CHAPTER 1
INTRODUCTION

1.1 GLASSES: AN OVERVIEW

The first question we need to address is 'what is a glass?' The traditional view is that glass is a solid obtained by supercooling a liquid or arresting the liquids structure into the solid state. On the other hand, the term “glass” is synonymously used often by a term “amorphous”, where it implies absence of long-range order - no regularity in arrangement of atoms in the structural units on a scale larger than a few times the size of the smallest units. More commonly, nearly all the glassy solids that possess a unique property called glass transition temperature ($T_g$), which depends on the quenching rate and chemical constituents. At $T_g$, the second derivative thermodynamic properties, namely heat capacity, thermal expansivity and compressibility undergo more or less sudden changes. There are certain solids can be obtained in amorphous form but not necessarily it can be glass. For example, a solid can be transformed in to amorphous state by a number of methods such as condensation of vapours on cold substrates, bombardment of crystalline solids by neutrons or by other heavy particles, gelation of solutions followed by removal of solvents, mechanical shear, solvent evaporation or in some cases application of very high pressures. The resulting solid in all these processes leads to the absence of sharp x-ray diffraction patterns, which confirms the lack of crystalline features. Thus, all the amorphous materials need not be glass but all the glasses are amorphous.

Therefore, it is assumed, unless stated otherwise, that glasses are only those amorphous solids which are obtained by the supercooling of melts. When a liquid is cooled from a high temperature to its melting temperature, it generally solidifies to a crystalline product. It is only rarely that melts do not crystallize when they are cooled slowly. Therefore, in order to obtain a glass the rate of supercooling has to be such that crystallization is bypassed. This requires rapid quenching in order to bypass crystallization. Thus, the rapid cooling or quenching rate, $Q$, which becomes a kinetic parameter, has great significance for glass formation. Crystallization is governed by
the two factors, nucleation and growth, both nucleation and growth rates exhibit rapid increase followed by a slowing down as the temperature is lowered below $T_m$.

1.1.1 Glass transition and Glass formation

Normally, upon cooling a melt continuously, the crystallization occurs at the freezing temperature, if the cooling rate is low. This melt-crystal transformation is accompanied by discontinuous changes in first order thermodynamic parameters such as volume, entropy, enthalpy etc. (Figure 1.1). Let us envision a liquid at a temperature well above the melting temperature of that substance. As we cool the liquid, the atomic structure of the melt gradually changes and it will be the characteristic of exact temperature at which melt was held. Upon cooling, at any temperature below the melting point of crystal would result in conversion of liquid to crystalline state with formation of long-range, periodic atomic arrangement of atoms. If the liquid is cooled below the melting temperature sufficiently fast enough by prohibiting the crystallization a glass is obtained.

![Figure 1.1: The two general ways of solidifying a melt namely, slow cooling to the crystalline state and the rapid quenching to the amorphous (glassy) state.](image-url)
The structure of liquid continues to remain the same as the temperature decreases with no abrupt decrease in volume due to smooth transformation of structure from the liquid to glassy state. This eventually becomes significant that atoms can no longer rearrange to equilibrium liquid structure, during the time scale of the experiment. An atomic structure begins to lag behind the equilibrium state and other thermodynamic quantities deviate from the ideal energy configurations, following a curve of gradually decreasing slope until the viscosity becomes significantly high. The temperature region lying between the limits where the enthalpy is that of equilibrium liquid and that of frozen solid, is known as Glass Transformation Region.

It is interesting to note that the temperature where the volume departs from the equilibrium curve is controlled by viscosity. The slower cooling rate will allow volume to follow equilibrium curve to lower temperature and the glass transformation region will shift to lower temperature. The glass obtained with slower cooling rate will have lower enthalpy than the glass obtained by faster cooling rate. The atomic arrangements will be the characteristic of the equilibrium liquid at lower temperature than more rapidly cooled glass. Although glass transformation occurs over a temperature range, but if we extrapolate glass and supercooled liquid lines, they intersect at a temperature called as fictive temperature, where structure of glass is that of equilibrium liquid.

1.1.2 Time-Temperature-Transformation Diagram

Most of the liquid that would crystallize during normal cooling but it can be brought to vitreous state by more rapid cooling. The main concern is the rate at which the liquid should be cooled and to obtain glassy state. It is a well established fact that rate of cooling should be fast enough to avoid any crystallization. The crystallization requires the formation of nuclei, in addition to measurable growth rate of the nuclei. Formation of glass from melt involves cooling in such a manner to avoid crystallization. In order to describe the glass formation in the right perspective, we consider the time temperature-transformation diagram (TTT diagram) for crystallization of an undercooled melt (Figure 1.2). At the thermodynamic melting
temperature \( (T_m) \), the time necessary for crystallization tends to infinity since the driving force to form crystalline nuclei vanishes. With an increased undercooling below \( T_m \) the nucleation rate increases, since the driving force for nucleation becomes larger. At larger undercooling the crystallization rate is very sluggish, because diffusion and/or the growth rate of crystalline nuclei becomes very slow.

As a consequence, for intermediate undercooling the crystallization rate has a maximum in the TTT diagram, which looks like an ugly ‘nose’. All combinations of heat treatment, times and temperatures to the left of this curve yield samples in the undercooled liquid or glassy state, while all combinations of time and temperature to the right of this curve yield a partial or totally crystallized material. In order to get a glass, cooling must be so fast that the crystallization nose can be avoided and below the glass-transition region the undercooled melt becomes a glass. The position of the ‘nose’ in the TTT diagram for crystallization of an under cooled melt is a measure for the glass-forming ability of a material. For example, the conventional metallic glasses time scale is in the 0.1 to 1 milliseconds range at the ‘nose’ of the nucleation curve. The rapid cooling techniques with rates of about \( 10^6 \) Ks\(^{-1} \) is required to form such glasses.

Figure 1.2: Schematic time-temperature-transformation diagram (TTT diagram) for the crystallisation of an undercooled melt.
1.2 CLASSIFICATION OF GLASSES

Glasses are formed in a great variety of systems including manmade and natural glasses. In the following, we list major classification of glasses:

1.2.1 Oxide Glasses

Oxide glasses are historically the oldest and industrially the most exploited. They are all silicate or aluminoborosilicate glasses containing a variety of mono- and divalent oxides. The oxide glasses without silica are generally of limited volume in terms of consumption and used only in specific applications.

1.2.1.1 Silicate glasses

Silicate is the archetypal glass former with three-dimensional network structure. Silicon is coordinated to four oxygen’s and each oxygen coordinated with two silicon atoms by forming corner shared \([\text{SiO}_4/2\] tetrahedra. The distribution of Si-O-Si bond angle is the primary factor in removing the three-dimensional periodicity of the crystalline form and the Si-O bond lengths in the glassy and crystalline forms are comparable. With an addition of alkali oxide, silicate glasses undergo different kind modification depending upon the alkali oxide content. It is generally assumed that the disruption of the three-dimensional network occurs as the alkali concentration increased. The modification results in the formation of meta, pyro and ortho-silicates in the order, \([\text{SiO}_{4/2}]^0\), \([\text{SiO}_{3/2}O]^1\), \([\text{SiO}_{2/2}O_2]^2\), \([\text{SiO}_{1/2}O_3]^3\) and \([\text{SiO}_4]^4\), which are present in these glasses and designated as \(Q^4\), \(Q^3\), \(Q^2\), \(Q^1\), and \(Q^0\) respectively, where the subscripts indicate the number of bridging oxygen atoms (BOs) centered on the given Si atom through which it is connected to other Si atoms in the glass structure [4].

1.2.1.2 Borate glasses

Borate glasses have been widely investigated, although their technological applications are mostly in combination with silicate. \(\text{B}_2\text{O}_3\) can be considered as having the highest glass formation tendency because molten \(\text{B}_2\text{O}_3\) does not crystallize by itself even when cooled at the slowest rate and it crystallizes only under pressure. In the simplest binary alkali borate glasses, alkali oxide initially converts the trigonal
borons ([BO$_{3/2}$] units, B$_3$) to tetrahedral borons ([BO$_{4/2}$] units, B$_4$) by the coordination of O$^{2-}$ to two trigonal borons. The formation of B$_4$ units proceeds till the 50 % B$_3$ are converted into B$_4$. The composition in which B$_3$ and B$_4$ are equal is the diborate composition, and the corresponding mole fraction of the alkali oxide is 0.33[3].

1.2.1.3 Germanate glasses

Germanate glass is another archetypal glass forming oxide with close structural similarity with silicate structure. However, with the addition of alkali oxide into GeO$_2$ network, the structure become more rigid by formation of six-fold coordinated Ge atoms and above 20 mol % alkali oxide, it converts into the four-fold coordination with the formation of NBOs (Non-Bridging Oxygen). The formation of octahedral coordination of Ge atoms and change into the tetrahedral environment has been reflected in number of properties of alkali germanate glasses, which exhibit anomalous variations [5].

1.2.1.4 Glasses containing transition metal oxides

Apart from the conventional glass forming oxides, there are oxides which form glass with more than one oxide such as MoO$_3$, WO$_3$, V$_2$O$_5$, TeO$_2$, etc. also form glasses, but generally in combination of two or more oxides. Glasses of molybdophosphates and tungsto-phosphates are important glass forming systems which has been investigated in their structural and physical properties in the glassy state [6].

1.2.2 Non-oxide Glasses

1.2.2.1 Chalcogenide glasses

The chalcogenide glasses which contain one or more chalcogen elements, (sulphur, selenium and tellurium) in a combination with elements from III, IV or V group of the periodic table. They find applications in infrared optics, xerography, phase change memory, fiber optics and, x-ray imaging plates. An incredibly large number of glasses have been synthesized using a combination of both chalcogens and other elements [7].
1.2.2.2 Uranium boride glasses

Uranium boride (UB₂), a compound of uranium and boron, is a very stable glassy boride material that is insoluble in water. It is being explored as a method of immobilising uranium based radioactive waste, and rendering it safe for long term storage. Some applications in endocurietherapy, a method of radiation therapy where in radioactive microspheres are implanted directly into the treatment site and allowed to remain for an extended period of time, may also use this class of material as it would not be attacked while in situ [8].

1.2.2.3 Heavy metal fluoride glasses

Heavy metal fluoride glasses were accidentally discovered in 1975 by Poulain and Lucas at the University of Rennes in France [9], including a family of glasses ZBLAN with a composition ZrF₄-BaF₂-LaF₃-AlF₃-NaF. ZBLAN glass is the most stable fluoride glass known and is most commonly used to make into optical fiber. ZBLAN optical fibers are used in different applications such as spectroscopy and sensing, laser power delivery and fiber lasers and amplifiers.

1.2.2.4 Halide glasses

Halide glasses like BeF₂ and ZnCl₂ have been known for a long time. These glasses are obtained by simply quenching halides from their molten state. Structures of simple BeF₂ and ZnCl₂ seem to be based on tetrahedrally coordinated Be and Zn and with halogens forming bridges between tetrahedra. Trivalent halides like AlF₃, FeFs, CrFs and GaFs are known to form glasses only in combination with divalent fluorides like ZnF₂, MnF₂ and PbF₂. Trivalent ions appear to be present in octahedral coordination of fluorines as MF₆ [6].

1.2.3 Oxy-Nitride Glasses

Oxynitride glasses are the oxide glasses in which O has been substituted by N to varying extents. In thioborate and thiosilicate glasses, where oxygen is substituted by chalcogen, novel structural features such as edge sharing of structural units and lowering of dimensionality. Substitution of the O by N leads to enhanced
crosslinking. This is because N being from Group V is capable of forming 3 covalent bonds. Substitution by N in oxide glasses increases the network connectivity and dimensionality, which in some sense is the opposite of substitution by chalcogens. Nitridation of phosphate glasses has also been studied extensively [10]. Nitrogen substitutes both for bridging and terminal (double bonded O) in the phosphate structure and complete substitution of O by N is equivalent to the preparation of pure nitride glasses. Glasses based on Li$_3$N-Ca$_3$N$_2$-P$_3$N$_5$ have been prepared by rapid quenching of melts, held under pressure of around 10 kbar and 1000°C [11].

1.2.4 Organic Glasses

Organic glasses contain carbon-carbon chains which are so entangled that rapid cooling of the melt prevents reorientation into crystalline regions. These structures closely resemble those of vitreous sulphur and selenium, which also consist of entangled chains. The chains in organic glasses can also be crosslinked, just as they are in chalcogenide glasses, with consequent changes in their property. Increasing the degree of crosslinking increases the viscosity of the melt and glass transition temperature. In general, the properties of organic glasses closely resemble those of inorganic glasses with chain based structures, including the ability to produce materials with oriented properties by application of stress during forming.

Small regions of oriented chains often exist in organic glasses so that many of these materials often resemble low crystalline glass ceramic. Polycarbonate (PC), Polystyrene (PS), Polymethylmethacrylate (PMMA) are most widely studied organic glasses[12].

1.3 BIOACTIVE GLASSES: HISTORICAL BACKGROUND

The history of biomaterial can be divided into three eras. Prior to 1850 nonmetallic materials, such as wood and ivory, and common metals, such as iron, gold, silver, and copper, were used to fabricate simple prosthetic devices and to hold fractured bones together while they healed. The second era of biomaterials, between 1850 and 1925 was defined by rapid development of surgeries because of the advent of anesthesia, which made long surgeries possible and X-ray, which can reveal the nature of many
skeletal problems. The period from 1925 to present is the third era, in which the primary advances in the various surgical specialties have resulted from three important developments. The first was the development of cobalt chrome and stainless steel alloys in the 1930s and 1940s, respectively. The second was the development of polymer chemistry and plastics in 1940s and 1950s. The third was the discovery of ways to produce useful antibiotics. The ability to further reduce surgical infection rates and to fabricate many devices that are compatible with biological tissues significantly advanced the ability of surgeons to treat a great variety of problems. Figure 1.3 illustrates the historical developments and forecast of the future in the biomaterial scientific community. It depicts the changes that took place over the time in biomaterials. Earlier, the focus was on removal of tissues, when tissues became diseased or damaged, but this led to only marginal improvement in quality of life. A revolution in medical care began with the successful replacement of tissues. Two alternatives became possible (Figure 1.3): (1) transplantation or (2) implantation. The gold standard in the reconstructive surgery for damaged or diseased bone is the Autografts which involves transplanting the patient’s own tissue from donor site to host site. Alternatives are Homografts (transplanting from other patient) and Xenografts (tissues from different species, e.g. freeze dried bovine bone). However, there are limitations to these techniques, in which the autografts have low availability and cause death of the donor site healthy tissue. On the other hand, homografts carry risk of disease transmission and are less in supply. The xenografts are large in supply but have greater risks like immune rejection, disease transmission, and in-situ degradation [13].

The second in the revolution was the development of man-made materials to interface with living, host tissues, e.g. implants made from biomaterials. The implants are significantly advantageous over transplant owing to their availability, reproducibility and reliability. However, these implants lack the three most important characteristics of living tissue (i) the ability to self repair (ii) the ability to maintain blood supply and (iii) the ability to modify in response to stimuli such as mechanical load. Moreover, all these implants have limited life span [14, 15].
During the last decade considerable attention has been directed towards bioactive fixation, defined as “interfacial bonding of an implant to the tissue by means of formation of a biologically active hydroxyapatite layer on the implant surface” [16]. However, the prostheses made from these materials (bioactive glasses, ceramics and glass-ceramics) have evolved from trial and error and long term survivability has not been improved much[13]. The Replacement of tissues by transplant and implants had remarkably increase the quality of life, however, continuing the same approach is not likely to reach a goal of 20-30 years implant survival ability needed. Therefore, there is a need for an alternative to an autograft as well as a paradigm shift from replacement to regeneration of the tissue may provide the solution [17].

![Diagram](image)

**Figure 1.3:** Biomaterial historical development and the forecast of the future [13].
1.4 BIOMATERIALS

By L. L. Hench [18]

“The human body rejects metallic and synthetic polymeric materials by forming scar tissue because living tissues are not composed of such materials. Bone contains a hydrated calcium phosphate component, hydroxyapatite [HA] and therefore if a material is able to form a HA layer in vivo it may not be rejected by the body.”

The first generation biomaterials were selected to be bio-inert to minimize formation of scar tissue at the interface with the host tissues. They were investigated during 1960s and included metals or alloys (titanium, stainless steel, cobalt–chrome) and dense or porous ceramics Al2O3 (alumina) and ZrO2 (zirconia) [19]. They have high mechanical strength and hardness but even these bio-inert materials elicit a reaction with the tissues once implanted. The tissue response to biologically inactive materials is the formation of a non-adherent fibrous capsule made up primarily of collagen, which prevents further interactions with the tissues and hence this implant cannot last for a long time. Eventually, the deterioration occurs and removal is necessary [20].

The second generation biomaterials were developed around 1970 [21]. The aim of these bioceramics was a favorable interaction with the living body. In this context, the most significant bioceramics are crystalline calcium phosphates, bioactive glasses and glass-ceramics clinically used for applications such as the bone tissue augmentation, bone cements or the coating of metallic implants [22-24]. At the end of the 20th century, it was clear that bioceramics by themselves could not give a complete response to the clinical needs of biomaterials for implants. Currently, the bioceramics with more demanding properties were required. This led to the arrival of so-called third generation of bioceramics able to induce regeneration and repair of living tissues based on gene activation [25-28]. Therefore, the concept of replacement of tissues has been substituted with regeneration of tissues. Second and third generations of biomaterials are called bioactive glasses. Before discussing more about bioactive glasses, the structure of bone are presented in the next section.
1.5 STRUCTURE OF BONE

An identification of equivalent artificial material with similar properties of human bone is great task, since the structure of the bone is highly complex and therefore it is important to understand its structure at the atomic level [29]. In Figure 1.4, we show the hierarchical structure of bone at its various length scales. Bone is a natural composite consisting of collagen fibrils (polymer) embedded, well arrayed, nanocrystalline, rod-like inorganic materials with 25-50 nm in length scale [30-32]. The structural order in bone occurs at several hierarchical levels and reflects the type of materials and mechanical properties of its components (Figure 1.4).

Collagen is a triple helix of protein chains that has high tensile and flexural strength. On the other hand, bone mineral is a crystalline calcium phosphate ceramic
(hydroxycarbonate apatite, HCA) that provides the stiffness and high compressive strength of bone (D). The close chemical similarity of HCA to natural bone has led to the extensive research effort to use synthetic HCA as a bone substitute and/or replacement in biomedical applications [33, 34]. The most internal part of bone contains the marrow, where stem cells are, which can give rise to all types of blood cells. The resident cells are surrounded by cell membrane receptors that respond to specific binding sites (C) and the well-defined nanoarchitecture of the surrounding extracellular matrix. The two most important types of bone are cortical and cancellous bone. Cortical bone also known as compact bone surrounds the marrow and is a dense structure with high mechanical strength (A). In compact bone, parallel rods of collagen and apatite are bundled together, arranged in circles around the harvesian channels, or osteons where blood vessels and nerves pass (B). Near the end of the bone, the bonehead, a less dense type of bone is found, called cancellous, or trabecular, spongy bone [35,36].

The process of bone regeneration (osteogenesis) involves two types of cells: osteoblasts (bone generating cells) and osteoclasts (bone regenerating cells). The extracellular matrix of mineralizable collagen is laid down by osteoblasts (osteogenic cells), which develop (differentiate) from stem cells. They secrete collagen which then mineralizes to form an HCA-collagen structure. An osteoblast that becomes surrounded by concentric rings of mineralized tissue is called an osteocyte (Figure 1.4). The aim of regenerative medicine is to stimulate the body to reactivate osteogenic cells to re-create the natural three-dimensional architecture of bone.

1.6 BIOCERAMICS

In general, ceramics revolutionized the world by their usage to improve the quality of human life since last four decades. The revolution is the innovative use of specially designed ceramics for the repair, reconstruction, and replacement of diseased or damaged parts of the body. The ceramics used for this purpose are termed as “bioceramics”. Bioceramics are needed to alleviate pain and restore the damaged parts of the body. As the tissues are progressively deteriorated with the age so these substitutions are becoming important for human survivability. Bone density
decreases, when osteoblasts progressively become less productive in making new bone and repairing micro fractures. The lower density greatly deteriorates the strength of the porous bone called trabecular or cancellous bone, present at ends of long bones and vertebrae. Consequently, leading to fractures collapsed vertebrae and spinal problems. This century has seen the most remarkable accomplishment by the excellent performance of specially designed bioceramics that have survived all the required clinical conditions.

Remarkably, the bioceramics are implanted in the defective bone and elicits a response from the living tissue. It is interesting to note that different types of materials receives different response when implanted and these responses form the basis of selection of the material used for implants. More commonly, four types of responses are usually described by Hench after implanting the materials [37]:

- If the material is toxic, the surrounding tissue would die.
- If the material is non-toxic but bioinert, the fibrous tissue layer will form on the interface, which adversely effects the attachment.
- If the material is non-toxic and bioactive, an interfacial bond forms.
- If the material is non-toxic and dissolves, the surrounding tissue replaces it.

**Table1.1: Summarizes the types of bioceramics and their tissue attachments.**

<table>
<thead>
<tr>
<th>TYPE 1</th>
<th>Type of attachment</th>
<th>Examples of bioceramics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dense, non-porous, almost inert ceramics attach by bone growth into surface irregularities by cementing the device into the tissue, or by press-fitting into a defect.</td>
<td>Al₂O₃ and ZrO₂</td>
</tr>
<tr>
<td>TYPE 2</td>
<td>For porous implants, bone in growth occurs, which mechanically attaches the bone to the materials.</td>
<td>Porous hydroxyapatite</td>
</tr>
<tr>
<td>TYPE 3</td>
<td>Surface-reactive ceramics, glasses, and glass-ceramics attach directly by chemical bonding with the bone</td>
<td>Bioactive glasses, Bioactive glass-ceramics</td>
</tr>
<tr>
<td>TYPE 4</td>
<td>Resorbable ceramics and glasses in the bulk or powder form designed to be slowly replaced by bone.</td>
<td>Tricalcium Phosphate, Calcium sulfate</td>
</tr>
</tbody>
</table>
When bioceramics are almost inert with type 1 in Table 1.1 and the interface is not chemically or biologically bonded, there is relative movement and progressive development of a non-adherent fibrous capsule in both the soft and hard tissues. This movement eventually leads to bone deterioration of both the tissues and implant or either of one. The bone at an interface with these types of bioceramics is very often structurally weak because of the cement fixations or stress shielding. In type 2 porous ceramics attaches to the bone by growth of tissue into pores of the surface or on the implant [38]. These types of biological fixations are more successful than the morphological fixation but these implants have limitations too. For tissue to be viable and healthy pore size must be larger than 100-150 \( \mu m \). The type 4 materials listed in Table 1.1 are resorbable biomaterials designed to degrade gradually over time and replace by natural host tissue [39, 40]. These provided solutions to implants were strength and short term performance can be met. However, there are other limitations like maintenance of strength and stability of interface during degradation periods matching the resorption rates to the repairing rates of body tissues etc. Therefore, the resorbable materials are rapidly replaced with the regenerated bones. Another approach for interfacial attachment is the use of bioactive materials (Type 3 in Table 1.1). The concept of bioactive material is intermediate between resorbable and bioinert materials [41]. Bioactive materials are produced with wide range of bonding rates and thickness of interfacial bonding layers [42]. The bioactive materials available commercially for clinical uses are 45S5 bioactive glass, A/W bioactive glass ceramic, dense synthetic hydroxyapatite or bioactive composites such as a polyethylene-HA mixture.

### 1.7 CLASSIFICATION OF BIOACTIVE MATERIALS

“A bioactive material is one that elicits a specific biological response at the interface of the material which results in the formation of a bond between the tissues and the material.”[21]

A bioactive material creates an environment compatible with osteogenesis (bone growth), with the mineralizing interface developing as a natural bonding junction between living and non-living materials. These materials are intermediate
between resorbable and bioinert [43, 44]. This concept has been expanded to include large number of bioactive materials with wide range of bonding and thickness of the interfacial bonding layers. They include bioactive glasses such as Bioglass®, bioactive glass ceramics such as Ceravital®, A/W glass-ceramics and machineable glass-ceramics, dense calcium phosphate ceramics such as synthetic hydroxyapatite (HA), bioactive composites such as polymer-HA, and a series of bioactive coating materials. In these classes of materials, the mechanism of bonding, the time dependence of bonding, the strength of bonding are different. The rate of development of the interfacial bond can be referred to as the level of bioactivity [23, 45]. However, there exists a large difference in the rate of bone bonding to bioactive implants occurring at the implant-tissue interface due to different factors. Hench proposed a specific classification for biomaterials intended to be used for orthopedic implants in which bioactive materials are divided into two types [46-48]:

1. **Class A**, These materials not only bond with bone and are *Osteoconductive*. But they are also *Osteoproductive* i.e. they stimulate the growth of new bone on materials away from bone/implant interface and can bond to soft issues. e.g. **Bioactive glass**. Osteoproduction occurs when bone proliferates on the particulate surfaces of the mass due to enhanced osteoblast activity.

2. **Class B**, These materials are bond with hard tissues and stimulate bone growth along the surface of bioactive materials i.e. they are only *Osteoconductive*. e.g. bioactive glass ceramics like synthetic hydroxyapatite (HA), tri-calcium phosphate ceramic etc.

### 1.8 BIOACTIVE GLASSES

Hench and his co-workers discovered in 1969 that the bone could bond chemically to glass with certain compositions. This group of glasses is referred to as bioactive glasses or bioglasses. An important characteristic of these glasses is the formation of a hydroxycarbonate apatite (HCA) layer on their surface in physiological solutions. This layer posses the similar chemical composition and structure as the mineral phase of bone. Bioactive glasses can be produced in a various forms and serve various functions in the body. Since the late 1960s, when Hench described the first bioactive
glass 45S5, various kinds of glasses have been found to bond to bone [49]. Bioactive glass 45S5® Bioglass (46.1%SiO₂, 24.4% NaO, 26.9% CaO, 6% P₂O₅, in mol%) was the first material introduced by Hench in 1971 [21]. The base components of bioactive glasses are SiO₂, Na₂O, CaO and P₂Os. In Table 1.2, we present chemical compositions (percentage in weight) of the most common bioactive glasses. Due to differences in composition, structure and constituent phases, the bone bonding properties of these materials are also different. The relative bioactivity among materials can be evaluated by measuring the rate of bone formation on the surface of the material [50].

The bioglass 45S5 is the most commonly studied and used in clinical applications which has been prepared by conventional melt derived method at the earlier stages. The abbreviation indicates that it contains 45% in weight of SiO₂ and the molar ratio between Ca and P is of 5:1. There are three key compositional features to SiO₂–Na₂O–CaO–P₂O₅ bioactive glasses that distinguish them from traditional soda – lime – silica glasses: (1) less than 60 mol% SiO₂, (2) high Na₂O and CaO content, (3) high CaO/P₂O₅ ratio. These are the silent features that make the surface of bioactive glasses highly reactive when it is exposed to physiological solution.

**Table 1.2: Composition of common bioactive glasses [21, 43, 51, and 52]**

<table>
<thead>
<tr>
<th>Components in wt %</th>
<th>45S5 Bioglass®</th>
<th>45S4.5F Bioglass®</th>
<th>45B15S5 Bioglass®</th>
<th>52S4.6 Bioglass®</th>
<th>52S4.3 Bioglass®</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiO₂</td>
<td>45</td>
<td>45</td>
<td>30</td>
<td>52</td>
<td>42</td>
</tr>
<tr>
<td>P₂O₅</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>CaO</td>
<td>24.5</td>
<td>14.7</td>
<td>24.5</td>
<td>21</td>
<td>19.5</td>
</tr>
<tr>
<td>Na₂O</td>
<td>24.5</td>
<td>24.5</td>
<td>24.5</td>
<td>21</td>
<td>19.5</td>
</tr>
<tr>
<td>CaF₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B₂O₃</td>
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<td>15</td>
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<td>Class</td>
<td>A</td>
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<td>A</td>
<td>A</td>
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</tbody>
</table>

Although 45S5 bioactive glass has various applications such as, in middle ear prostheses to restore the ossicular chain and treat conductive hearing loss, as oral implants to preserve the alveolar ridge from the bone resorption that followed tooth
extraction, employed as a coating for artificial dental roots that could be used as self standing dental implant. In 1990s, bioactive glass composites had become the standard for repairing and replacement of bones in the middle ear, but it also suffers from various limitations [53]. One of these limitations is that it needs very high temperature for melting, and it lacks microporous structure leading to low specific surface area; therefore bioactivity of these glasses depends mainly on silica content. Besides silicate glasses, phosphate glasses were also studied for bone regeneration application. It has been suggested that that unlike silica-based glasses, phosphate-based glasses, which are similar to the inorganic part of the bone, have a unique property that their degradation rate can be adjusted by adding various oxides according to end application [54, 55]. Phosphate bioceramics and hydroxyapatite ceramics has been widely used for bone replacement and regeneration but compared to bioactive glasses, hydroxyapatite ceramics seems to have poor in vitro bioactivity and degradation [23]. Therefore, an effort to overcome the limitations of melt quenched bioactive glasses, sol-gel derived bioactive glasses came in. Owing to its greater surface area and inherent porosity, they showed wider range of bioactive compositions, and exhibit higher rate of bone bonding, degradation and resorption properties. However, these sol-gel prepared glasses also suffer from some limitations like non-uniform micropore distribution and inadequate drugs loading and release [53, 56]. In order to overcome all these issues, the research work on in this field has shifted to bioglasses having ordered/disordered mesoporous structures.

Osteomyelitis caused by bacteria is the main complication in bone reconstruction surgeries. Wound drainage, implant removal, surgical debridement are some of the conventional treatments [57]. However, these treatments are not much successful and extra surgeries were needed. Thus, in order to overcome the limitation of conventional bioactive glasses, new generations bioactive glasses were designed and developed that combines efficient drug delivery and excellent bioactivity. A new concept was developed by Vallet Regi [58] and Yu and co-workers [59] simultaneously. They reported the preparation of mesoporous bioactive glass (MBG) by the combination of the sol-gel method and the supramolecular chemistry of surfactants. They were able to synthesis MBGs based on CaO-SiO₂-P₂O₅ composition
with highly ordered mesoporous channel structure and narrow pore size distribution. Compared to the conventional prepared sol-gel bioactive glass the MBGs possess more optimal surface area, pore volume, ability to induce in vitro apatite mineralization in SBF and excellent cytocompatibility [60,61].

1.9 MECHANISM OF BIOACTIVITY

In order to explain bioactivities of these glasses, Hench and his co-workers [62] have investigated the chemical reactions during formation of the HCA layers carefully and proposed a sequential reaction mechanism. The underlying bioactive mechanism proposed by Hench involves the following steps:

**Stage 1:** Rapid exchange of cations such as Na\(^+\) and Ca\(^{2+}\) with H\(^+\) or H\(_3\)O\(^+\) from the solution, causing hydrolysis of the silica groups, which creates silanols (Si-OH):

\[
\text{Si-O-Na}^+ + \text{H}^+ \rightarrow \text{Si-OH} + \text{Na}^+(\text{aq})
\]

\[
\text{Si-O-Ca}^{2+} - \text{O-Si} + 2\text{H}^+ \rightarrow 2\text{Si-OH} + \text{Ca}^{2+}(\text{aq})
\]

**Stage 2:** Stage 1 increases the hydroxyl concentration of the solution, which leads to breakage of the silica glass network. A soluble silica is lost in the form of Si(OH)\(_4\) to the solution, resulting from breaking of Si-O-Si bonds and continued the formation of Si-OH(silanols) at the glass-solution interface:

\[
\text{Si-O-Si} + \text{H}_2\text{O} \rightarrow \text{Si-OH} + \text{OH-Si}
\]

**Stage 3:** Condensation and re-polymerization of Si-OH groups, leaving a silica-rich layer on the surface, depleted in alkalis and alkaline-earth cations.

\[
\text{Si-OH} + \text{OH-Si} \rightarrow -\text{Si-O-Si-} + \text{H}_2\text{O}
\]

**Stage 4:** The migration of Ca\(^{2+}\) and PO\(_4\)^{3-} groups to the surface through the silica rich layer and from the surrounding fluid forming a CaO-P\(_2\)O\(_5\)-rich layer on the top of silica rich layer, followed by growth of amorphous CaP.

**Stage 5:** The amorphous CaO-P\(_2\)O\(_5\) layer crystallizes as it incorporates OH\(^-\) and CO\(_3\)^{2-} anions from the solution to form a mixed HCA layer.
The surface of an implanted bioactive glass seemingly undergoes the five-described steps irrespective of whether a tissue is present and is shown schematically in Figure 1.5. However, for a bioactive glass to bond to a tissue a series of additional interfacial reactions, that are not properly defined as biological process involved with it is poorly known, are required. According to Hench and Andersson [17, 63] the interfacial reactions occur in the following sequences:

(a) Adsorption of biological components on the HCA layer
(b) Precipitation of Ca and P from the glass and solution between the biological components, especially collagen.
(c) Attachment of stem cells
(d) Differentiation of stem cells
(e) Generation of matrix
(f) Crystallization of matrix

Figure 1.5: Schematic representation of Hench’s Mechanism.
Osteoblasts (bone-growing cells) lay down extracellular matrix (collagen matrix), which mineralizes to create nanocomposite of mineral and collagen on the surface of the bioactive glass implant while dissolution of the glass continues over time [64].

1.10 GLASS STRUCTURE AND BIOACTIVITY

Most of the bioactive glasses are silica based ternary or quaternary systems with high amount of alkali/alkaline-earth oxides. Silicate glasses have an amorphous three dimensional network structure based on the SiO$_4^{4-}$ tetrahedron as the structural unit. The tetrahedral units are linked to each other only via oxygen ions at the corners. In crystalline silica, these tetrahedral units are regularly arranged as shown in Figure 1.6(a). On the other hand, in amorphous silica, these tetrahedral units are still linked together but with an intrinsic disorder caused by the variation in the bond angle and bond lengths (Figure 1.6 (b)). Additionally, with an introduction of network modifying cations, the network structure becomes more open due to the creation of non-bridging oxygen (NBOs) ions. In this circumstance, the silica is called as network former, since glass structure is mostly kept together by silicate tetrahedra. Similar to silicate, the other oxides that act as network formers are GeO$_2$, P$_2$O$_5$ and B$_2$O$_3$. More commonly, alkali and alkaline-earth oxides act as network modifiers, as they disrupt the network structure by creating NBOs, which act as charge compensator for alkali and alkaline-earth ions (Figure 1.6c). The resulting structure is called random network structure, and was first hypothesized by Zachariasen in 1932 [65].

Silicate and alkali modified silicate glasses are typical glass-forming systems well suited for investigating the structure, transport and dynamics of mobile species. A key aspect of their short-range structure is the distribution of tetrahedral units (Q$^n$) (n = 0-4), meaning the different kinds of SiO$_4$ tetrahedra present, where the superscript n corresponds to the number of the bridging oxygen (BO) atoms and 4-n is the number of non-bridging oxygen (NBO) atoms per tetrahedra. The Q$^n$ speciation depends strongly on the alkali oxide content, temperature, pressure and thermal history.

\[
\text{Si-O(BO)-Si} + \text{Na}_2\text{O} \rightarrow 2\text{Si-O}^-_{(NBO)} + 2\text{Na}^+
\]

OR

\[
\text{Si-O(BO)-Si} + \text{CaO} \rightarrow 2\text{Si-O}^-_{(NBO)} + \text{Ca}^{2+}
\]
The bond between NBOs and cations is ionic and weaker than the Si-O bond. In general, the network connectivity (NC) defined as the average number of BO atoms per glass-forming unit, was introduced to correlate the bioactivity and glass structure [66-68]. By comparing the NC of glass compositions with different bioactivities (measured either as the rate of formation of the HCA layer or as the bone-bonding ability), an empirical upper limit around NC=3 was proposed, separating bioactive (NC<3) from bioinert (NC>3) glasses. Low NCs denote open and fragmented glass structures, whose rapid partial dissolution in an aqueous physiological environment will lead to HCA layer formation and bone bonding in a shorter time scale, compared with glasses with a more interconnected network.

Figure 1.6: (a) Crystalline silica (b) Amorphous silica (c) Effect of introduction of network modifier cations in a silica network [69].
The classification based on the NC is not always accurate as was demonstrated by Hill, who considered a wider range of compositions [65-68]. He showed that even some glasses with NC<3 were bio-inert. The reason is that the NC estimated from the glass composition is based on the assumptions of regular coordination for all the network-forming species and of a homogeneous glass structure. The importance of a fast initial dissolution of silicate fragments in the bioactive process was confirmed by Acros et al. [70]. Linear silicate chains have a higher mobility and can approach the glass–tissue interface faster, compared with more bulky features such as rings. When thermal treatment is used to promote the condensation of chains into rings of tetrahedra, the whole dissolution process is slowed down [71]. The migration, detachment and release of silicate units initially incorporated in a ring require the breaking of a larger number of covalent Si–O bonds, compared with the release of a linear silicate chains. This is due to the fact that Si atoms incorporated in chains are, on average, less interconnected than Si atoms in rings. Moreover, the opening of stable (five- or six-membered) silica rings is energetically unfavoured, which further inhibits the release of soluble silica incorporated in ring-like structures. The randomness enhanced by the presence of network modifiers gives rise to the high reactivity of these glasses in aqueous environments.

1.11 FACTORS INFLUENCING BIOACTIVITY

The interfacial attachment or bonding between the bioactive glass and bone can be controlled by different methods including [72-75]:

**Physicochemical methods:** This method is based on the variation of surface composition and/or creation of surface charges (positive or negative), which would accelerate the chemical reactions and subsequently enhance the rate of apatite formation. Thermal poling technique can be used to accelerate and decelerate bone-like apatite formation on the surface of hydroxyapatite and bioglass® [76-78]. Based on this technique, a dc voltage is applied to the material for a given time interval and temperature. The experimental conditions are so chosen such that the applied voltage causes movement of mobile charge carriers. Then the material is cooled to room
temperature under same applied dc voltage. Thereby, the dipolar units and charge carriers are frozen to a position strongly influencing the chemical and physical properties of the materials. An overgrowth of calcium phosphate layers was observed on the negative side owing to the surface charges [77]. The experimental study has been carried out on 45S5 glass and it was found that the surface charges persist long enough to result in a significant enhancement of the bioactivity [76].

**Morphological methods:** New strategies have been developed for synthesis of bioactive materials such as sol-gel process and polymer templating methods. Sol-gel method is used to prepare bioglasses, which exhibits faster bone bonding rates together with excellent degradation/resorption properties as it effectively increases the porosity and surface area of bioglass thereby enhancing the nucleation sites [79, 80]. Moreover sol-gel process combined with the supramolecular chemistry of surfactants results in a new generation mesoporous materials for biomedical application such as drug delivery system and bone tissue regeneration because there unique structural properties may enhance their bioactive behavior [81].

**Biochemical methods:** This method is based on loading of osteogenic agents or biofunctionalization with different organic functional groups. The association of bioactive materials with the osteogenic agents such as growth factors like proteins, hormones or peptides could contribute significantly to promoting the new bone growth in vivo. By modifying with different functional groups, the biofunctionality of the matrices could be enhanced [82-84]. For instance carboxylic groups could accelerate the formation of HCA on silicon wafer surfaces, while amino groups impeded the formation of HCA [85].

### 1.12 TYPES OF BIOACTIVE GLASS

**1.12.1 Melt-derived Bioactive Glass**

The original bioglass was produced by melt processing route, which involves melting high purity oxides in the platinum crucible at high temperature, which is then poured
into preheated moulds to produce as cast components. The compositional range for the bonding of bone to bioactive glass and glass-ceramic is illustrated in Figure 1.7. All the compositions lying in the region A, in the centre of the Figure 1.7, were bioactive and show reasonable bonding character with the bone. All of them contain less than 60% of SiO₂ with their bioactivity diminishing dramatically with slight increase of silica proportion. The region A includes a central composition zone bound by dotted line region S where the glasses bond to both bone and soft tissues. On the other hand, the glasses in region B (compositions with greater than 60% SiO₂ content) behave as bioinert materials and were encapsulated by fibrous tissue upon implantation. The glasses in region C were reabsorbed within few days of implantation. Finally, in the region D bulk glasses cannot be obtained.

**Figure 1.7:** Composition diagram for bioactivity of melt-derived silicate Glasses (constant 6 wt% P₂O₅ in the system SiO₂-Na₂O-CaO-P₂O₅)

It has been observed that by partially replacing CaO with MgO or CaF₂, and Na₂O with K₂O causes significant change in bioactivity. In contrast, by adding fluoride decreases the dissolution rate and alters the position of the boundary between the regions
A and C. Additionally, B\textsubscript{2}O\textsubscript{3} and Al\textsubscript{2}O\textsubscript{3} have been used to alter the production process of the glasses or their surface dissolution rate. The presence of Al\textsubscript{2}O\textsubscript{3} greater than 1.5 wt\% in the glass inhibited bone bonding behavior by slow HCA formation or reducing the dissolution rate to prevent calcium phosphate built up within the layer and by stabilizing silica structure [86]. Also, by adding the multivalent cations such as Al\textsuperscript{3+}, Ti\textsuperscript{4+} and Ta\textsuperscript{5+}, to the glass shrinks the bone-bonding region A and can even suppress bioactivity altogether, as found by Gross and Strunz [87].

1.12.2 Sol-Gel Bioactive Glass

There are several limitations encountered in the case of melt-derived bioactive glasses, which has been discussed in the previous sections. In order to overcome these limitations, the newest approach to prepare bioactive glasses with desired properties is called sol-gel technique. Based on this technique, one can widen the glass forming regions and it provides the superior textural properties. In early 1990’s Li et al prepared the first sol-gel derived bioactive glass with 60SiO\textsubscript{2}-36CaO-4P\textsubscript{2}O\textsubscript{5} composition, which is very similar to melt-derived composition previously studied [88] and they observed faster HCA surface layer formation than any melt-derived glass [89]. One of the main differences between sol-gel and melt-derived composition lies in the textural properties. Remarkably, sol-gel prepared glasses possess high surface area, typically ≥ 200m\textsuperscript{2}/g, about two orders of magnitude greater than the melt-derived glasses [90]. This is because sol-gel glasses contain a nanoporous network that is inherent to the sol-gel process, whereas melt-derived glasses are fully dense matrix. Alternatively, the sol-gel route requires noticeably lower temperature than melt-quenching method for obtaining bioactive glasses. Using this technique, different glass systems have been synthesized with high amount of silica and the fast rate of HCA formation noticed [91-95]. It can be understood that the enhanced bioactivity is due to the nanoporosity and high surface area, which causes increased rate of dissolution, accelerating stage 1 and 2 Hench mechanism. On the other hand, melt derived glasses are dense and hence follow the stages 1 and 2 to achieve high surface area due to ion dissolution. Therefore, sol-gel prepared glasses are considered as highly bioresorbable glasses. It has been shown that even in the case of binary
glasses containing 70 mol%SiO₂-30mol%CaO (70S30C) form HCA layer as rapidly as the 58S glass composition [96].

An important reason for the 70S30C glass to nucleate HCA layer even though it does not contain phosphate is the presence of Si-OH groups in the as prepared glass sample. These groups are thought to play an important role in the HCA layer nucleation. In melt-derived glasses these groups are formed during the second stage of Hench mechanism but in sol-gel glasses there are several Si-OH groups present in the unreacted glass that can quickly act as nucleation sites. Li et al [97] showed that glasses with high concentration of Si-OH group shows faster nucleation of HCA. Sol-gel glasses inherently have large number of OH groups in the glass network. The glass-network is therefore not completely cross-linked. Hence several sol-gel silica-based glasses have microporosity, which causes high surface area, hence rapid dissolution of glass network that have even high silica content [98]. Another advantage of sol-gel glasses is that their surface can be modified by variety of surface-chemistry methods with different organic functional groups [81-83].

Clinical products involving sol-gel bioactive glasses have only just started to appear. Novabone Corp. recently modified their product by adding sol-gel glass (58S) particles to the Bioglass particles. Also, Novathera Ltd. (Cambridge, UK) has developed Theraglass®, a wound healing gel that incorporates particles with the 70S30C gel glass composition, modified by addition of 2mol% silver ions. Silver ions present in low concentration have been found to be bactericidal [99]. In Figure 1.8, we represent a scheme of the conditions and parameters that determines the in-vitro bioactivity by changing the chemical composition and stabilization temperature of sol-gel glasses. Three most important properties – from the point of view of the in vitro bioactivity – could be controlled, i.e. network former (NF) to network modifier (NM) ratio (network connectivity, NC), textural properties (surface area and porosity). The NC directly depends on the chemical composition. The textural properties depend on the chemical composition and stabilization temperature, and it determines the bioactive behavior through the ion release and Si-OH surface density.
Figure 1.8: Scheme representing the synthesis conditions and parameters that influence the bioactive process in the sol-gel glasses [100].

1.13 MESOPOROUS BIOACTIVE GLASSES

Synthesis of multicomponent ordered mesoporous materials with same composition as conventional sol-gel glasses are denoted as “Templated Glasses”.

Mesoporous bioactive glasses are materials with pores in the range of 2–50 nm according to the IUPAC classification [101]:

- **Micropores** have a diameter < 2 nm
- **Mesopores** have a diameter between 2 and 50 nm and
- **Macropores** have a diameter > 50 nm.
The mesoporous materials exhibit excellent bioactivity than the conventional sol-gel glasses due to their superior textural properties such as surface area and porosity as well as the capability to host agents into the pore system that contribute to tissue healing processes [102]. Although their bioactivity is, in part, believed to display composition-property relationships similar to those found for melt and sol-gel glasses, the enhanced textural properties are recognized as being dominating contribution to the superior in vitro bioactivity.

General Properties of Templated Glasses [96]

- Templated glasses constitute a new generation of nanostrutured bioceramics with unique structural properties, which exhibit order at mesosopic scale (2-50nm) and disorder at atomic scale.

- The mesoporous channels are divided by amorphous walls, which are typical feature of conventional glasses but with added value of exhibiting mesoporous arrangement of cavities arranged on lattice.

- Such mesoporous arrangement originates surface area and pore volume significantly much higher than glasses obtained by conventional sol-gel method.

- This mesoporous arrangement presents also a narrow pore size distribution.

This new class of BGs has been synthesized by using non-ionic block copolymers as structure-directing agents (SDA) through an evaporation induced self-assembly (EISA) process. This new synthesis route produces mesoporous bioactive glasses (MBGs) with uniform and controllable pore sizes, large pore volumes and superior *in vitro* bioactivity compared to the conventional sol-gel derived BGs [59]. It has been shown that the mesostructure of the MBGs play crucial role with regard to their bioactivity [104]. Structure–bioactivity correlations for MBGs is very different as compared to conventional sol-gel derived BGs [105].

Due to their unique properties, MBGs proved to be excellent candidate for the biomedical applications such as drug delivery systems [106, 107] and bone tissue regeneration [108, 109]. The drug molecules can be hosted into the mesopores and
released via a diffusion-based mechanism without drug-material interaction. It has been shown that amount of drugs loaded is greatly influenced by mesostructure and is three times more than the conventional sol-gel prepared glasses [110]. Thus, it is worthwhile to say that with increasing specific surface area and pore volume of bioactive glasses greatly accelerates the HCA formation and therefore enhances the bioactive behavior.

1.14 MECAHNISM OF BIOACTIVITY IN MESOPOROUS BIOACTIVE GLASSES

Due to the unique physicochemical characteristics exhibited by MBGs, the Hench mechanism of HCA formation have been reformulated. The mechanism formulated for the formation of HCA onto the MBG surface is similar to that proposed by Hench et al for conventional BG. However, there are some important differences that lead to an accurate biomimetism in MBG with respect to natural bone [112]. Such differences are summarized in Figure 1.9.

The steps followed in the above pictorial representations are discussed below:

**Stage 1:** Rapid exchange of Na\(^+\) and Ca\(^{2+}\) with H\(^+\) from the surrounding fluid medium.
In the case of MBG, a high accessible porosity, surface area, and material reactivity accelerate the surface process, which permit a more intense ionic exchange and higher H\(^+\) incorporation compared with the conventional BG.

**Stage 2:** In this stage, the formation of silanol (Si-OH) groups at the glass surface occurs. In the case of MBGs a higher density of silanols groups are present because of high surface area and larger H\(^+\) incorporation than conventional BG.

**Stage 3:** It is observed that the polycondensation of silanol groups forms a hydrated silica gel followed by a highly protonated silica-rich layer with depleted cations.

**Stage 4:** The migration of Ca\(^{2+}\) and PO\(_4^{3-}\) groups to the surface through the silica rich layer and from the surrounding fluid forming a CaO-P\(_2\)O\(_5\)-rich layer on the top of silica rich layer, followed by growth of amorphous CaP (ACP). In case of MBGs, higher ACP precipitation occurs as compared to conventional sol-gel glasses.
**Stage 5:** The crystallization of ACP leads to form HCA by incorporation of $\text{Ca}^{2+}$ and $\text{HPO}_4^{2-}$ ions. Thus, the overall time period for HCA formation is varying in both the glasses.

*Figure 1.9:* Bioactive mechanism in simulated body fluid (mimicking human plasma described in next chapter) of conventional BG (proposed by Hench in 1970) vs MBG.
Therefore, the texture-property correlations play an important role in formation of HCA layer in MBGs, which is very much different from that proposed for conventional bioactive glasses, owing to high surface area, pore size and pore volume.

1.15 FACTORS AFFECTING TEXTURES OF MESOPOROUS BIOACTIVE GLASSES

One of the factors affecting textural properties of the sol-gel derived bioactive glasses is the compositions of the glasses. The studies carried on sol-gel derived bioactive glasses containing SiO$_2$ and P$_2$O$_5$ as network former and CaO as network modifier revealed that an increase of CaO increases pore size and pore volume whereas the surface area decreases [111,112,108]. The reason being, CaO acting as network modifier, which causes increase in the number of NBOs. With a continuous breakage of silica network some of the portions of micropores would become mesopores, thus producing lower surface area. On the other hand, with a fixed amount of CaO an increase of P$_2$O$_5$ content would give the opposite trend, i.e. the pore size and pore volume decrease whereas surface area increases [113]. This can be attributed to the bonding of calcium to P$_2$O$_5$ thus decreasing the amount of calcium that interacts with the silica network as P$_2$O$_5$ content increases. An increase of the SiO$_2$ content produces similar effects to that by increasing the P$_2$O$_5$ content due to the similarity in the textural property of SiO$_2$ and P$_2$O$_5$, which act as the network formers.

Another important factor influencing the texture of the sol gel derived bioactive glasses is the type of precursor used and pH of the reaction medium [114]. When inorganic precursor such as Ca(NO$_3$)$_2$ and organometallic precursor like Ca(C$_2$H$_7$O$_2$)$_2$ were used as the CaO precursors to synthesize bioactive glass with same composition, respectively. It was observed that the glasses synthesized using Ca(NO$_3$)$_2$ possessed larger pore size and pore volume than those of the glasses produced by Ca(C$_2$H$_7$O$_2$)$_2$ as the starting material. Similarly, glasses obtained under acidic reaction conditions using nitrate precursors showed better textural properties as compared to glasses obtained under less acidic reaction conditions i.e. using weak acids. [115]. It is noteworthy that the calcination temperature also influences the textural properties of bioactive glasses in the sol gel process [116]. Higher calcination temperature leads to the reduction of surface area and pore volume. This is due to the
densification process driven by viscous flow or diffusion, and as a result, the porosity level of bioactive glasses gets reduced significantly. At high calcination temperatures the porous glass becomes densified and as result the surface area decreases.

Additionally, calcinations at higher temperature leads to the collapse of the structural ordering and further leads to crystallization of MBGs. Therefore, control of crystallization is an important factor for the structural ordering, because formation of large crystals disrupts the establishment of the curved surfaces associated with the mesoporous structure on the nanoscale [117]. Recently, it has been reported that the addition of an appropriate surfactant (discussed in the next chapter) and their concentration could also modify the textural properties of the sol-gel derived bioactive glasses [118]. MBGs with same composition but different types of surfactant e.g. P123, F127 and B50 6600 show different pore structure [59]. The low surfactant concentration induces heterogeneous reaction between surfactant and the inorganic precursors, which lead to the inferior textural properties. Moreover, the introduction of co-surfactants tailors the pore morphology as well as it act as swelling agents (used for pore enlargement) such as 1,3,5-trimethylbenzene (TMB), amines and decane which results in loss of structural periodicity and poor reproducibility [119-122]. There are co-surfactants such as Cetyl trimethylammonium bromide (CTAB) and Cetyl trimethylammonium Chloride (CTAC), a cationic surfactant, reduce the pore size continuously by controlling the micelle properties of the P123 [123]. These co-surfactants could induce hydration of the hydrophobic PO block, even breaks up the micelles of the copolymer, meaning that the volume of the hydrophobic surfactant chain of P123 can be decreased continuously, which implies that pore size could be reduced continuously. The common inorganic salts also impose important effects on the micelle properties [124]. The addition of inorganic salts effect the energy required to create the volume accommodating a hydrophobic solute due to water-ion interaction. When surfactant and salt are mixed in solution, salting-out phenomenon often happens. According to hydration theory, salting-out is the result of preferential movement of water molecules, which immobilize and quench their role as solvents, from coordination shells of surfactant molecules to those of salts. With the addition of inorganic salts, the reduced electrostatic repulsion among the surfactant headgroups is a key factor to influence the morphology of aggregates in ionic surfactant solutions. For conventional single-chain cationic surfactants, micelles may change from global to rodlike or wormlike with the addition of inorganic salts [125,126].
OBJECTIVES AND OUTLINE OF THE THESIS

THESIS OBJECTIVES

Silica based bioactive glasses are bioceramic material, which are successfully used in different bone defects and soft tissue treatments during last decades. The high biocompatibility and the positive biological effects of their reaction products (both leached or formed at the surface) after implantation, have made silica-based glasses one of the most interesting bioceramics during the last 40 years. Currently, the scientific community in this field has been focused to combine fascinating properties of silica based mesoporous materials (regarding their textural and structural characteristics) with bioactive response of conventional sol-gel glasses. An increase of the specific surface area and pore volume of bioactive glasses greatly accelerates the apatite formation and therefore enhances the bioactive behavior. In this context, mesoporous materials are found to be suitable candidate for the bone tissue regeneration. Moreover, when these MBGs are loaded with osteogenic agents, they promote bone growth \textit{in vivo} and can be used as scaffolds for bone tissue regeneration.

The present thesis work is broadly divided into two parts. In the first part, we provide new insights into the strong link between alkali ions dynamics and different sites associated with it in the melt derived bioactive and bioinert glasses. These correlations have been explored by using the high temperature Raman spectroscopy and Nuclear Magnetic Resonance (NMR) spectroscopy. An understanding of ion transport in these glasses is an important aspect since the influence of surface charge on the HCA formation was confirmed by the overgrowth of CaP layers in the SBF, the proliferation of certain cells in physiological fluids, and by an enhanced osteoconductivity in the body. Additionally, the release of alkali and alkaline-earth ions is the key factor for effective integration of the implants through interfacial bonding.

The second part of the thesis work is to synthesize mesoporous porous bioactive glasses and compare with melt-derived counterparts. Although various
studies have been done to investigate porosity and composition of bioactive glasses, the work carried out in the present thesis is unique. We report, for the first time, a method to prepare novel mesoporous alkali-oxide containing bioactive silicate glasses in binary system. Subsequently, we adopted this novel technique to synthesize mesoporous bioactive glasses with ternary and quaternary system with SiO_2-CaO-Na_2O-P_2O_5 as the main constituents close to 45S5 bioglass. We have studied the different glass compositions by tuning the network modifier/former ratios to understand their influence of joint presence of CaO and P_2O_5 on in-vitro bioactivity. Additionally, we have also investigated and compared the structure and bioactivity of sol-gel derived mesoporous glasses and glass-ceramics in quaternary system with constant alkali and by varying alkaline earth content.

OUTLINE OF THE THESIS

The thesis is organized in the following layouts: Chapter 1 has reviewed the common features of bioactive glass and glass-ceramics, mechanism of bioactivity, mesoporous bioactive glasses and their mechanism of bioactivity. It also describes the thesis objectives and thesis layouts. Chapter 2 describes the important experimental details employed in this thesis work. Chapter 3 and 4 details the strong link between the alkali ion dynamics and different structural units of network former, quantified by high temperature Raman spectroscopy and nuclear magnetic resonance etc. Chapter 5 details synthesis of wormhole-like bioactive mesostructured sodium silicate glasses with different compositions by acid assisted sol-gel method followed by evaporation induced self assembly (EISA) process using non-ionic block copolymer as structure directing agent. Furthermore, we studied the effect of alkali content on the local structural changes and textural properties such as pore sizes, pore volume and surface area and on their bioactivities. Chapter 6 presents the synthesis of sodium oxide containing bioactive quaternary glasses close to 45S5 Bioglass® along with two different ternary silicate systems by modified sol-gel process. With an aid of three different glass systems, a systematic analysis has been made on phosphorous-bearing and phosphorous-free bioactive glasses to investigate the role of phosphorus and calcium on in vitro bioactivity of various silicate glasses with constant alkali oxide
Chapter 7 details the synthesis of bioactive glasses and glass ceramics in the quaternary system with constant alkali concentration but varying alkaline-earth content, to study the influence of variable CaO content on structure and bioactive properties. An effort has been made to understand the presence of glass-ceramic phases on the textural properties as well as on the in-vitro bioactivities. General conclusions and suggestions for future scope of work are presented in Chapter 8.
REFERENCES


