are typically confined to the outer or superficial layers of the tissue constructs due to limitations in the flow of oxygen and nutrients. Consequently, bone development is minimal in the central areas of the scaffold, which could be considered for further research to address these challenges [202].

These issues represent crucial topics for further study and development to fully realize the potential of bioactive glasses, glass ceramics, and ceramic composites in regenerative medicine and other fields.

6. Conclusion

Glass ceramics, ceramic composites, and bioactive glasses have become essential materials in various biomedical fields, particularly bone regeneration and tissue engineering. These materials possess unique qualities such as bioactivity, biocompatibility, and the ability to promote osteoconduction without creating fibrous tissue, making them ideal for dental applications and tissue engineering. However, despite their excellent bioactive properties, they often exhibit mechanical strength and fracture toughness limitations, hindering their use as direct replacements for human bone. Composites can enhance mechanical performance while preserving bioactivity, stemming from recent advancements focused on elevating these attributes. Moreover, incorporating therapeutic ions such as strontium and magnesium, along with antibacterial ions like copper, zinc, and silver, has broadened their applicability in regenerative medicine.

Future challenges include addressing the degradation rates of these materials to align with tissue regeneration rates, exploring novel fabrication techniques like additive manufacturing, and enhancing the chemical composition to balance bioactivity with mechanical properties. As research evolves, these materials hold significant potential to advance healthcare technologies, particularly in medical fields.

Author contributions

Tanaz Ghasabpour: Conceptualization and Writing – Original Draft Preparation. **Fariborz Sharifianjazi:** Writing – Original Draft Preparation and Writing – Review & Editing. **Leila Bazli**: Writing – Original Draft Preparation and Writing – Review & Editing. Nino **Tebidze:** Investigation, Writing – Review & Editing. **Matin Sorkhabi:** Writing – Original Draft Preparation.

Funding

No funding was received for this study.

Conflict of interest

Given their role as Editor-in-Chief, Fariborz Sharifianjazi had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to another journal editor.

Data availability

No data is available.

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