2 Literature Review

2.1 Introduction

Ceramic materials are non-metallic, inorganic solids that contain crystalline ceramic and amorphous glass compounds. The word "bioceramics" refers to the ceramics used to restore and rebuild diseased or injured musculoskeletal system components (Hannink et al., 2011). Dental implants, coatings for orthopaedic and maxillofacial prosthetics, bone fillings, bone scaffolds, and alveolar ridge augmentation are only a few of the surgical uses for bioceramics, which may be dense or brittle. They are strong, stiff, and biocompatible materials in general, but they are often brittle and fragile in stress (Rahaman et al., 2017). Bioceramics are classified into three types depending on their biological response: nearly bioinert materials like alumina, and zirconia, bioactive materials like HA and bioactive glasses, and biodegradable materials like TCP. Bioactive ceramics, such as bioactive glasses, glass-ceramics, and calcium phosphates, can promote the creation of bone-like hydroxyapatite deposits at their surface and provide an interface that leads to the tissue's functional durability (Huang et al., 2017). Researchers found that bioceramic materials can establish a good attachment to connective tissue through a bioactive response. The physiological composition of bone and the implant environment is investigated as a result of this (Ratner et al., 2013).

2.2 Bioactive glass

Due to the rapid cooling of the molten ceramic, bioactive glass is an amorphous substance with a random arrangement of atoms. SiO_2, Na_2O, CaO, and P_2O_5 are the key components of most bioactive glasses. Bioactivity, osteoconductivity, and biodegradability are depending upon the precise composition of the bioactive glass. When the silica content of the bioactive glass is between 42 and 53 percent, fast bonding to bone happened, whereas bonding took 2-4 weeks with glasses containing 54 to 60 percent silica, and there was no

direct bonding between the bioactive glasses and bone with glasses containing more than 60 percent silica (Hench et al., 2010). Several changes in the composition of the bioactive glasses are done to develop silicate-based, phosphate-based, and borate-based glasses. They have been used in bone scaffolds, middle ear replacements, and tooth root replacements, etc (Essien et al., 2016). Bioactive glasses can bond with living bone tissue through the chemical reaction on the surface of the material, accompanied by cellular reactions. The ion leaching/exchange occurs at the implant's surface, resulting in the dissolution of the glass network, as well as the formation and development of calcium deficiency (Rahaman et al., 2017).

Glass-ceramics have been developed to overcome the drawbacks of bioactive glasses. Glass-ceramics are crystallized glasses, made up of a crystalline phase (crystal sizes varying from 0.1 to 10 μm) and a glassy phase. The heat treatment of a base glass to cause controlled crystallization and convert it into a glass-crystal mixture is part of the glass-ceramics production process. The heat treatment encourages the formation and development of crystalline phases with fine grain sizes. As a result, the crystallization and formation of crystal phases can be regulated to achieve a range of specific properties, including bioactivity, machinability, and enhanced mechanical properties (Best et al., 2008). Bioglass has poor mechanical properties which restrict them for major load-bearing applications. These are used where regeneration is important and mechanical strength is not necessary (Palmero et al., 2016).

2.2.1 Bioactive Compositions

Figure 2.1 shows a ternary phase diagram of Na_2O–CaO–SiO_2 with P_2O_5 at 6 wt%.

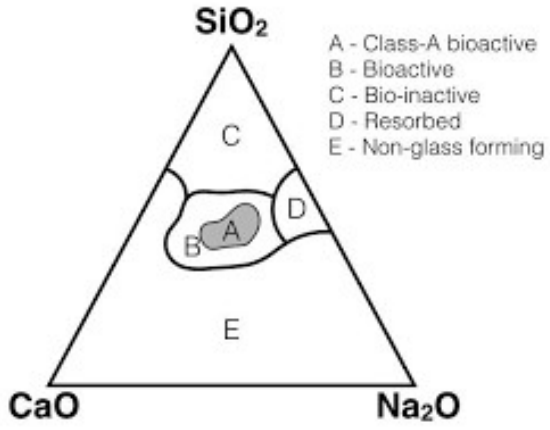

Figure 2.1 Property changes of bioglass materials (Henao et al., 2019).

Region A is a subcategory of region B, where certain glasses have been found to form soft tissue bonds. Region B is considered bioactive and completely binds to the bone; Owing to insufficient network access, glasses with compositions in region D are degraded too easily, e.g. within 10-30 days of implantation. The ratio of surface area to solution determines the boundary between B and D. Due to higher network connectivity and low modifier amounts, glasses in region C do not dissolve and behave as inert materials (Cao et al., 1993) (Henao et al., 2019).

There are two established techniques for producing bioactive glass powders; melt quenching and sol-gel processing. Both are discussed in this section.

2.2.2 Producing bioactive glasses by melt quenching

In melt quenching, the components of desired bioactive glasses in required amounts are melt together to achieve the desired composition. The melt is quenched and grind into powder. The molten glass can be quenched in water or liquid nitrogen. Glass powder can be made by collecting and milling granules of various sizes known as frits. By pouring the liquid

mixture into molds with specific sizes, the desired scale and form can be achieved. This technique can be used to create a wide variety of bioactive glasses (Karasu et al., 2017).

2.2.3 Producing bioactive glasses by sol-gel processing

The second method for producing bioactive glass is the sol-gel method which is a wet chemical low-temperature process. In the sol-gel process, the solution of essential precursors in the required amount is undergoing a hydrolysis and polycondensation reaction at room temperature for gel formation. This formed gel is dried and heated to get the amorphous structure of glass. This sol is cast into a petri dish for gel formation. The aging of the gel is done which strengthens the bonds. The gel is dried and milled to get powder (Yadav et al., 2020). A metal alkoxide of M-(OR)x type is a molecule that consists of a central metallic ion (M) bound to functional organic groups (R) by an oxygen linkage (O). Due to their ability to react with water, metal alkoxides such as tetraethoxysilane (TEOS) and tetramethoxysilane (TMOS) are often used as silica precursors. The hydrolysis reaction results in the substitution of the alkoxy side chain with hydroxyl groups. Hydrolysis happens as the oxygen atom in the water molecule attacks the silicon atom with a nucleophilic attack.

Hydrolysis Reaction: $M\text{-}(OR)_4 + 4(H_2O) \rightarrow HO\text{-}M(OR)_3 + R\text{-}OH$

R stands for an alkoxy functional group, such as C_2H_5OH. The reagent ratios can be changed to control the degree of hydrolysis, which results in clusters or branched polymeric chains. In polycondensation, viscosity increases due to an increase in the interconnectivity of the inorganic network.

Condensation reaction:

$(OR)_3M\text{-}OR + HO\text{-}/M(OR)_3 \rightarrow (OR)_3M\text{-}O\text{-}M(OR)_3 + ROH$

$HO\text{-}M\ (OR)_3 + HO\text{-}M(OR)_3 \rightarrow (OR)_3M\text{-}O\text{-}M(OR)_3 + H_2O$

The condensation reaction releases alcohol and water as a by-product. The water remains in the pores of the gel. The aging mechanism retains water in the pores, allowing for a localized

solution and solid network reprecipitation. This increases the thickness of interparticle necks and increases the density and strength. The aging process usually takes place at elevated temperatures for several hours/days. At the drying stage, the pore liquid and residual alcohols are separated from the monolith, leaving small interconnected pores with diameters ranging from 1 to 20 nm. Stabilization at higher temperatures causes further drying and removing surface silanol groups and forming three-dimensional silica rings (Hench et al., 1990). This method improves density, strength, and hardness, as well as converting the glass network to mimic its melt-derived counterpart. The oxides of phosphorous and calcium are produced by mixing reagents like tri-ethyl phosphate (TEP) with calcium chloride or calcium nitrate. Glasses with higher purity and homogeneity can be made using the sol-gel method. Furthermore, all of the steps in this method are completed at temperatures that are significantly lower than those used to produce glasses with the melting process (Li et al., 1991).

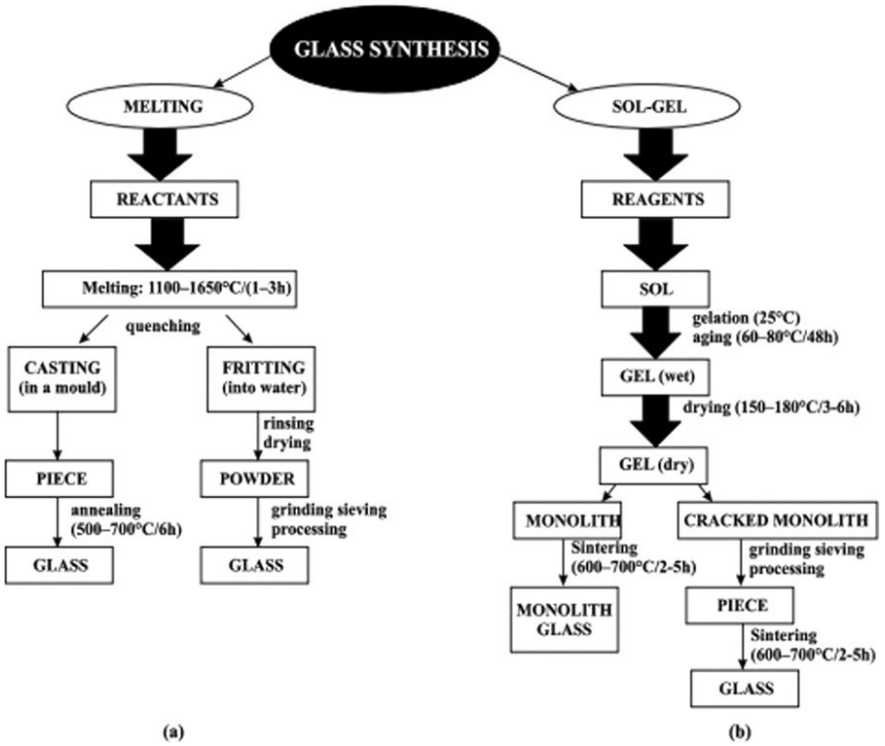

Figure 2.2 Schematic presentation of bioglass synthesis (a) melt method, (b) sol-gel method (Kaur et al.,2016)

2.2.4 Stimulating bone growth

In bioglass, the bone growth stimulation occurs in two stages: first, the formation of hydroxy carbonate apatite (HCA) due to dissolution and precipitation, and after that, the interaction of the HCA layer with the weak collagen fibrils to form a bond with the bone. The dissolution products stimulate cells throughout the process. HCA formation occurs in 5 stages, similar to those of conventional glass corrosion mechanisms (Jones, 2013).

- Rapid cation exchange (for example, Na^{+}, K^{+}, Mg^{+2} , and Ca^{+2}) in the glass reacts with H^{+} from the solution to form silanol bonds (Si-OH) on the surface. This raises the local pH, resulting in the formation of a silica-rich area near the glass surface. (If phosphate is present in the glass composition, it is also released at this first stage.)
- Due to an increase in pH, OH^{-} ions interact with the silica glass network and break the Si–O–Si bonds and form $Si(OH)_4$ which leads to the formation of Si-OH (silanol) at the glass–solution interface.
- Si-OH groups condense near the glass surface in the silica-rich layer.
- Migration of Ca^{+2} and PO_4^{-3} groups occur from the solution and the bulk glass to the surface of the silica-rich layer thus creating an amorphous $CaO–P_2O_5$ layer;
- Incorporation of hydroxyls and carbonate ions from solution and crystallization of the $CaO–P_2O_5$ form HCA (Jones, 2013, O'Donnell, 2012).

Figure 2.3 shows a schematic image of hydroxycarbonate apatite (HCA) formation on the surface of bioactive glasses.

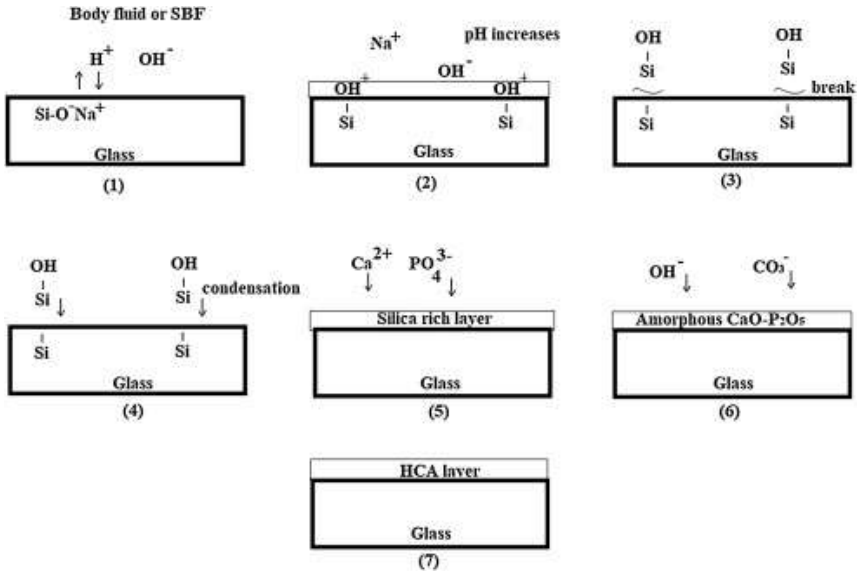

Figure 2.3 formation of hydroxycarbonate apatite (HCA) on the bioactive glass surface.

(1) formation of silanol bonds (Si-OH) on the glass surface, (2) increasing the pH of the solution to promote the formation of a silica-rich area close to the glass surface, (3) breaking down of silica bonds, (4) further formation of silanol at the glass–solution interface, (5) precipitation of a silica-rich layer, (6) formation of an amorphous CaO–P2O5 on the formed silica-rich, (7) crystallization of the amorphous CaO–P2O5 layer to apatite (Henao et al., 2019).

The bioactive glass composition affects the apatite layer formation and bone growth around the implant. Low silica content in bioactive glass is associated with a less connected network. This promotes bioactive glass dissolution and also increasing the rate of apatite formation. The activation energy of silica dissolution in glasses is often related to bioactivity. However, their bioactivity is dependent upon the amount of silica in glass and the glass network connectivity. Multivalent ions such as Al^{+3} or Ti^{+4} in bioglass reduce bioactivity and solubility while cations such as sodium and calcium increase the dissolution rate and bioactivity (Aparicio et al., 2015). Glasses with high silica have lower dissolution and bioactivity due to a highly linked network. As a result, network modifiers that can weaken the

glass network are important for bioactivity and dissolution. Bioactive glasses can interact with the physiological environment stimulates the *in-vivo* osteogenesis on the implant surface making them ideal for cell attachment and proliferation (Henao et al., 2019).

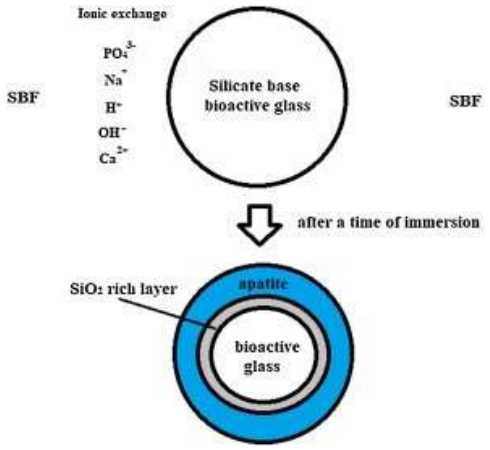

Figure 2.4 Schematic representation of the dissolution behavior of silicate bioactive glasses in simulated body fluid (Henao et al., 2019).

2.3 Hydroxyapatite ceramic

Several bioceramics have been studied to replicate the chemical similarities to the bone. Synthetic calcium phosphate ceramics like hydroxyapatite (HA) are designed to imitate the chemical inorganic component of the bone (Witek et al., 2013). To affect the biological response of the implant, different types of calcium phosphate ceramics have been developed by varying the Ca/P ratio (Shepherd et al., 2012). Some of these are biodegradable means they degrade in the body and can be substituted with the bone after implantation. The solubility rate is very important and should not surpass the rate of tissue regeneration to be used as an implant. The hexagonal crystal structure of hydroxyapatite allows for a variety of modifications (Fihri et al., 2017). These substitutions have an impact on the composite's lattice parameters, crystal morphology, crystalline structure, solubility, and thermal stability. One of the major advances in bioceramic in the last 40 years was the use of hydroxyapatite as

a coating for prostheses to extend the usable life of an implant. Clinical trials compared hydroxyapatite-coated femoral stems of hip prostheses to non-coated stems and found that they increased implant life and were beneficial for younger patients (Witek et al., 2013). However, because of its poor mechanical properties, hydroxyapatite has only been used in non-load-bearing applications (Eliaz et al., 2017).

In the calcium phosphate compound, hydroxyapatite is the second most stable and least soluble compound after fluorapatite. The Ca/P ratio of stoichiometric hydroxyapatite is 1.67, and the chemical formula is $Ca_5(PO_4)_3(OH)$. $Ca_{10}(PO_4)_6(OH)_2$ is a common abbreviation for hydroxyapatite, which signifies that the hexagonal unit cell is made up of two molecules (Dorozhkin, 2009). Due to its chemical and structural resemblance to natural bone mineral, it has been widely used as a bone graft replacement or as a coating for orthopedic devices (e.g. hip-joint prosthesis) and dental implants (Best et al., 2008). In in-vitro, it affects osteoclastic and osteoblastic responses and bone loss and regeneration in in-vivo. Carbonate substituted apatite is the most abundant apatite found in bone, with a carbonate content of 3-8 wt% and a Ca/P ratio of less than 1.67, making it more soluble than pure HA (Dorozhkin et al., 2002).

Hydroxyapatite powders are synthesized by dry methods (solid-state method), wet methods (precipitation, hydrolysis, sol-gel, emulsion, and hydrothermal synthesis), and alternative energy input methods (microwave-assisted, ball-milling, and sonochemical methods) are used to make hydroxyapatite. The preparation technique has a significant effect on the powder morphology, specific surface, stoichiometry, and crystallinity. Precipitation is the most simple and widely used process for the preparation of HA among these techniques. In the presence of other additives such as base or acid, it consists of a reacting source of PO_4^{-3} ligand with a source of calcium (Cao et al., 1996). This method is normally carried out at pH values varying from 3 to 12 and at temperatures ranging from room temperature to the boiling temperature of the water, using various sources of these two reagents (Chen et al.,

2012). This method often produces non-stoichiometric Hydroxyapatite (Ca/P 1.67). The solid-state method is commonly used for Hydroxyapatite synthesis and result in a stoichiometric and well-crystallized product. But this requires high temperatures and long heat-treatment periods. Natural resources such as fish bones, seashells, eggshells, bovine bones, and shrimp shells may also be used to extract HA (Suchanek et al., 1998).

Hydroxyapatite is manufactured as a dense or macroporous material. Dense HA has a porosity of less than 5% and is also known as microporous HA (Szcześ et al., 2017). Due to poor mechanical properties, dense HAs are usually used in unloaded tooth root substitutes. Porous HA has been commonly used as a bone replacement because of its good bonding to the bone. Furthermore, the pores have a mechanical interlock, resulting in a stronger material fixation. Porous HA with pores smaller than 10 μm in diameter is needed for body fluid circulation, while pores larger than100 μm are required for colonization of target cells. Large pores, on the other hand, dramatically reduce the implant's strength. As a result, porous HA implants can't bear a lot of weight and are only used to fill minor bone defects. Drug delivery systems, alveolar ridge augmentation, and orthognathic reconstruction are some of the other uses of porous HA (Suchanek et al., 1998, Suchanek et al., 2005).

Table 2.1 Methods for the preparation of HA (Sadat-Shojai et al., 2013) (Szcześ et al., 2017).

Dry methods:	Wet methods:	High-temperature processes:	Synthesis from biogenetic sources	Combustion Procedures:
1. Solid-state method 2. Mechanochemical method	1.Sol-gel method 2.Chemical precipitation method 3.Hydrothermal method 4.Emulision method 5.Sonochemical method	1.Combustion method 2.Pyrolysis method		

Rizwan et al., 2020 prepared composites of hydroxyapatite (HA) and Bioglass® (BG) to evaluate their physical, chemical, and biochemical characteristics. In this study, the sintering was performed at 1130°C, slightly below the melting point of BG of 1200°C. This lower sintering temperature prevents excessive reactions between the precursors even with BG content as high as 10 wt%. The absence of undesirable phases (containing BG < 10 wt%) resulted in enhanced bioactivity and a moderate resorption rate.

Azis et al., 2018 prepared composites containing bioglass of composition SiO_2-$CaCO_3$-Na_2O_3-P_2O_5-CaF_2 with 10wt% of hydroxyapatite. The mechanical properties were measured in terms of temperatures ranging from 500 to 1000°C with 50°C increments. The improvement in mechanical properties was attributed to the improved densification. However, both hardness and compressive strength were decreased with further increasing sintering temperature from 850-1000°C. This study shows that the mechanical properties greatly depend on the microstructure properties at each stage of sintering temperature.

Cozza et al., 2018 prepared hydroxyapatite (HAP)-45S5 bioactive glass composite and compared it with synthetic hydroxyapatite. The cuttlefish bone powder was co-sintered with 30 wt% of 45S5Bioglass to synthesize HAP-based powders. Composites made with cuttlefish bone powder exhibited increased apatite deposition, alkaline phosphate activity, and cell proliferation compared with commercial synthetic HAP.

Rizwan et al., 2018 prepared hydroxyapatite (HAP)-45S5 bioactive glass composite. They reported that high-temperature sintering of HA-based systems results in crystallization of bioglass and/or excessive reaction with HA, which has negative effects on the bioactivity, resorption, and osseointegration.

Youness et al., 2018 prepared bioglass of composition 80.7SiO_2, 13B_2O_3, 4Na_2O, 2.3 Al_2O_3 (in wt%) was mixed with carbonated hydroxyapatite (CHA) and selenium dioxide. They found that the presence of glass encouraged the partial CHA decomposition to

tricalcium phosphate (TCP) phase along with calcium silicate ($CaSiO_3$) one which led to a significant increase in the bioactive character of the prepared nanocomposites and a considerable increase in their mechanical properties. Although the addition of SeO_2 to the prepared nanocomposite samples did not influence their mechanical properties, the studied bioactivity is positively affected.

Yazdanpanah et al., 2015 prepared Hydroxyapatite/ sodalime bioactive glass composites with 0 to 5 wt% of bioglass and investigate the effect of sintering temperature on density, micro hardness, and compressive strength. They found that density and hardness of composites increased with sintering temperature while bioglass addition decreased the hardness and density. Moreover, the compressive strength was improved with glass addition in hydroxyapatite.

Ashuri et al., 2012 prepared the bioceramic-based composite by mixtures of hydroxyapatite (HA) and sol–gel-derived bioactive glass (64 SiO_2-26 CaO-5 MgO-5 ZnO) (based on mol %) powders. HA powder was mixed with different concentrations of the glass powders up to 30 wt%. The composite with 20wt% bioglass had the highest compressive strength (before soaking in SBF) amongst other compositions. The matrix of this composite contained β-TCP and due to degradation of this phase in SBF, a gradual decrease in compressive strength (up to 65%) was observed in-vitro. composite with 20wt% bioglass showed remarkably higher ALP activity for SaOS-2 cell line cultures compared with SaOS-2 cell line cultured on polystyrene plates.

Kapoor et al., 2010 prepared composites on addition of 30%CaO-30%P_2O_5-40%Na_2O bioglass in 2, 5, and 10 wt% in hydroxyapatite. It found that composites have higher compressive strength as compared to hydroxyapatite and the bioactivity was improved with bioglass addition.

2.4 Calcium zirconium silicate ceramic

Calcium zirconium silicate ceramic is also known as Baghdadite [$Ca_3Zr(Si_2O_7)O_2$ or $Ca_3ZrSi_2O_9$] was first discovered in melilite skarns in Qala-Dizeh, Iraq, and published in 1986 (Al-Hermezi et al.,1986). It was later discovered in melilite skarns in Flekkeren, Oslo Rift, Norway, Akaggane mine in Iwate prefecture, Japan, spurrite-rich skarns in Fuka, Okayama prefecture, Japan, and skarned carbonate xenoliths in the Yoko-Dovyren massif, Russia. Finally, in the Canary Islands, a solid solution containing baghdadite, cuspidine, and niocalite was discovered (Biagioni et al., 2010). Calcium-silicate (Ca-Si) based ceramics have gained a lot of attention in the last two decades as promising biomaterials for bone and skeletal tissue regeneration. High bioactivity and biodegradability are two of their most advantageous properties in the biomedical field. However, in addition to their brittle nature and low strength, Ca-Si ceramics have a higher dissolution rate, which affects cell growth (due to high pH values), and subsequent osseointegration, as well as their long-term stability (Sadeghzade et al., 2017).

One of the well-known strategies for overcoming the drawbacks of those materials is to introduce the third component into the structure of Ca-Si ceramics. Magnesium (Mg), zinc (Zn), and zirconium are some of the elements used to enhance or regulate the chemical stability, bioactivity, and mechanical properties of Ca-Si ceramics. Because of its biocompatibility and adequate mechanical ability, Zr has been widely used in the production of implants and prosthetic devices, especially in bone and dental applications. Zr is a quadrivalent ion, similar to Ti and Si, and can form a network that ionically connects Ca ions, improving the stability of Ca-Si-based ceramics and allowing the forming of baghdadite (Jodati et al., 2020). Natural baghdadite is a rare mineral that belongs to the cuspidine silicates series and has the general formula $M_4(Si_2O_7)X_2$, where M denotes cations of different charges. The unit cell dimensions of natural baghdadite are a=10.432°, b=10.163°,

c=7.356°, and β=90.96°, with the space group $P2_1/a$. The natural baghdadite crystals had lattice parameters that matched the crystal structure of synthetic baghdadite **(Figure 2.1)**, which was calculated for the first time using neutron powder diffraction data by Plaisier et al., 1995. The only distinction between crystal structures was the preference of the $P2_1/a$ space group in natural baghdadite over $P2_1/c$ in synthetic baghdadite, and this was due to the same orientation as other cuspidine group members.

The crystal structure of BAG is composed of 4-columns-wide polyhedral walls. Unit cell includes four independent cation polyhedra, where three of them are Ca-centered and the other is Zr-centered. Each disilicate group $(Si_2O_7)^{-6}$ connects three walls, and each wall is linked to six disilicate groups and four other walls (Biagioni et al., 2010).

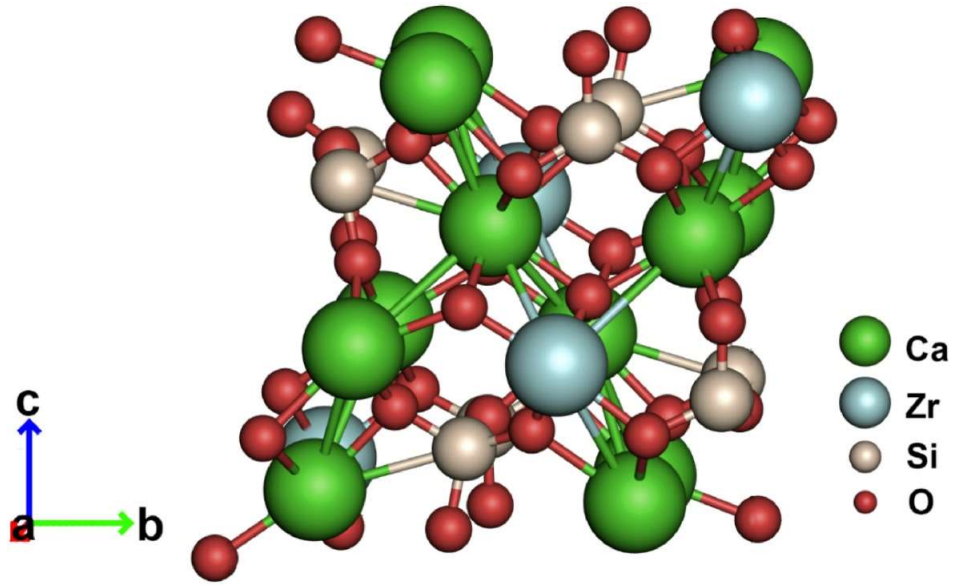

Figure 2.5 Crystal structure of baghdadite along the a-axis (Jodati et al., 2020).

This section covers the characterizations of synthetic baghdadite ceramics and their possible applications in biomedical fields. The synthesis methods, as well as the properties of baghdadite, are briefly discussed.

2.4.1 Processing of Calcium Zirconium silicate ceramic

In general, there are two methods for synthesizing the baghdadite powder: the sol-gel form and the direct solid-state reaction. The sol-gel technique is the most common and has been used in several studies (Jodati et al., 2020). Ca, Si, and Zr sources were calcium nitrate tetrahydrate ($Ca[NO_3]_2.4H_2O$), tetraethyl orthosilicate (TEOS, $Si[C_2H_5O]_4$), and zirconia oxide nitrate ($ZrO[NO_3]_2$). To hydrolyze TEOS, it is mixed and stirred with ethanol and 2 M nitric acid (HNO_3) for half an hour. The Zr and Ca sources are then added to the solution in a 1:3:2 molar ratio = $ZrO[NO_3]_2$:$[NO_3]Ca.\ 4H_2O$: $Si[C_2H_5O]_4$. The reactants are stirred at room temperature for 5-6 hours, and the transparent solution is dried for several days at 60-100°C to produce the dry gel, which is calcined above 900°C (Sadeghzade et al., 2017). In the solid-state method, the baghdadite is synthesized by combining calcium oxide (CaO) or calcium carbonate ($CaCO_3$), silicon dioxide (SiO_2), and zirconium dioxide (ZrO_2) as starting materials with molar ratios of 3:2:1, respectively. The mixture is then sintered at temperatures exceeding 1000°C (Najafinezhad et al., 2017).

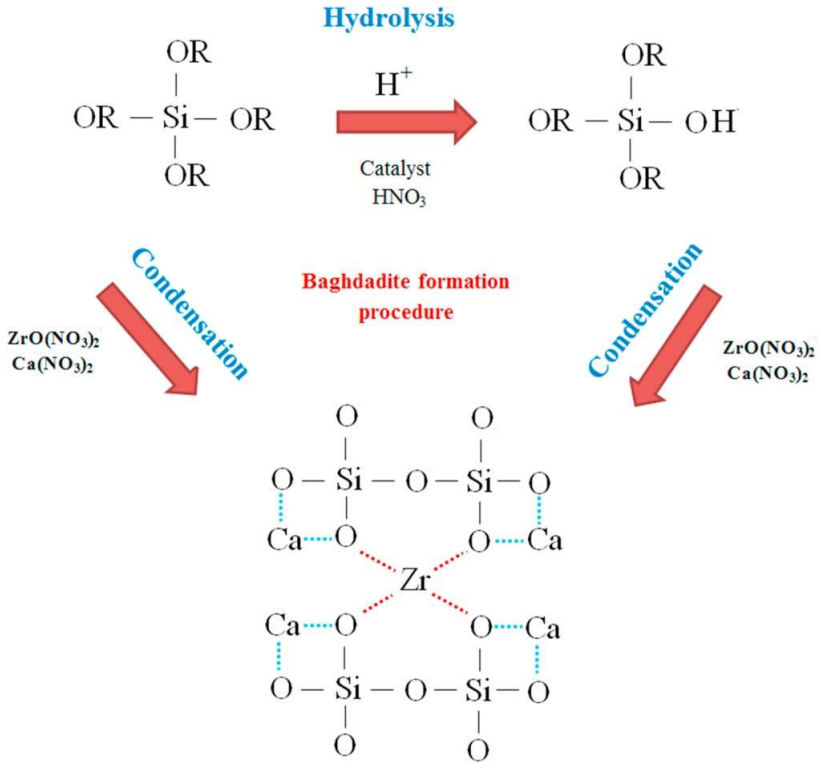

Figure 2.6 Baghdadite synthesis by sol-gel method (Sadeghzade et al., 2017).

2.5 Zinc Oxide

Zinc is known as the "calcium of the twenty-first century." Because of their inherent physiological importance, biocompatibility, biodegradability, and pro-regeneration properties, zinc-based degradable biomaterials have recently appeared. Metal zinc alloys, zinc ceramic nanomaterials, and zinc metal-organic frameworks are the most common zinc-based biomaterials (MOFs). Zn is the second most abundant micronutrient in living organisms, and it is important for cell biology, human anatomy, and physiology. Humans consume 4-14 mg of zinc a day on average, with normal plasma levels ranging from 70-120 μg/dL, with levels less than 60μg/dL considered inadequate. Zinc deficiency can result in growth failure (Su et al., 2019). There are several methods to synthesize zinc oxide ceramic. Its properties depend upon several factors such as particle size, chemical composition, and

surface chemistry. It has a good antibacterial activity which makes it applicable in cotton fabric, rubber, and food packaging industries (Pandurangan et al., 2015).

Table 2.2 Present the ZnO ceramic processing, properties, and biomedical applications (Su et al., 2019).

Methods	Characteristics	biomedical applications
Hydrothermal Sol-gel Vapor-liquid-solid Physical vapor deposition Chemical vapor deposition Biosynthesis	Easy fabrication Antibacterial pH-responsive Large surface/volume ratio Wide bandgap Efficient excitonic blue and near-UV emission Phototoxic effect Good biocompatibility	Orthopedic regeneration Drug and gene delivery Bioimaging Cancer therapy

Zn^{+2} ions released from Zn-based ceramic reacted with bacterial surfaces, results in charge imbalance, cell deformation, and bacteriolysis. Zn-based biodegradable materials have antibacterial properties. Photocatalytic and nanoantibiotic mechanisms, which generate reactive oxygen species (ROS) and complex nanostructures, respectively, predominate over these antibacterial mechanisms (Zhu et al., 2016). Nanostructured Zn-based ceramic materials, especially photocatalytic ZnO and ZnS have excellent antibacterial properties as a result (Su et al., 2019).

Ali et al., 2020 prepared bioactive glass scaffold of composition (54.6-X) SiO_2–$6Na_2O$-$7.9K_2O$-7.7MgO–22CaO-$1.74P_2O_5$-XZnO (where X = 0.0, 0.5, 1.0, 2.0; mol %). The in vitro bioactivity study suggested minimal alterations in biomineralization after ZnO introduction to the parent glass. Furthermore, in vitro cytocompatibility assessment upon ZnO substitution to the glass system was also found efficacious. The cellular metabolism,

viability, growth, cell attachments, differentiation, and proliferation were found significantly better for the ZnO substituted scaffolds.

Mohan Babu et al., 2020 incorporated zinc oxide up to 10wt% in phosphate-based glass by the melt-quenching process. The physical, thermal, and other structural properties of doped bioglasses were measured, and found that these properties were enhanced with zinc oxide content up to 8wt%.

Neščáková et al., 2019 prepared zinc doped mesoporous bioactive glass of SiO_2-CaO system with 8mol% of zinc oxide. They found no change in the morphology with the addition of zinc while the surface area was increased in comparison to parent bioactive glass. They also found no apatite layer formation on the surface of zinc doped bioglass after 14 days of SBF immersion which suggests that zinc inhibited the formation of hydroxyapatite on the surface. They also found that zinc-doped bioglass promotes the differentiation of osteoblast like-cells and also has high protein adsorption in comparison to parent bioactive glass.

Goudarzi et al., 2019 prepared the bioactive glass of $60SiO_2$–$4P_2O_5$–31CaO-xSrO-(5-sx) ZnO ($0 \leq x \leq 5$%mol) sol-gel route. Bioglass sample containing 1%mol Sr and 4%mol Zn showed a statistically significant increase in osteoblast G292 proliferation. The antibacterial tests showed that all Zn containing bioglass created clear inhabitation zones.

Huang et al., 2017 prepared zinc oxide doped SiO_2-Na_2O-CaO-P_2O_5 bioglass up to 3 mol%. The biological studies depict that zinc oxide improves the proliferation of human dental pulp stem cells (hDPSCs).

Atkinson et al., 2016 prepared mesoporous bioactive glasses of composition $70SiO_2$-(26-*x*) CaO-$4P_2O_5$-*x*ZnO (*x*= 0, 3 and 5 mol %) by a sol-gel method. The rate of HA precipitation on the sample surface was increased with zinc oxide amount in the bioglass sample. High inhibition rates of 91.3% for *Bacillus subtilis* and respectively 89.4%

for *Pseudomonas aeruginosa* after 2 h of incubation indicate a very good antibacterial activity of the glass with 5mol% ZnO.

Sánchez-Salcedo et al., 2014 reported the cytocompatibility and antibacterial properties of 80%SiO_2-15%CaO-5%P_2O_5 (mol%) mesoporous bioactive glass (MBG) scaffolds substituted with 4.0% and 7.0% of ZnO. Cell proliferation, morphology, differentiation, and cytotoxic effects of Zn^{+2} ions released from the samples were examined by culturing human osteoblast-like cells (HOS). Results show that the Zn-MBG scaffolds possess a hierarchical meso-macropore structure suitable for osteoblast growth. Furthermore, the amount of Zn^{+2} released from the scaffold with 4.0% ZnO was found to be more favorable for HOS cell development than that released from the scaffold including 7.0% ZnO. Zn^{+2} released to the medium from both scaffolds exhibited antibacterial properties against *S. aureus*. Thus, the cytocompatibility and the antibacterial ability exhibited by the MBG scaffold containing 4.0% ZnO make it a suitable candidate for bone regeneration applications.

Anand et al., 2014 prepared a zinc oxide doped SiO_2-Na_2O-CaO-P_2O_5-MgO bioglass to 10wt%. They found a slow dissolution rate and apatite formation after 7-day immersion in SBF.

Shahrabi et al., 2011 prepared bioglass of composition 25CaO-5MO-70SiO_2 (M = Sr, Zn). It is found that strontium ions in the glass composition provoke apatite formation whereas zinc ions inhibit the precipitation and growth of calcium phosphate phase. Both strontium and zinc ions exhibit stimulating effect on osteoblastic cells by increasing alkaline phosphatase activity and rate of proliferation, respectively.

Balamurugan et al., 2007 prepared bioglass of 64% SiO_2, 26% CaO, 5% P_2O_5, 5% ZnO, mol% composition by sol-gel method. Incorporation of Zn into a bioglass system does not diminish the bioactivity of such a material. Addition of Zn is beneficial for cell attachment

and for maintaining the pH of SBF within the physiological limit by forming zinc hydroxide in the SBF solution. In vitro biocompatibility assessments indicate that substitution of limited amounts of Zn in the bioglass system stimulates early cell proliferation and promotes differentiation.

Oki et al., 2004 prepared $CaO-P_2O_5-SiO_2-ZnO$ bioglass with 5mol% zinc oxide and examined the bioactivity and alkaline phosphatase (AP) activity of human fetal osteoblastic (*hFOB)* cells. They found the higher AP activity in zinc contains bioglass which confirms the stimulation in bone cell production.