

CHAPTER 2

THEORY AND LITERATURE REVIEW

Ceramics, glasses, and glass-ceramics include a broad range of inorganic/nonmetallic compositions. In the medical industry, these materials have been essential for eyeglasses, diagnostic instruments, chemical ware, thermometers, tissue culture flasks, and fiber optics for endoscopy. Insoluble porous glasses have been used as carriers for enzymes, antibodies, and antigens, offering the advantages of resistance to microbial attack, pH changes, solvent conditions, temperature, and packing under high pressure required for rapid flow [1].

Ceramics are also widely used in dentistry as restorative materials such as in gold-porcelain crowns, glass-filled ionomer cements, and dentures.

This chapter focuses on ceramics, glasses, and glass-ceramics used as implants. This chapter describes the chemical and microstructural basis for their differences in physical properties, and relates properties and tissue response to particular clinical applications.

2.1 Glass

Glasses are classified in a familiar group of ceramics. Typical applications of glasses are containers, windows, lenses, and fiber-glass. Glasses are noncrystalline materials or are said to be amorphous or glassy [2] as is shown in Fig. 2.1, comparing the random amorphous structure of silica glasses and long range structure of silicon dioxide crystals. The compositions of several common glass materials are shown in Table 2.1 [3]. However, a typical glass is called soda-lime glass consisting of approximately 70 wt% SiO_2 , the balance being mainly Na_2O (soda) and CaO (lime). One of the most important properties of these materials is transparency, resulting from complete lack of grain boundaries or inclusions which would cause the reflection of light.

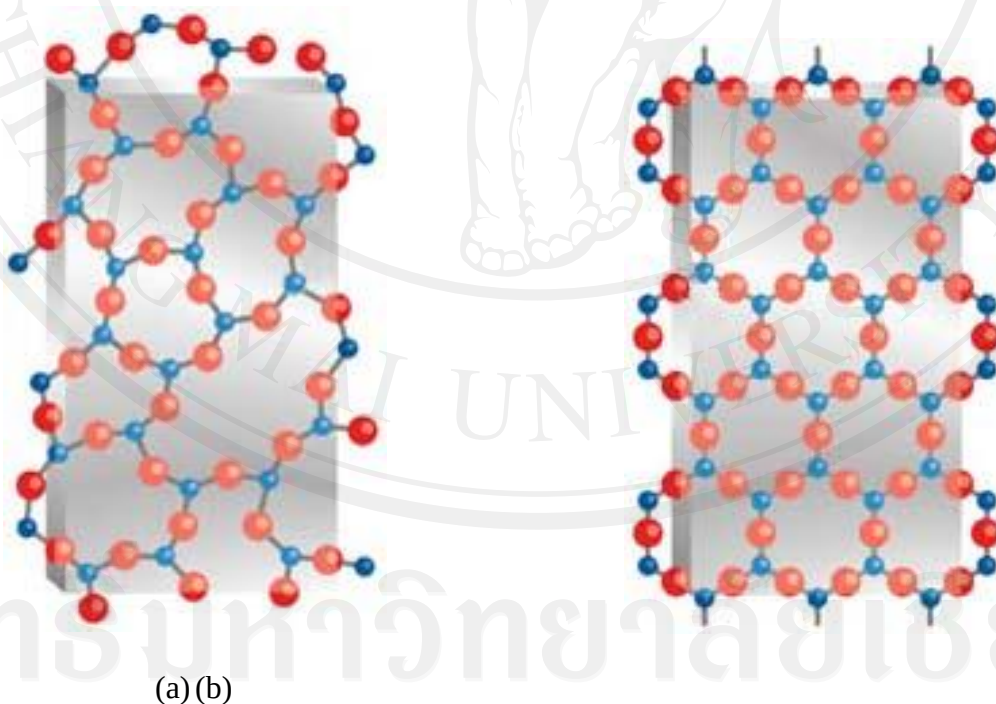


Fig. 2.1 Comparison of glass structure: (a) random amorphous structure and (b) ordered crystalline structure. [4]

Table 2.1 Composition and characteristics of some common commercial glasses. [3]

<i>Glass Type</i>	<i>Composition (wt%)</i>						<i>Characteristics and Applications</i>
	<i>SiO₂</i>	<i>Na₂O</i>	<i>CaO</i>	<i>Al₂O₃</i>	<i>B₂O₃</i>	<i>Other</i>	
Fused silica	>99.5						High melting temperature, very low coefficient of expansion (shock resistant)
96% Silica (Vycor)	96				4		Thermally shock and chemically resistant—laboratory ware
Borosilicate (Pyrex)	81	3.5		2.5	13		Thermally shock and chemically resistant—ovenware
Container (soda-lime)	74	16	5	1		4MgO	Low melting temperature, easily worked, also durable
Fiberglass	55		16	15	10	4MgO	Easily drawn into fibers—glass-resin composites
Optical flint	54	1				37PbO, 8K ₂ O	High density and high index of refraction—optical lenses
Glass-ceramic (Pyroceram)	43.5	14		30	5.5	6.5TiO ₂ , 0.5As ₂ O ₃	Easily fabricated; strong; resists thermal shock—ovenware

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2.1.1 Theory of glass

The most widely used definition of a glass, proposed by the ASTM, is “a glass is an inorganic product of fusion that has cooled to a rigid condition without crystallizing” [5]. Organic substances, for examples glucose and glycerol, would not be included in this definition, although they can be supercooled to a rigid condition without crystallizing. Moreover, such a definition would exclude amorphous substances which are not prepared by melt cooling methods, but by other techniques, such as vacuum evaporation [6]. A precise definition of glass is that “a glass or a substance in the glassy or vitreous state, is a material, formed by cooling from the normal liquid state, which has shown no discontinuous changes (such as crystallization or separation into more than one phase at any temperature) but has become more or less rigid through a progressive increase in its viscosity” [6]. This definition regards viscosity as defining a natural boundary to the glassy state. It is useful because any materials cooled below its liquid state, but whose viscosity has not yet reached this limiting value, is called a super-cooled liquid. There is no exact limiting value for viscosity but it can be assumed that the viscosity of the melt at the transformation temperature should be greater than about 10^{13} poises.

Glasses are characterized by many properties which reflect their liquid-like structures. One of the most important properties of glass is transparency, resulting from complete lack of grain boundaries or inclusions, which would cause the reflection of light. The property is usually found in the liquid state rather than in the solid crystalline state.

The relationship between liquid and solid can give a clearer understanding of the origin of the structure of a glass. The arrangement of atoms in a liquid has short-range order while that of a crystalline solid has both short-range and long-range order showing that the regularity in the solid is almost complete. Thus, a glass, which has a liquid-like structure, exhibits a lack of long-range periodic order. Moreover, the X-ray diffraction patterns of glass contain a few broad features reflecting the short-range radial distribution of atoms while that of a crystalline substance has sharp lines indicating the long-range 3D order. Glasses have broad melting behavior unlike the sharp melting points of crystalline solids.

These phenomena, which occur during the cooling of melts, are very important for understanding the relationship between the glassy state, normal liquid and solid state. Fig. 2.2 shows the relationship between these states by means of a volume- temperature diagram. This diagram can also be presented in terms of an enthalpy temperature because volume and enthalpy behave in a similar manner.

The liquid has a structure characteristic of the temperature at which the melt is held and, during cooling, the atomic structure of the melt will slowly change but still keep the characteristic short-range order of the primary liquid. In general, when melt is cooled below the melting temperature (T_m), crystallization occurs and it becomes solid. As a rapid decrease of enthalpy appropriate value is occurred the crystal. On continued cooling, the enthalpy will decrease slowly controlled by the heat capacity of the crystal. However, if the liquid can be cooled below the melting point by avoiding crystallization, there will be an undercooling of the melt to give a supercooled liquid. No discontinuous

rearrangement happens in this case as the temperature decreases, the overall enthalpy gradual changes. Further cooling produces deviation from the equilibrium line since the viscosity of the melt greatly increases, inhibiting atom movement, leading to difficulty in the rearrangement of atoms in the equilibrium liquid structure. Then as the temperature decreases, the viscosity increases rapidly, resulting in frozen-in, liquid-like structure. The slope after this is determined by the heat capacity of the frozen liquid. The glass transformation region, as it appears in the graph, may be defined by the temperature region joining the equilibrium liquid state and the frozen liquid state. Hence, the frozen liquid is a glass [7, 8].

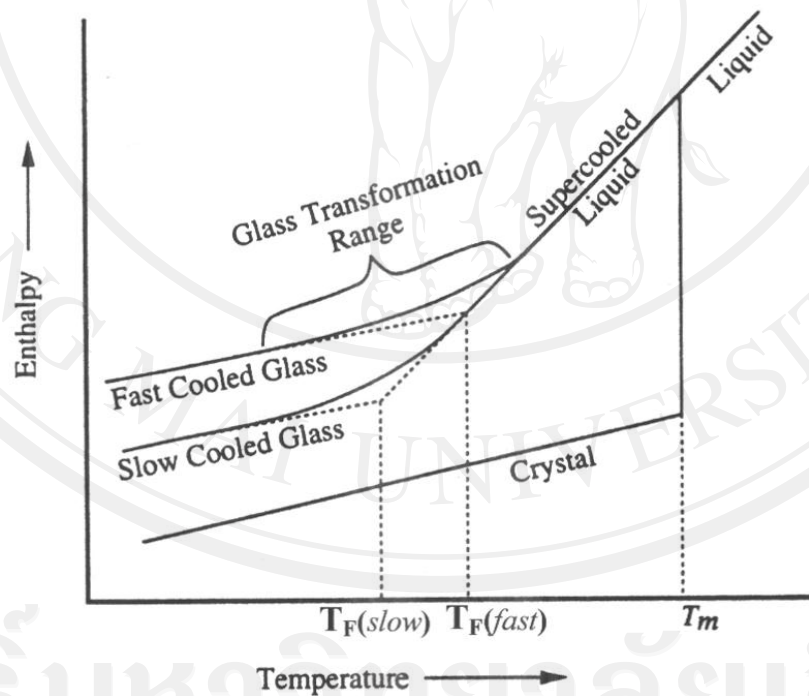


Fig. 2.2 Effect of temperature on the enthalpy of a glass forming melts.

[After Varshneya, A.K [8]]

As shown in Fig. 2.2, the intersection point between the glass and supercooled liquid lines is the fictive temperature (T_F), which may be defined as “the temperature at which the glass would find itself in equilibrium if suddenly brought to it from its given state” [7]. The structure of an equilibrium liquid at this temperature is similar to the structure of glass. Moreover, T_F can be changed by thermal history such as cooling rate. A high cooling rate freezes the liquid into a glassy state at lower density and higher specific volume than a lower cooling rate. The glass formed by slow cooling has a tendency to be more stable than that of fast cooling. This is because the atomic arrangement of the slow cooled glass is closer to that characteristic of the equilibrium liquid than the more rapidly cooled glass [7, 9-10].

2.1.2 Raw materials for glass melting

In general, glasses are either produced from high-quality, chemically pure components or from a mixture of far less pure minerals. Research specimens, optical glasses and many glasses used for low-volume, high-technology applications are produced using those chemicals we might routinely encounter in any chemical laboratory. Bulk commercial products, on the other hand, are produced from minerals, which typically have names and compositions which are not familiar to the novice.

Regardless of the source of the components used to produce a specific glass, the batch materials can be divided into five categories on the basis on their role in the process: glass former, flux, property modifier, colorant and fining agent. The same compound may be classified into different categories when used for different purposes.

Alumina, for example, serves as a glass former in aluminate glasses, but is considered as

a property modifier in most silicate glasses. Arsenic oxide may be either a glass former or a fining agent, depending upon the purpose for which it has been added to the batch.

The most essential component of any glass batch is always the glass former. Every glass contains one or more components which serve as the primary source of the structure. While these components are commonly designated as glass formers, they are also called “network formers or glass forming oxides” [7] in many oxide glasses. The identity of these components usually serves as the basis for the generic name used for the glass. If most of the glass former present in a specific sample is silica, for example, that glass is called a silicate. If a significant amount of boric oxide is also present in addition to silica, the sample is termed a borosilicate glass.

The primary glass formers in commercial oxide glasses are silica (SiO_2) and phosphoric oxide (P_2O_5) which all readily form single component glasses. A large number of other compounds may act as glass formers under certain circumstances, including GeO_2 , Bi_2O_3 , As_2O_3 , Sb_2O_3 , TeO_2 , Al_2O_3 , Ga_2O_3 and V_2O_5 . With the exception of GeO , these oxides do not readily form glasses by themselves unless very rapidly quenched or vapor deposited, but can serve as glass formers when mixed with other oxides. The elements S, Se and Te act as glass formers in chalcogenide glasses. Although halide glasses can be made in many systems, with many different compounds acting as glass formers, the two most common halide glass formers are BeF_2 and ZrF_4 .

Although the number of possible glass compositions is effectively unlimited, the vast bulk of commercial glasses are based on silica as the glass former. While silica itself forms an excellent glass, with a wide range of applications, the use of pure silica glass for

bottles, windows and other bulk commercial application would be prohibitively expensive due to the high melting temperature ($> 2000^{\circ}\text{C}$) required to produce vitreous silica. Production of silicate glasses requires the addition of a flux to reduce the processing temperature to within practical limits, e.g. $< 1600^{\circ}\text{C}$. The most common fluxes are the alkali oxides, especially Na_2O and PbO . Most commercial glasses contain soda, including those used for containers and window glasses. Potassium oxide is also used extensively in commercial glasses, while lithium oxide is used in a number of commercial glass-ceramics. Rubidium and cesium oxides are frequently used in the laboratory, for studies of trends in behavior due to changes in the identity of the alkali oxide present in glasses, but are rarely used in commercial products due to their high cost. PbO , which is an excellent flux, is becoming much more limited in use due to concerns regarding the toxicity of heavy metals. PbO is especially useful in dissolving any refractory or other impurity particles which might otherwise result in flaws in the final glass.

While the addition of fluxes to silica leads to a decreased cost of glass formation, the addition of large amounts of alkali oxides results in serious degradation of in many properties. In particular, the chemical durability of silicate glasses containing large concentrations of alkali oxides is degraded to the point where they can no longer be used for containers, windows or insulation fibers. The property degradation is usually countered by the addition of property modifiers, which include the alkaline earth and transition metal oxides, and, most importantly, aluminum oxide (alumina). While these oxides partially counter the reduction in processing temperature obtained by the addition

of fluxes, they also improve many of the properties of the resulting glasses. The properties can thus be modified, or adjusted, by careful control of the amount and concentration of these oxides to obtain precisely the desired results. Since many of these oxides are actually very weak fluxes for silica, and the property modifiers are usually added in lesser quantities than the fluxes, their use does not lead to excessively high processing temperatures. Colorants are used to control the color of the final glass. In most cases, colorants are oxides of either the 3d transition metals or the 4f rare earths. Uranium oxides were once used as colorants, but their radioactivity obviously reduces their desirability for most applications. Gold and silver are also used to produce colors by formation of colloids in glasses. Colorants are only used if control of the color of the glass is desired, and are usually present in small quantities. Iron oxides, which are common impurities in the sand used to produce commercial silicate glasses, act as unintentional colorants in many products. When colorants are used to counteract the effect of other colorants to produce a slightly gray glass, they are referred to as decolorants.

Finally, fining agents are added to glass forming batches to promote the removal of bubbles from the melt. Fining agents include the arsenic and antimony oxides, potassium and sodium nitrates, sodium chloride (NaCl), fluorides such as CaF_2 , NaF and Na_3AlF_6 and a number of sulfates. These materials are usually present in very small quantities ($< 1 \text{ wt } \%$) and are usually treated as if they have only minor effects on the properties of the final glasses. Their presence, however, is essential in many commercial

glasses, which would be prohibitively expensive to produce without the aid of fining agents in reducing the content of unwanted bubbles in the final product [7, 117].

2.2 Glass-ceramics

2.2.1 History

Glass-ceramics may be defined as polycrystalline solids prepared by controlled crystallization of glasses. Crystallization can be achieved by putting appropriate glasses through a regulated heat treatment schedule that causes nucleation and growth of crystal phases inside the glass. However, a small amount of residual glass often occurs and strongly affects a number of important properties of glass-ceramics [6].

It has been known for centuries that most glasses can be crystallized if they are subjected to heating for a sufficient length of time at a suitable temperature. There was no systematic development until the discovery of the first true glass-ceramics in 1957 by Dr. Stanley Donald Stookey [12, 13] at Corning Glass Works. He found that it is possible to form glass objects by conventional methods and transform them to fine-grained ceramics by heat treatment. After that, he successfully invented photochromic glasses, machinable glasses and polychromatic glasses. These products have far more mechanical strength than in their original forms. The effective nucleating catalyst used in most of Stookey's system was TiO and in 1970 McMillan *et al* [14] reported that the use of metallic phosphates (P_2O_5) could also promote controlled crystallization in glasses. In addition to these, other oxides, such as ZrO_2 , SnO_2 , CrO_3 and V_2O_5 [15] were later discovered to be effective nucleating agents.

Important aspects of glass-ceramics are nucleation and crystallization. Glass forming liquids are generally very viscous; therefore, processes of diffusion and atomic rearrangement are slow, which enables control of nucleation and crystal growth. The rapid quenching process can be applied to the viscous liquids in order to avoid the crystallization process during cooling and the resulting glass product can be used for further investigation of glass-ceramics. Another important phenomenon is amorphous phase separation, which can be important in both glass-ceramics formation and the stability of glasses. Because a glass melt is a good solvent for most oxides, a wide range of composition can be obtained, leading to the potential formation of glass-ceramics containing many crystal types, such as metastable phases and solid solutions within a variety of chemical environments. The ultra fine grains, typically less than one micrometer of glass-ceramics provide valuable materials properties, such as good mechanical strength and good fracture toughness. These ultra fine grains make glass-ceramics stronger than ordinary glasses and conventional ceramics. Due to this, it is possible to control the degree of crystallinity in glass-ceramics, leading to the studies of mechanical failure and the investigation of the properties, involving diffusion, for example: ionic conductivity. Normally, glass-ceramics are not transparent to visible light. However, transparent glass-ceramics can be derived if the crystals present are smaller than the wavelength of visible light or by minimizing the difference between the refractive indices of the parent glasses and crystals [16].

2.3 Types of bioglass, bioceramics and bioglass ceramics-Tissue interface

It is essential to recognize that no one material is suitable for all biomaterial applications. As a class of biomaterials, ceramics, glasses, and glass-ceramics are generally used to repair or replace skeletal hard connective tissues. Their success depends upon achieving a stable attachment to connective tissue.

The mechanism of tissue attachment is directly related to the type of tissue response at the implant—tissue interface. No material implanted in living tissue is inert because all materials elicit a response from living tissues. There are four types of tissue response (Table 2.1) and four different means of attaching prostheses to the skeletal system (Table 2.2).

Type 1 Nonabsorbable or Relatively Bioinert Bioceramics

Relatively bioinert ceramics maintain their physical and mechanical properties while in the host. They resist corrosion and wear and have all the properties listed for bioceramics in Table 2.1. Examples of relatively bioinert ceramics are dense and porous aluminum oxides, zirconia ceramics, and single-phase calcium aluminates. Relatively bioinert ceramics are typically used as structural-support implants. Some of these are bone plates, bone screws, and femoral heads.

Type 2 bioceramics, on porous metal are developed to prevent loosening of implants. The growth of bone into surface porosity provides a large interfacial area between the implant and its host. This method of attachment is often called BIOLOGICAL FIXATION. It is capable of withstanding of more stress than type 1

implant which achieve only morphological fixation. A limitation of type 2 porous implant is the necessary for the pores to be at least 100 micrometer in diameter. Large pore size is required so that capillaries can provide a blood supply to the ingrown connective tissue. If pores < 100 micrometer then even if the micro movements occur, Capillary can be cut off leading to tissue death. When the porous implant is metal, interfacial area can provide a focus for corrosion of implant and loss of metal ion into the tissue, which may cause a variety of medical problem. Coating of these porous metals with HA, diminishes some of these limitations. The Ha coating also improve the rate of bone growth into pores. But coating dissolves with time which limits its effectiveness.

Type 3 Bioactive implant is another approach to achieve interfacial attachments. This is intermediate concept between resorbable (type 4) and bioinert behavior. A bioactive material undergoes chemical reaction in the body, but only at surface leading to bonding of tissue at the interface. Thus a bioactive material is defined as “a material that elicits a specific biological response at the interface of material which results in the formation of a bond between the tissue and the material”. The bioactive concept has been expanded to include many bioactive materials with a wide range of bonding rate and thickness of interfacial bonding layer. These include bioactive glass, bioactive glass-ceramics, dense synthetic hydroxyapatite, bioactive composites, bioactive coating. The time dependence of the bonding, strength of bond, the mechanism of bonding, the thickness of bonding zone, and the mechanical strength differ for various materials.

Type 4 is Resorbable implants which are designed to degrade gradually with time and be replaced with natural tissue. A very thin or non existent interfacial thickness is the final result. This is the optimal solution to problem of interfacial stability. It leads to the generation of tissue instead of their replacement. The difficulty is meeting requirement of strength and short term mechanical performance of implant while regeneration of tissue is occurring. The resorbtion rate is must be matched to repair rate of body tissue but some material dissolve too slowly and others too fast. Since large quantities of materials being handled by cells so the constituents of resorbable implants should be metabolically acceptable.

Table 2.2 Desired Properties of Implantable Bioceramics

If the material is toxic, the surrounding tissue dies.

If the material is nontoxic and biologically inactive (nearly inert), a fibrous tissue of variable thickness forms.

If the material is nontoxic and biologically active (bioactive), an interfacial bond forms.

If the material is nontoxic and dissolves, the surrounding tissue replaces it.

Table 2.3 Types of Bioceramic—Tissue Attachment and their Classification

Type of attachment	Example
1. Dense, nonporous, nearly inert ceramics attach by bone growth into surface irregularities by cementing the device into the tissues or by press-fitting into a defect {termed "morphological fixation"),	Al_2O_3 (single crystal and polycrystalline)
2. For porous inert implants, bone ingrowth occurs that mechanically attaches the bone to the material (termed "biological fixation"). Hydroxyapatite-coated porous metals	the Al_2O_3 (polycrystalline)
3. Dense, nonporous surface-reactive ceramics, glasses, and glass-ceramics attach directly by chemical bonding with the bone (termed "bioactive fixation").	Bioactive glass-ceramics Hydroxyapatite
4. Dense, nonporous (or porous) resorbable ceramics are designed to be slowly replaced by bone.	Calcium sulfate (plaster of paris) Tricalcium phosphate Calcium-phosphate salts

Ceramics are ideal candidates as they have the key advantages of biocompatibility, biofunctionality and they are widely available elsewhere

2.4 The discovery of Bioglass®

Bioactive glasses are amorphous silicate-based materials which are compatible with the human body, bond to bone and can stimulate new bone growth while dissolving

over time. They therefore have the potential to restore diseased or damaged bone to its original state and function (bone regeneration).

The first bioactive glass was discovered by Larry Hench and colleagues in 1969, at the University of Florida, and was the first material seen to form an interfacial bond with host tissue after implantation [17]. The glass composition of the first bioactive glass was 46.1% SiO_2 , 24.4% Na_2O , 26.9% CaO and 2.6% P_2O_5 , in mol%, termed 45S5 Bioglass[®], which is now a trademarked name. Hench chose this composition as it provided a large amount of CaO with some P_2O_5 in a Na_2O – SiO_2 matrix. The composition is very close to a ternary eutectic, making it easy to melt. The first implants were in rat femora. After 6 weeks they were removed with great difficulty. A quantitative evaluation of interfacial shear strength in rat and monkey models showed that the strength of the interfacial bond between Bioglass[®] and cortical bone was equal to or greater than the strength of the host bone.

Hench's discovery launched the field of bioactive ceramics and Bioglass[®] particulate has been in clinical use since 1985 (US Biomaterials Corp., Alachua, Florida). Later studies have found that other compositions and glass types are bioactive, some even bonding to soft tissue. The interest in bioactive glasses now focuses on their ability to stimulate new bone growth and its potential to be used in the development of constructs that can stimulate the body's own regenerative mechanisms to restore damaged bone to its original state and function.

2.5 Melt-derived bioactive glasses

The first Bioglass[®] was prepared by traditional melt-quench method, which involves melting highly pure oxides (SiO_2 , Na_2CO_3 , CaCO_3 , P_2O_5) in a crucible placed in a high temperature furnace at 1370°C [17]. Platinum crucibles must be used to avoid any contamination of the glass. The melt is poured into the water to quench, forming a frit.

The frit is then dried in an oven and ground to obtain the required particles size. Bioglass[®] can also be poured into a pre-heated graphite mould to prepare as-cast components or rods. Fig. 2.3 shows the compositional range of bioactive glasses and glass-ceramics as per bone bonding ability. The majority of bioactive glasses lie in the middle region (S) of the SiO_2 - CaO - Na_2O diagram (assuming a constant value 6 wt% of P_2O_5) [18]. Compositions having slower bonding rates lie between 52 and 60 wt% of SiO_2 in the glass. Compositions having greater than 60% SiO_2 lie in region B and are bioinert. Addition of multi-valent cations, such as Al^{3+} , Ti^{4+} or Ta^{5+} to the glass composition reduces the bone bonding capability [19].

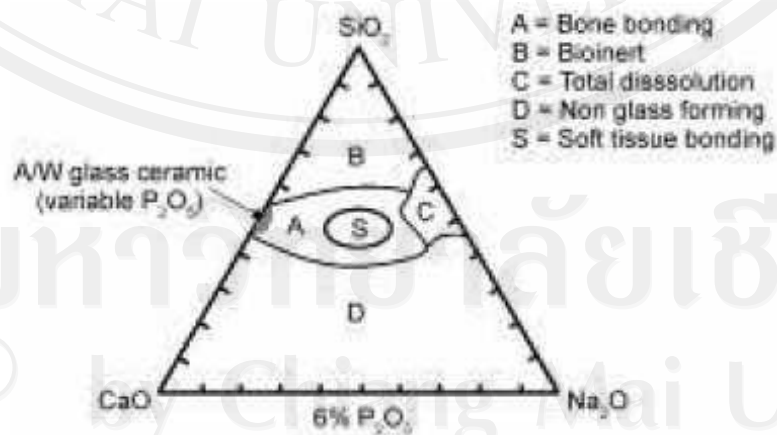


Fig. 2.3 Composition diagram of SiO_2 - CaO - Na_2O bioglass [20]

The dissolution rate of the glasses determines the scientific basis for compositional ranges. Andersson et al. [21] made some modifications in the 45S5 bioglass composition and implanted 16 different compositions of the system $\text{SiO}_2\text{-CaO-Na}_2\text{O-P}_2\text{O}_5\text{-Al}_2\text{O}_3\text{-B}_2\text{O}_3$ into the rabbit tibia. Only those glasses bonded to the bone that could develop HCA layer when immersed in Tris-buffer solution in vitro. The presence of alumina in the composition restricted bone bonding mechanism by slowing down the rate of HCA formation and stabilizing the silica network enough to prevent the calcium phosphates build up across the layer. It is suggested that up to approximately 1.5 wt% Al_2O_3 can be added to the glass without compromising the bioactivity. Glass compositions within the boundaries of the compositional diagram (Fig. 2.3) bonded to bone and the glasses outside the boundary did not bond to the bone.

Table 2.4 Composition of Bioactive glasses and Glass-ceramics (in Weight Percent) [22]

Composition	Bioglass ^{8,1} 45S5	S53P4 ²	Glass-ceramic ³ Ceravital [®]	Glass-ceramic ⁴ CeraBone [®] A-W	Glass-ceramic ⁵ IImaplan [®] L1	Glass-ceramic ⁶ Bioverit [®]	Sintered ^{7,8,9} hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ > 99.2%	Sintered ^{10,11} $\beta\text{-3CaO} \cdot \text{P}_2\text{O}_5$ > 99.7%
Na_2O	24.5 wt%	22.6 wt%	5–10 wt%	0 wt%	4.6 wt%	3–8 wt%		
K_2O	0		0.5–3.0	0	0.2	3–8 wt%		
MgO	0		2.5–5.0	4.6	2.8	2–21		
CaO	24.5	21.8	30–35	44.7	31.9	10–34		
Al_2O_3	0		0	0	0	8–15		
SiO_2	45.0	53.9	40–50	34.0	44.3	19–54		
P_2O_5	6.0	1.7	10–50	16.2	11.2	2–10		
CaF_2	0			0.5	5.0	F 3–23		
B_2O_3	0							
Phase	Glass	Glass	Apatite	Apatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{O,F})_2$)	Apatite	Apatite	Apatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$)	Whitlockite ($\beta\text{-3CaO} \cdot \text{P}_2\text{O}_5$)
			Glass	β -Wollastonite ($\text{CaO} \cdot \text{SiO}_2$)	β -Wollastonite	Phlogopite ($(\text{Na,K})\text{Mg}_3(\text{AlSiO}_{10})\text{F}_2$)		
Density (g/cm^3)	2.6572			Glass 3.07	Glass	Glass 2.8	3.16	3.07
Hardness (Vickers) (HV)	458 ± 9.4			680		500	600	
Compressive strength (MPa)			500	1080		500	500–1000	460–687
Bending strength (MPa)	42(Tensile)			215	160	100–160	115–200	140–154
Young modulus (GPa)	35		100–150	118		70–88	80–110	33–90

2.6 Mechanism of bioactivity

Since the report of its bone-bonding properties nearly 40 years ago [23], the bioactive glass designated 45S5, sometimes referred to by its commercial name Bioglass®, has been the most widely researched glass for biomedical applications [24-27]. This glass is a silicate glass based on the 3-D glass-forming SiO₂ network in which Si is fourfold coordinated to O. The key compositional features that are responsible for the bioactivity of 45S5 glass are: 1) less than 60 mol% SiO₂ content (when compared to more chemically durable silicate glasses) 2) high Na₂O and CaO (glass network modifiers) content, and 3) high CaO/P₂O₅ ratio.

The mechanisms of bioactivity and bone bonding of 45S5 glass have been widely studied, and described in detail elsewhere [28-29]. Based on those studies, the bonding of 45S5 glass to bone has been attributed to the formation of a carbonate substituted hydroxyapatite-like (HCA) layer on the glass surface in contact with the body fluid. Because this HCA layer is similar to the mineral constituent of bone, it bonds firmly with living bone and tissue. While some details of the chemical and structural changes are not clear, the HCA layer is generally believed to form as a result of a sequence of reactions on the surface of the bioactive glass implant, as described by Hench [20]:

Stage 1: Rapid ion exchange reactions between the glass network modifiers (Na⁺ and Ca²⁺) with H⁺ (or H₃O⁺) ions from the solution, leads to hydrolysis of the silica groups and the creation of silanol (Si–OH) groups on the glass surface: e.g.



The pH of the solution increases due to the consumption of H⁺ ions.

Stage 2: The increase in pH (or OH⁻ concentration) leads to attack of the SiO₂ glass network, and the dissolution of silica, in the form of silicic acid, Si(OH)₄, into the solution, and the continued formation of Si–OH groups on the glass surface:



While the solubility of silica is low, the products of 45S5 glass and glass–ceramic dissolution in aqueous solutions have shown an increase in Si concentration [30], indicating that dissolution of silica is an important mechanism. However, other mechanisms could also contribute to the increase in Si concentration.

Stage 3: Condensation and polymerization of an amorphous SiO₂-rich layer (typically 1–2 μm thick) on the surface of the glass depleted in Na⁺ and Ca²⁺.

Stage 4: Further dissolution of the glass, coupled with migration of Ca²⁺ and (PO₄)³⁻ ions from the glass through the SiO₂-rich layer and from the solution, leading to the formation of an amorphous calcium phosphate (ACP) layer on the surface of the SiO₂-rich layer.

Stage 5: The glass continues to dissolve, as the ACP layer incorporates (OH)⁻ and (CO₃)²⁻ from the solution and crystallizes as an HCA layer.

With the initial formation of an HCA layer, the biological mechanisms of bonding to bone are believed to involve adsorption of growth factors, followed by attachment, proliferation and differentiation of osteoprogenitor cells [31]. Osteoblasts (bone-forming cells) create extracellular matrix (collagen), which mineralizes to form a nanocrystalline mineral and collagen on the surface of the glass implant while the degradation and conversion of the glass continues over time [32].

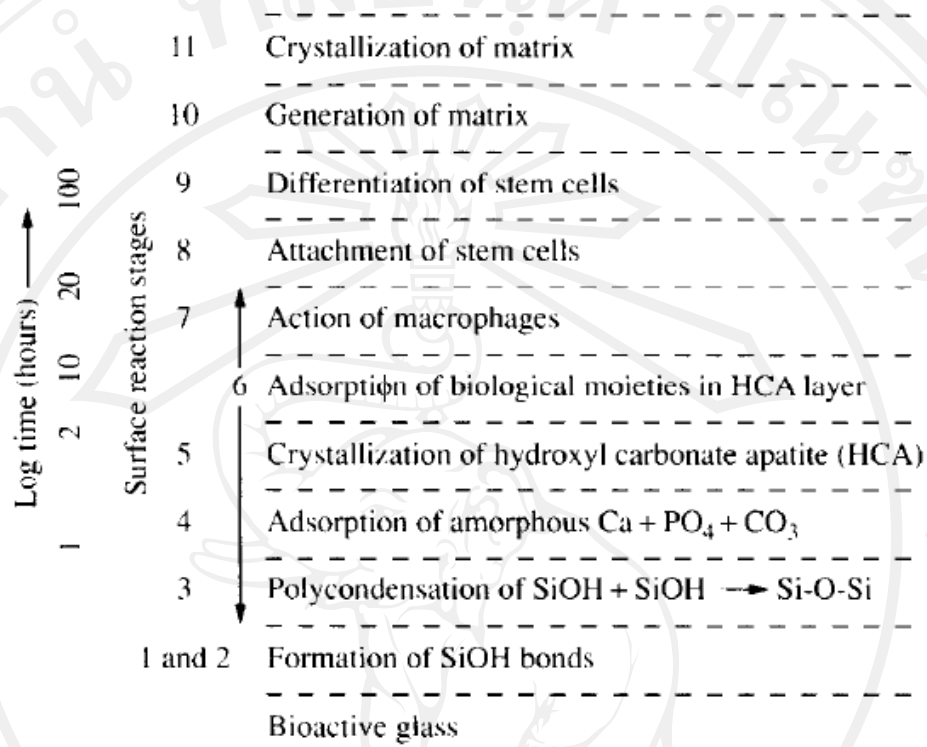


Fig. 2.4 Sequence of interfacial reactions involved in forming a bond between tissue and bioactive glasses [33]

2.7 Magnetism

Magnetic phenomena have been known for many centuries. In fact it was the mineral magnetite, which is the principal magnetic material investigated in this thesis, that was observed by the ancient Greeks to attract iron to itself.

A magnetic dipole is best visualised as being a microscopic bar magnet. The magnetic dipole moment is analogous to the electric dipole moment and is a vector quantity. The magnetic moment direction is from the south to the north of the magnet.

- *Hysteresis*

Hysteresis is an important phenomena exhibited by magnetic materials. This is looked at in the form of hysteresis loops which are a measure of the magnetization (M) or applied field (B) against the magnetic field intensity (H). M and B are directly proportional as shown in Equation 1 (where μ_0 is the permeability of free space, χ_m is the magnetic susceptibility) [34]

$$M = \mu_0^{-1} \chi_m B \quad (1)$$

If the magnetic field is in vacuo then we get H as shown in Equation 2;

$$B = \mu_0 H \quad (2)$$

Magnetisation, M, has the units Am^{-1} as does H. M and B are intrinsically linked by the Equation 3; [35, 36]

$$B = \mu_0 (H + M) \quad (3)$$

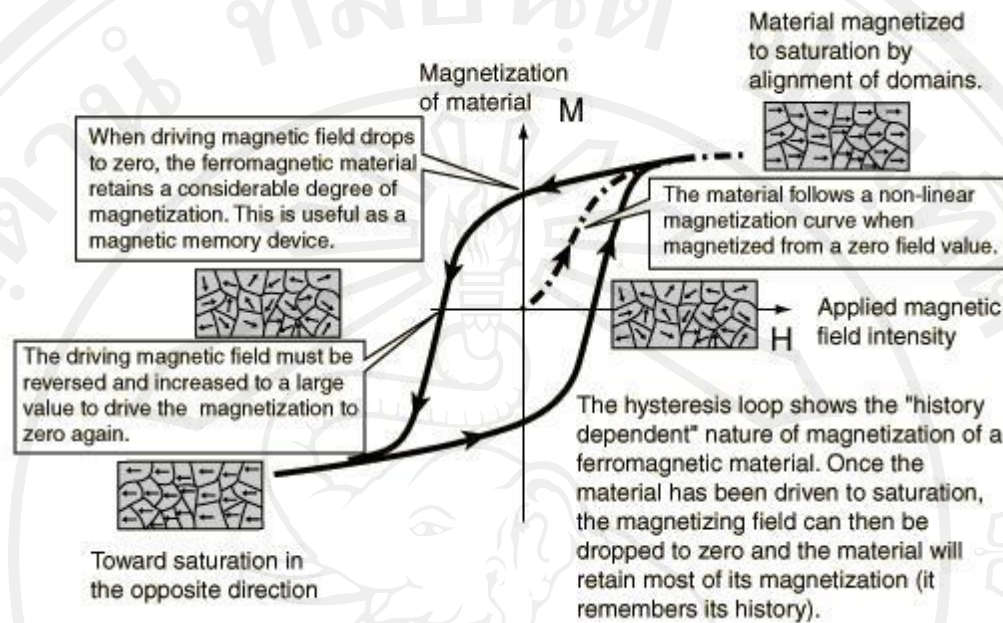


Fig. 2.5 Hysteresis Loop of Magnetic Materials [37].

Once at the maximum saturation value the applied field is reversed but the values of the magnetisation do not match that as before and are instead negative. The value on the y axis at which $x = 0$ is referred to as the remanent magnetisation. Conversely the value at x where $y = 0$ is the coercivity and this is essentially the strength of the applied field required to bring the magnetisation of the sample to zero after it has been fully saturated in one direction. It is the value of the coercivity that defines whether a material is a hard or soft magnet. Hysteresis means 'to lag' and this is exactly what is seen in a hysteresis loop [20]. There is a time lag for the moment to realign with the field causing a loop to be formed, as opposed to the original path being followed, as shown by the dotted line in Figure 2.5.

The remanence, magnetisation and coercivity are also directly dependent on grain size, and multi-domain particles tend to be soft with low coercivity and remanence. This is because only low fields are required to translate the domain walls. However in hard magnets which tend to be single domain particles, you must reverse the magnetisation giving rise to high coercivity and remanence, thus giving a bigger hysteresis loop [38].

2.8 The Classifications of Magnetism

There are many types of magnetism that have been observed. Different classifications are defined in this section. It should be noted that the most commonly seen are diamagnetic, paramagnetic, ferromagnetic, antiferromagnetic and ferrimagnetism. All materials have a diamagnetic component but can also be assigned to other magnetic classifications.

2.8.1. Diamagnetic

As detailed above, diamagnetic is seen in all materials as it arises from paired electrons, and is therefore the most observed. Despite this, commonly only materials that display only this type of phenomena are termed diamagnetic as the magnitude of the susceptibility is small, and therefore the other types of magnetism dominate.

Diamagnetic, unlike all other types of magnetic, is independent of temperature and the field applied. It can be considered as negative magnetisation, in that the magnetisation and its susceptibility are negative, therefore essentially repulsive. This is analogous to Lenz's Law of 1834 on electromagnetism. Essentially this law states that an induced emf will make a current that opposes the current that induced it [39].

2.8.2. Paramagnetic

Paramagnetic occurs in materials which have unpaired electrons. These electrons are randomly orientated and essentially have their own magnetic moment due to weak coupling being overcome by thermal energy. The magnetic susceptibility of a paramagnetic material is now positive, meaning that they are attracted to magnetic fields, not repelled as in diamagnetism. When there is an external magnetic field some of the spins align with the field, depending on the moment of the material and the external field. Removal of the field enables thermal agitation to dominate which randomises the spins so no net magnetisation is seen. Thus by cooling a paramagnetic material the spins are easier to align when an external magnetic field is applied.

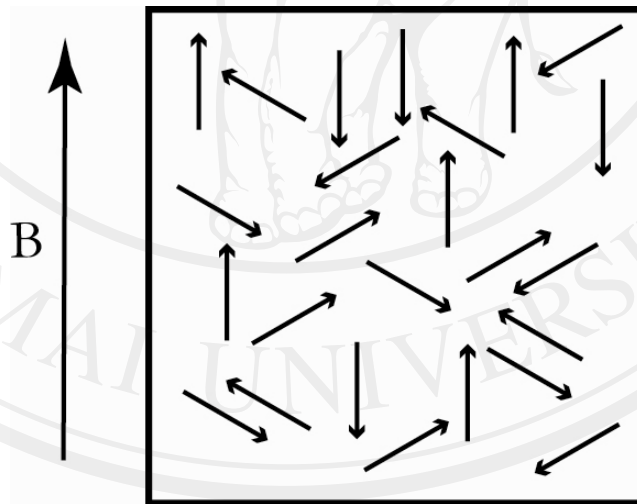


Fig. 2.6 A schematic representing the random spin orientations seen in paramagnetic.

2.8.3. Ferromagnetic

The ferromagnetic has a long range order, whereby the spins in different environments are aligned in parallel below the Curie temperature (T_c). This alignment is very strong (albeit not strong enough to form a covalent bond), and produces a large net magnetic moment.

Ferromagnetic materials produce hysteresis curves, as described in 2.7, as M is not proportional to H . There are two types of ferromagnetic; hard and soft. The hysteresis loops of hard ferromagnetic are large and wide and M is still large when there is no applied field present, these materials are useful for permanent magnets, an example of a hard ferromagnetic is cobalt steel. Soft ferromagnetic have much smaller/narrower hysteresis loops and has a small M when there is no applied field. They vary and have a greater dependence on H .

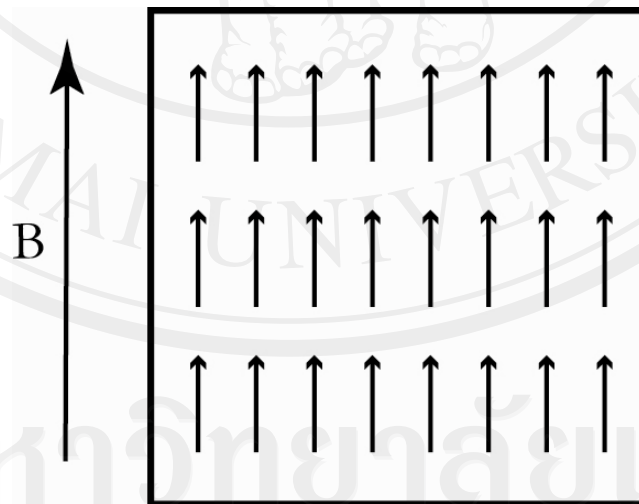


Fig. 2.7 A schematic showing the spin alignments in a ferromagnetic.

However, when T_c is reached and exceeded thermal agitation of the ions becomes favoured over the long range order of the magnetic moments. It is the point where a material loses its 'magnetism' due to the randomised nature of the now unaligned moments and thus becomes paramagnetic.

2.8.4 Antiferromagnetic

In an antiferromagnetic the spins in the different environments are antiparallel when below the Néel temperature (T_N), they are coupled using a superexchange mechanism (not to be confused with a double exchange mechanism which is seen in the coupling in Fe_3O_4). These spins are of equal size giving little overall net magnetisation, the magnetic susceptibility being comparable to paramagnets (see Figure 2.6) [40].

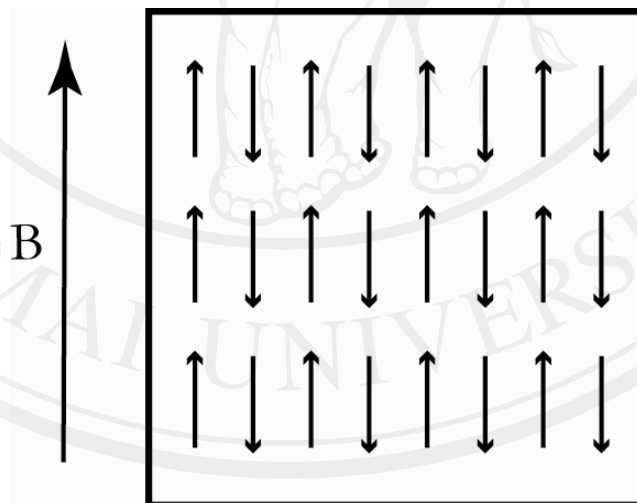


Fig.2.8 A schematic showing the ordering of spins in an antiferromagnetic.

The superexchange sees the covalent bonding of metal ions with a bridging ligand which is 2-(often oxygen). The two electrons in the ligand p-orbital go to the two neighboring metal positive ions and give rise to the two metals having spins that are

antiparallel [41]. With increasing metal-ligand orbital overlap the superexchange coupling is stronger, but with increasing metal-ligand angles the lessening in overlap makes for a weaker superexchange, and as this reaches 90° the superexchange mechanism can also cause ferromagnetic coupling, although this is far less common than for antiferromagnetic. Like in case of T_c , when T_n is reached the thermal agitation disorganizes the spins and the material becomes paramagnetic.

2.8.5 Ferrimagnetic

Ferrimagnetism has similarities to antiferromagnetic, whereby the metal ions in the two different environments are opposing, however the two environments have magnetic moments of different magnitudes. These results in a net magnetic moment being produced (Fig. 2.9). Both ferrimagnetism and antiferromagnetic were discovered by Louis Néel [42].

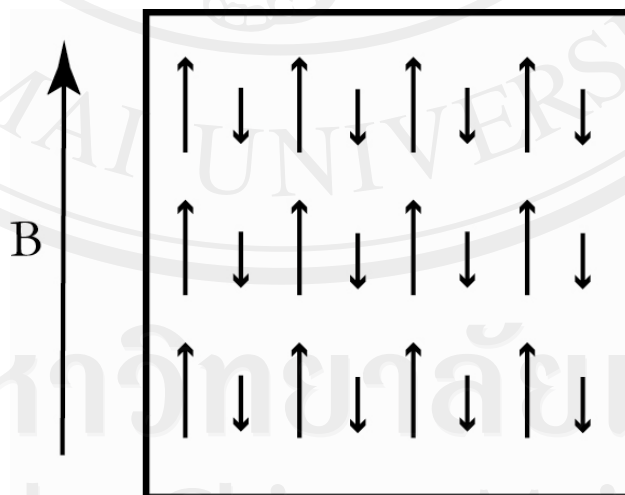


Fig. 2.9 schematic showing the spin alignments in a ferrimagnetic

Again, as seen in both ferro- and antiferro-magnetic once the temperature of a material is increased, the thermal energy overpowers the desire for long range order, the spins are randomised and the material becomes paramagnetic. This temperature is named the ferrimagnetic Néel temperature (T_{fN}).

2.9 Biomaterials and magnetism

Magnetism, which is an intrinsic property of every atom, has a profound influence on living organisms. The hemoglobin in our blood is an iron complex and is magnetic in nature. Magnetotactic bacteria are perhaps the first living organisms to orient themselves with the earth's magnetic field [43]. These bacteria are known to contain aligned chains of magnetite particles of various shapes. There is now substantial evidence that all living organisms, including animals and humans, contain magnetic particles and act as magnetic receptors [44]. It is established that the magnetism and magnetic materials have a strong role to play in health care and biological applications [45-49]. Some of the early medical applications of magnetic materials were, for example, the removal of metallic objects from the body of animals and humans [50]. The use of materials in biological environment for implantation or for replacement of a part or a function of the body in a reliable and physiologically acceptable manner was a challenge for the last several decades. Of late the combination of fine particles and magnetism in the field of biology and biomaterials has been found useful in sophisticated bio-medical applications such as cell separation [51-53], drug delivery [54] and magnetic intracellular hyperthermia treatment of cancer [55-56]. Similarly, the development of magnetically responsive

micro-spheres can be used in vitro to direct the particles so that they remove bound cells and molecules and in-vivo to target and hold the magnetic carriers at specific sites for applications in protein and cell separation. Further the purification of bone marrow cells from tumor cells using immuno-magnetic beads is also an established method in clinical therapy. The development of nano technology along with involvement of magnetism, opened new windows of sophisticated biomedical applications such as diagnostic, therapy etc[57]. In this article, we review some of the most recent advances in areas, where magnetic materials particularly when of nano size, are used in biological applications. Some of these are:

- Magnetic bioseparation
- Drug delivery
- MRI contrast agent
- Therapy – Hyperthermia treatment of cancer

The section on hyperthermia would include magnetic fluid hyperthermia (MFH) or intracellular hyperthermia. Though the field of magnetic hyperthermia had been known for several decades, it came into prominence during the last ten years or so. It appears that this mode of treatment perhaps combined with chemotherapy/radiotherapy could prove one of the most suitable for cancer therapy. A more detailed discussion on magnetic hyperthermia for cancer therapy is included in this review.

2.10 Role of magnetism in biomaterials

Magnetism has a strong role to play in some specific bioapplications. For example, in sorting of cells, interactions between biological cells and magnetic nano particles occur which lead to separation under the action of magnetic field gradient. The characteristics of hard and soft magnetic materials as well as the particle size dependent properties have been exploited for different bio applications. Magnetic properties change dramatically when particle size reduces beyond a critical limit and goes to single domain and sub-domain regions. Below a critical size, it shows superparamagnetic (SP) properties. This is exploited extensively for magnetic bioseparation, MRI contrast agent and drug delivery. For bioapplications (e.gMRI contrast agent, bioseparation etc.), superparamagnetic particles are found superior to ferro/ferri magnetic particles due to absence of remanance. Since a magnetic material exhibits magnetic properties only in the presence of a magnetic field, in bioseparation, it can be removed from suspension by applying a magnetic field. After separation it is easy to redisperse it in a homogeneous mixture in the absence of a magnetic field [58].

In magnetic hyperthermia, the ferro, ferri, as well as superparamagnetic properties of particles are useful. The losses due to magnetization and reorientation of these particles depend upon the type of demagnetization process, which is determined by intrinsic properties such as magnetocrystalline anisotropy and extrinsic properties such as particle size and microstructure. Magnetic hysteresis is a useful attribute of the material. Hysteresis loss represents the energy consumed in cycling a material between positive and negative fields. The area inside the second quadrant of the loop determines the

energy consumed in one cycle. The hysteretic power loss of an AC device can be obtained by frequency multiplied by hysteretic loss per cycle. The power loss can be dissipated in the form of heat for hyperthermia applications. When there is a reduction in size these magnetic nano particles behave super paramagnetically. These SP particles would not exhibit hysteresis losses. But Neel relaxation in them is equally useful in generating and dissipating heat.

- *Magnetic hyperthermia and cancer treatment*

Heat treatment of organs or tNo.s, such that the temperature is increased to 42–46°C and the viability of cancerous cells reduces, is known as hyperthermia. It is based on the fact that tumour cells are more sensitive to temperature than normal cells [59-60]. In hyperthermia it is essential to establish a heat delivery system, such that the tumour cells are heated up or inactivated while the surrounding tNo.s (normal) are unaffected. Though different hyperthermia techniques depend upon the heating methods used, each one has certain limitations. Boundary effects limit microwave, ultrasound, and RF hyperthermia. High frequency microwave beams have poor depth penetration and low frequency microwaves are difficult to focus on target areas. Though ultrasound has high penetration and focusing capabilities, applications are limited by strong absorption by bone and high reflection by air filtered cavities (lung etc.). By this technique it is difficult to heat up targets of high perfusion area to the desired temperature due to continuous dissipation of heat. Interstitial technique device is implanted into the tumour, which acts as a heat source by connection with external power sources [61]. In this review, however, we limit our discussion to only magnetic hyperthermia.

Magnetic hyperthermia is a technique used for cancer treatment. It is based on the fact that when magnetic nano-particles are placed inside an alternating magnetic field of high strength and frequency, heat energy is generated due to magnetic hysteresis loss [62]. Consequently, if magnetic nano-particles are placed inside a tumor and the tumor region is placed in an alternating magnetic field of a suitable frequency and amplitude, the tumor temperature would elevate [63]. This could destroy the tumor cells by necrosis if the temperature is raised above 45 °C. If the temperature is raised around 42 °C, it could improve the efficiency of chemotherapy [64]. Hyperthermia may kill or at least weaken the tumor cells [65], and is controlled for limited effects on the healthy body cells. Tumor cells, due to having an inefficient and abnormal blood capillary structure, have inefficient heat dissipating system. Hyperthermia may thus kill the cancerous cells, whereas healthy tissue cells are not harmed at this temperature due to the efficient blood capillary bed [66]. Research is in progress all over the world for the hyperthermia treatment of cancer. In Germany, the humans are being treated with this technique.

Magnetic induction furnace is the particular device that is used to generate the high frequency alternating magnetic field to heat the materials by hysteresis and eddy current losses. Temperature measurements in the study of hyperthermia may be carried out using alcohol or optic fiber thermometers. During the calorimetric measurements, the temperature inside the calorimeter is not homogeneous as the colloidal solution heated by the external magnetic field will be undergoing convection phenomena. So shaking of the solution while taking measurements or averaging the temperatures can ensure a more accurate temperature measurement.

2.11 Literature Survey [67]

Tumors occur due to the abnormal growth of cells and tissues. Nervous system and blood vessels are poorly developed around tumors due to which they are generally destroyed by the procedures involving heat treatments. Various kind of methods are being used for the cancer treatment such as x-rays, infrared rays, ultrasound, microwaves, hot water bathing, surgery, chemotherapy, immunotherapy and laser therapy etc. [67]. Nevertheless, the problem with these techniques is the difficulty of local regular heating of the tumor only, without damaging the normal tissues [68-69]. It has been reported that ferro/ferriimagnetic glass ceramics can heat the tumor locally under an alternating magnetic field, without damaging the normal tissues [70-72]. This is termed as Magnetic induction hyperthermia. Deep seated tumors are especially hard to be treated. Research is in progress on the development of suitable ferrimagnetic bioactive glass-ceramics for the hyperthermia treatment of cancer. These materials are especially effective in treating the deep seated tumors [73-75]. When implanted in granular form around the tumors, they bond with each other and with the surrounding tissue by forming biological hydroxyapatite layer. Such materials are termed as bioactive and adequate bioactivity is necessary for the implanting materials. Bioactivity of these materials [76-78] is related to calcium phosphates and calcium silicates that form the generally accepted model compound for bone mineral hydroxyapatite (CaOH_2) in a physiological environment. The other salient feature of such materials is ferromagnetism/ ferrimagnetism. The magnetic properties in these materials arise from magnetite (Fe_3O_4) that is produced from the Fe_2O_3 of the starting oxides [79]. When placed under an alternating magnetic field of high

frequency, these materials generate heat energy by hysteresis and eddy current losses [80-83]. The heat generated is controlled by various factors like microstructure [84] and composition of implant materials, frequency and strength of magnetic field and tissue characteristics etc. Tumor cells usually perish around 42-45 °C due to poorly developed circulatory system whereas healthy body cells remain unaffected at this temperature due to efficient heat dissipation system of blood vessels. Ferrimagnetic bioactive glass ceramics are potential candidates for the hyperthermia treatment of especially deep seated tumors [85-86]. These materials have also attracted growing interest in magnetic cell separation [87], magnetic drug delivery [88] and immunoassay [89] etc. Luderer et al. [90] initially worked on lithium ferrite containing glass-ceramics in 1980's, to be used as thermo seeds for the hyperthermia of cancer but their glass ceramic was not bioactive. Magnetite containing glass ceramic, for the first time, was reported in 1968 by O'Horo et al. [91] and later by Auric et al. in 1982 [92]. Auric et al. and Komatsxu et al. [93] reported that in iron oxide containing glasses, the iron existed in mainly two oxidation states: Fe^{2+} and Fe^{3+} . These two states could give a characteristic magnetic effect. Ebisawa et al. [94] showed in 1991 that heat treatment of a glass of the composition 40($\text{FeO}, \text{Fe}_2\text{O}_3$)-60(CaO, SiO_2) (wt%) at 950 °C gave a glass-ceramic containing 36% of magnetite (Fe_3O_4) in a matrix of CaO-SiO_2 based glass. The glass ceramics exhibited ferrimagnetism but lacked bioactivity. The absence of bioactivity was ascribed to the presence of Fe ions in the glassy matrix [94-96]. The same authors later reported [97-98] that even Fe_2O_3 -containing CaO-SiO_2 glass could show bioactivity if it contained some traces of B_2O_3 , Na_2O and/or P_2O_5 . This indicated that the ferrimagnetic glass ceramic

containing Fe_3O could reveal bioactivity if small amounts of these oxides were added to the composition of the parent glass. Meanwhile, Konaka et al. [99] prepared glass ceramics containing $\alpha\text{-Fe}$ for hyperthermia. In 2000, Lee et al. [100] investigated the effects of Fe states on the crystallization of Fe_3O_4 and dissolution behavior of the glass compositions in FeCaO-SiO_2 system. It was found that the higher CaO content disrupted the crystallization of magnetite as well as the oxidation of iron, i.e., the transformation from Fe. A sample containing large amounts of Fe^{2+} showed the faster increase in temperature when the alternating magnetic field was applied. In order to use the thermo seed for a hyperthermia, they suggested that the composition with low CaO content was the most attractive. Simon et al. [101] investigated the Electron paramagnetic resonance (EPR) and standard photo-pyroelectric (PPE) behavior of $\text{Fe}_2\text{O}_3\text{-CaO-P}_2\text{O}_5\text{-SiO}_2$ glass and glass-ceramic systems in 2001 in order to get information about the magnetic interactions between Fe ions introduced in $\text{CaO-P}_2\text{O}_5\text{-SiO}_2$ matrices and on the thermal diffusivity (α) of the samples. Arcos et al. [102] synthesized a novel biphasic material in 2002 from a sol-gel-derived glass (Si-Ca-P) and a glass-ceramic obtained from a melt-derived glass (Si-Ca-Fe). Both constituents of such a biphasic combination were bioactive, however having different kinetics for the growth of an apatite layer on the surface of these materials; only one day for the sol-gel derived glass and one month for the glass ceramic. The biphasic material, obtained from a mixture 1:1 of these constituents was bioactive, and its surface was coated after 15 days of immersion in SBF. The biphasic material also showed magnetic properties, useful for hyperthermia. Matsui et al. reported their work in 1986 [103] on the mechanism of heat generation by the eddy current, which relied on the

magnetic field, frequency of field, permeability, resistivity and the size of the implant. Furthermore, in order to attain the maximum heat generation, it was crucial that the direction of magnetic field was kept parallel to the long axis of the implant. Fe–Pt alloy needles were developed based on this idea and were used for the brain-tumors treatment in 1989 [104] and oral-malignant cancer treatment in 1996 [105]. Mitsumori et al. [105] and Shinkai et al. [106] reported in 2002 an investigations using Fe as a powder implant coated by dextran, injected into a mouse cancer. However, curie temperature, T_c of Fe_3O_4 , 858 K, was much higher than the adequate T (315-350 K) of the implant material. But there were many flaws in this work, e.g., high T , quantity of implant and the biocompatibility: It was important for the implant to be made of only biocompatible elements such as C, O, N, Na, Mg, Si, K, Ca, Ti, and Fe. From these viewpoints, Matsui et al. [107] in 2003, prepared the ceramic magnetic materials, such as $(\text{Mg}, \text{K})\text{Fe}_2\text{O}_4$, $(\text{Mg}, \text{Na})\text{Fe}_2\text{O}_4$, $(\text{Mg}, \text{Ca})\text{Fe}_2\text{O}_4$, $\text{Mg}(\text{Ti}, \text{Fe})_2\text{O}_4$ and $\text{Mg}(\text{Fe}, \text{Si})$, and the magnetic properties and the heat generation characteristics were investigated. It was found that $\text{Mg}_{1+x}\text{Fe}_{2-2x}\text{Ti}_x\text{O}$ ceramic gave some improved characteristics but ceramics were biocompatible, not bioactive. Kawashita et al. [108] prepared ferrimagnetic magnetite micro-spheres, 20–30 μm in diameter, for the first time in 2005 for in situ hyperthermia treatment of cancer. The micro-spheres are reported to be entrapped in the vessels bed of the tumors when implanted and heat tumors locally by hysteresis loss when placed under an alternating magnetic field. The saturation magnetization and coercive force of the heat-treated micro-spheres were 53 emug^{-1} and 156 Oe, respectively. The heat generation of the micro-spheres was estimated to be 41 Wg, under 300 Oe and 100 kHz fields. Eniu

et al. in 2005 [109] studied the structural effects caused by iron addition to calcium–silica–phosphate glasses and the magnetic interactions of Fe ions of $\text{CaO-P}_2\text{O}_5\text{-SiO}_2\text{-Fe}_2\text{O}$ glass and glass-ceramic samples. Leventouri et al. in 2005 [110] undertook a study of the physical properties of ferrimagnetic bioceramics $[0.45(\text{CaO}, \text{P}_2\text{O}_5)(0.52-x)\text{SiO}_2x\text{Fe}_2\text{O}_{30.03}\text{Na}_2\text{O}]$ and presented relationships between processing parameters, crystal structure, microstructure and magnetic properties of these multiphase systems. They further studied the effects of simulated body fluid (SBF) on the structure and microstructure of the same ferrimagnetic bioglass ceramics (FBC). The In vitro experiment illustrated that bioactivity of the glass ceramics varied with the composition, heat treatment, and time of soaking in SBF in a non-systematic way. A surface layer of Ca, Si and P partially covered the Fe, O dendrites, while arrangement and size of pores was determined by the specific processing parameters of the materials. Bretcanu et al. in 2005 [111-113] prepared co-precipitation derived ferrimagnetic glass-ceramic in the system $\text{SiO}_2\text{-Na}_2\text{O-CaO-P}_2\text{O}_5\text{-FeO-Fe}_2\text{O}$. The samples contained 45 wt% of magnetite having crystallite size of about 50 nm, homogeneously distributed in the amorphous residual matrix. The glass ceramic had a saturation magnetization of $34 \text{ A}\cdot\text{m}^2/\text{kg}$ and coercivity of 6.7 kA/m. The estimated magnetic loss/cycle under the magnetic field up to 796 kA/m was about 1.45 mJ/g. The specific power loss of this glass-ceramic under a magnetic field of 40 kA/m and a frequency of 440 kHz was 25 W/g. This material showed bioactivity, as after 2 weeks of immersion in a simulated body fluid, the formation of a hydroxyapatite layer on the surface was observed. This feature made it suitable for bone cancer as well. The authors analyzed the influence of the melting

temperature on the magnetic properties of these glass-ceramics [113]. The samples were melted at 1400, 1450, 1500 and 1550 °C for 30 min. in air atmosphere and then quenched onto copper plates. The highest specific power loss was obtained for the glass ceramic sample melted at 1550 °C (29 W/g), which had the highest hysteresis area. Dipping 1 g of this sample into 20 ml of distilled water, after two min. of application of the magnetic field, the temperature locally increased to about 41 °C. Bretcanu et al. in 2006 [98] prepared the ferrimagnetic glass ceramic of the same composition but with the traditional melting method and compared with that prepared by co-precipitation method. The two kinds of samples showed very similar magnetic and calorimetric properties. Few differences in these properties could be attributed to the slightly different microstructure of these two groups of samples. The highest power loss (61 W/g) was obtained for samples (traditionally) melted at 1500 °C.

2.10 Reference

1. Hench LL, Splinter RJ, Allen WC, Greenlee Jr TK. Bonding mechanisms at the interface of ceramic prosthetic materials. *J Biomed Mater Res* 1971;5:117–41.
2. Kenneth, G.B. and Michael, K.B. *Engineering Materials (Properties and Selection): Glasses*. 7th ed., Prentice Hall, New Jersey, pp. 290-296, 2002.
3. William, D. and Callister, J. *Fundamentals of Materials Science and Engineering (An Integrated Approach): Types of Ceramics*. 2nd ed., John Wiley & Sons, Inc., New Jersey, pp. 553-554, 2005.

4. ACME Design Company. 2002. "Glass and Sand Structure." [Online]. Available <http://www.acmecompany.com/Pages/glass.html> (5 January 2009).
5. American Society for Testing of Materials, Designation C 162-92 Standard Terminology of Glass and Glass Products. In: Annual Book of ASTM Standards 15.02, Philadelphia: ASTM (1993).
6. McMillan, P.W. Glass-Ceramics. 2nd ed. London: Academic Press, 1979.
7. Shelby, J.E. Introduction to Glass Science and Technology. 2nd ed., London: Royal Society of Chemistry, 2005.
8. Charles, A.H. Handbook of Ceramics, Glasses, and Diamond. New York: McGraw-Hill, 2001.
9. Varshneya, A.K. Fundamentals of Inorganic Glasses. London: Academic Press, 1994.
10. Osaka Sheet Glass Co. Ltd. 2002 "What is Glass." [Online]. Available http://www.osgco.com/eigo/e_glass.htm (15 November 2008).
11. Bo, S. Raw Materials for Glass Melting. Society of Glass Technology, 1997.
12. Wikipedia. 2001. "Stanley Donald Stookey." [Online]. Available http://en.wikipedia.org/wiki/S._Donald_Stookey (19 February 2009).
13. Corning Incorporated. 2009. "Dr. Stanley Donald Stookey." [Online]. Available http://www.corning.com/rd/century_of_research_development/stanley_stookey.aspx (7 March 2009).
14. McMillan, P.W., Hodgson, B.P. and Partridge, G., British Patent: Service Number 943-599, 1970.

15. Paul, A. Chemistry of Glasses. Chapman and Hall Ltd., 1982.
16. Hench LL, Wilson J. Introduction to Bioceramics. World Scientific, Singapore. 1993, Chapters 4 and 6
17. Komatsu T., Shioya K., Kim H.G., Sato R., Matusita K., Optical properties of transparent glass-ceramics in $K_2O-Nb_2O_5-TeO_2$ glasses. J. Non-Cryst. Solids. 1995; 189: 16-24.
18. Hench, L.L., J. Am. Ceram. Soc. 81 (1998) 1705-1728.
19. Greenspan, D.C., Hench, L.L., J. Biomed. Mater. Res. 10 (1976) 503-509.
20. Hench, L.L., J. Am. Ceram. Soc. 81 (1998) 1705-1728.
21. Andersson, O.H., Liu, G.Z., Karlsson, K.H., Niemi, L., Miettinen, J., Juhanoja, J., J. Mater. Sci. Mater. Med. 1 (1990) 219-227.
22. Jonathan B., Garth H, Handbook of Biomaterial Properties, Chapman & Hall (1998).
23. Hench L.L., Wilson J. (Eds.), An introduction to bioceramics, World Scientific, Singapore (1993)
24. Hench L.L., Wilson J. Surface active biomaterials Science, 226 (1984), pp. 630 - 636.
25. Yamamuro T., Hench L.L., Wilson J. (Eds.), Handbook of bioactive ceramics, vols. 1 and 2CRC Press, Boca Raton, FL (1990).
26. Hench L.L., Bioceramics, J Am Ceram Soc, 81 (1998), pp. 1705–1728

27. Rahaman M.N., Brown R.F., Bal B.S., D.E. Day Bioactive glasses for non-bearing applications in total joint replacement Semin Arthroplasty, 17 (2007), pp. 102–112.
28. Huang W., Day D.E., Kittiratanapiboon K., Rahaman M.N., Kinetics and mechanisms of the conversion of silicate (45S5), borate, and borosilicate glasses to hydroxyapatite in dilute phosphate solution , J Mater Sci Mater Med, 17 (2006), pp. 583–596.
29. Huang W., Rahaman M.N., Day D.E., Li Y., Mechanisms of converting silicate, borate, and borosilicate glasses to hydroxyapatite in dilute phosphate solution Phys Chem Glasses Europ J Glass Sci Technol B, 47 (2006), pp. 647–658.
30. Rohanová D., Boccaccini A.R., Yunos D.M., Horhavková D., Březovska I., Helebrant A. , TRIS buffer in simulated body fluid (SBF) distorts the assessment of glass-ceramic scaffold bioactivity, Acta Biomater, 7 (2011), pp. 2623–2630.
31. Hench L.L., Polak J.M., Third-generation biomaterials Science, 295 (2002), pp. 1014–1017.
32. Ducheyne P., Qiu Q., Bioactive ceramics: the effect of surface reactivity on bone formation and bone cell function, Biomaterials, 20 (1999), pp. 2287–2303.
33. Wanpeng C, L.L. Hench, Bioactive Materials, Ceramics International 22 (1996) 493–507
34. Orchard, A. F., Magnetochemistry. Oxford University Press: Oxford, 2003.

35. Atkins, P. W.; de Paula, J., Atkins' Physical Chemistry. 7th Edition ed.; Oxford University Press: Oxford, 2002.
36. Jiles, D., Introduction to Magnetism and Magnetic Materials. Chapman & Hall: London, 1991.
37. <http://hyperphysics.phy-astr.gsu.edu/hbase/solids/hyst.html>
38. Bertotti, G.; Basso, V.; Beatrice, C.; LoBue, M.; Magni, A.; Tiberto, P., Hysteresis in magnetic materials: the role of structural disorder, thermal relaxation, and dynamic effects." Journal of Magnetism and Magnetic Materials 2001, 226-230, (Pt.2), 1206-1212.
39. Buschow, K. H. J.; De Boer, F. R., Physics of Magnetism and Magnetic Materials. Kluwer Academic/ Plenum Publishers New York, 2003.
40. Chikazumi, S., Physics of Ferromagnetism. 2nd Edition ed.; Oxford University Press: 1997.
41. Anderson, P. W., "Antiferromagnetism - Theory of Superexchange Interaction." Physical Review 1950, 79, (2), 350-356.
42. Smart, J. S., "The Néel Theory of Ferrimagnetism." American Journal of Physics 1955, 23, (6), 356-370.
43. Blakemore R P, Frankel R B 1981 Magnetic navigation in bacteria. Sci. Am. 245: 58-65.
44. Urs H^äfeli 1997 In Scientific and clinical applications of magnetic carriers (eds) U H^äfeli, W Sch^ütt, J Teller, M Zborowski (New York, London: Plenum) p. 1.

45. Gruttner C, Rudershausen S, Teller J 2001 J. Magn. Magn. Mater. 225: 1–7.
46. Mykhaylyk O, Cherchenko A, Ilkin A, Dudchenko N, Ruditsa V, Novoseletz M, Zozulya, Yu 2001 J. Magn. Magn. Mater. 225: 241–247.
47. Kim D K, Zhang Y, Kehr J, Klason T, Bjelke B, Muhammed M 2001 J. Magn. Magn. Mater. 225: 256–261
48. Jordan A, Scholz R, Wust P, Fahling H, Felix R 1999 J. Magn. Magn. Mater. 201: 413–419
49. Koneracka M, Kopcansky P, Antalík M, Timko M, Ramchand C N, Lobo D, Mehta R V, Upadhyay R V 1999 J. Magn. Magn. Mater. 201: 427–430.
50. H^{afeli} U O In: Magnetism in medicine (eds) W Andr^a, H Novak (Berlin: John Wiley and Sons).
51. Del Gratta C, Della Penna S, Battista P, Di Donato L, Vitullo P, Romani G L, Di Luzio S 1995 Phys. Med. Biol. 40: 671–681.
52. Liberti P A, Rao C G, Terstappen L W M M 2001 J. Magn. Magn. Mater. 225: 301–307.
53. Zborowski M, Malchesky P S, Savon S R, Green R, Hall G S, Lewandowski J J, Nose Y 1987 Proceedings of the Ninth Annual Conference of the IEEE Engineering in Medicine and Biology Society (Cat. No.87CH2513-0) 3: 1161–1162.
54. Andra W, Nowark H 1998 Magnetism in medicine (Hand book) (Berlin: Wiley-

VCH)

55. Shinkai M, Yanase M, Suzuki M, Honda H, Wakabayashi T, Yoshida J, Kobayashi T 1999 *J. Magn. Magn. Mater.* 194: 176–184.
56. Jordan A, Wust P, Scholz R, Tesche B, Fahling H, Mitrovics T, Vogl T, Cervos Navarro J, Felix R 1996 *Int. J. Hyperthermia* 12: 705–722.
57. Olsvik-O, Popovic T, Skjerve E, Cudjoe K S, Hornes E, Ugelstad J, Uhlen M 1994 *Clin. Microbiol. Rev.* 7: 43–5.
58. Lea T, Vartdal T, Nustad K, Funderud S, Berge A, Ellingsen T, Schmid R, Stenstad P, Ugelstad J 1988 *J. Mol. Recogn.* 1: 9.
59. Overgaard J 1977 *Cancer* 39: 2637–2645
60. Field S B, Hand J W 1990 *An introduction to the practical aspects of clinical hyperthermia* (London: Taylor and Francis).
61. Kneller E 1966 In: *Encyclopedia of physics*, vol. XVIII/2, Ferromagnetism (ed.) H.P.J. Wijn (New York: Springer-Verlag): 438–544.
62. De Wulf, M., Makaveev, D., Dupre, L., Permiakov, V., et al., *J. Appl. Phys.* 93 (2003) 8543.
63. Andra, W., d'Ambly, C.G., Hergt, R., Hilger, I., *J. Magn. Magn. Mater.* 194 (1999) 197.
64. Carolyn Freeman, C., Halperin, Edward, C., Brady, Luther, W., David, E., “Perez and Brady's Principles and practice of radiation oncology”, Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, ISBN: 0-7817-6369-X, (2008) 637–644.

65. Dollinger, Malin, Everyone's Guide to Cancer Therapy; Revised 5th Edition: How Cancer Is Diagnosed, Treated, and Managed Day to Day, Kansas City, MO: Andrews McMeel Publishing, ISBN: 0-7407-6857-3, (2008) 98–100.
66. Gian F. Baronzio, G.F., (2006) Hyperthermia In Cancer Treatment: A Primer (Medical Intelligence Unit), Berlin: Springer, ISBN: 0-387-33440-8, (2008).
67. SAQLAIN A. S., study of Zinc Ferrite Containing Ferrimagnetic Bioactive Glass Ceramics for the Hyperthermia Treatment of Cancer, GC UNIVERSITY LAHORE (2004).
68. Abeloff, M.D., Armitage, J.O., Niederhuber, J.E., Kastan, M.B., McKenna, W.G., Clinical Oncology, 3rd ed. Philadelphia, Elsevier; (2004) 1007–1023.
69. Garden, A.S., Asper, J.A., Morrison, W.H., Schechter, N.R., Glisson, B.S., Kies, M.S., Myers, J.N., Ang, K.K., Cancer 100 (2004) 1171–1178.
70. Stauffer, P.R., Cetas, T.C., Fletcher, A.M., DeYoung, D.W., Dewhirst, M.W., Oleson, J.W., Roemer, R.B., IEEE Trans. Bio-Med. Engng. BME-31 (1) (1984) 76–90.
71. Matuki, M., Murakami, K., et al., IEEE Trans. Magn. MAG-18 (6) (1982) 1788–1790.
72. Kobayashi, T., Tanaka, T., Kida, Y., Matsui, M., et al., J. Neuro-Oncol. 7 (1989) 201–208.
73. Jordan, A., Scholz, R., Maier-Hauff, K., et al., J. Magn. Magn. Mater. 225 (2001) 119.

74. Dupraz, A., Nguyen, T.P., Richard, M., et al., *Biomaterials* 20 (1999) 663.
75. Lee, Y.K., Choi, S.Y., *J. Am. Ceram. Soc.* 79 (1996) 992.
76. Bromer, H., Pfeil, E., Kos, H.H., *Ger. Pat. No.* 2,326,100 (1973).
77. Kokubo, T., Ito, S., Shigematsu, M., Yamamuro, T., *J. Mater. Sci.* 20 (1985) 2001.
78. Kokubo, T., Ito, S., Sakka, S., Yamamuro, T., *J. Mater. Sci.* 21 (1986) 536.
79. Gupta, A.K., Gupta, M., *Biomaterials* 26(18) (2005) 3995–4021.
80. Gray et al. “Targeted hysteresis hyperthermia as a method for treating diseased tissue”. *United State Patent* 6167313, 2000.
81. Matsuki, H., Yanada, T., *Mater. Sci. Eng.* A181/A182 (1994) 1366–1368.
82. Matsuki, H., Satoh, T., Murakami, K., Hoshino, T., Yanada, T., Kikuchi, S., *IEEE Trans. Magn.* 26 (1990) 1551–1553.
83. Tucker, R.D., *J. Endourol.* 17 (2003) 601–607.
84. Bahadur, D., Giri, J., *Sadhana* 28 (2003) 639.
85. Oh, S.H., Choi, S.Y., Lee, Y.K., Kim, K.N., *J. Biomed. Mater. Res.* 54 (2001) 360–5.
86. Arcos, D., del Real, R.P., Vallet-Regi, M., *J. Biomed. Mater. Res.* 65A (2003) 71–78.
87. Arcos, D., Penˆa, J., Vallet-Regi, M., *Chem. Mater.* 15 (2003) 4132.
88. Salinas, A.J., Martin, A.L., Vallet-Regi, M., *J. Biomed. Mater. Res.* 61 (2002)

89. Laczka, M., Cholewa-Kowalska, K., Laczka-Osyczka, A., Tworzydło, M., Turyna, B., *J. Biomed. Mater. Res.* 52 (2000) 602.
90. Luderer, A.A., Borreri, N.F., Panzarino, J. N., et al., *Radiat. Res.* 94 (1983) 190-198.
91. O'Horo, M., Steinitz, R., *Mater. Res. Bull.*, 3 (1968) 117-126.
92. Auric, P., Dang, N.V., Bandyopadhyay, A.K., et al., *J. Non-Cryst. Solids* 50 (1982) 97-106.
93. Komatsu, T., Soga, N., *J. Mater. Sci.* 19 (1984) 2353.
94. Ebisawa, Y., Sugimoto, Y., Hayashi, T., Kokubo, T., Ohura, K., Yamamuro, T., *Seramikkusu Ronbunshi* 1 (1991) 7-13.
95. Ebisawa, Y., Kokubo, T., Ohura, K., et al., *J. Mater. Sci.: Mater. Med.* 1 (1990) 239-244.
96. Ohura, K., Ikenaga, M., Nakamura, T., Yamamuro, T., Ebisawa, Y., Kokubo, T., Kotoura, Y., Oka, M., *J. Appl. Biomater.* 2 (1991) 153.
97. Ebisawa, Y., Kokubo, T., Ohura, K., et al., *J. Mater. Sci., Mater. Med.* 4 (1992) 225-232.
98. Ikenaga, M., Ohura, K., Yamamuro, T., Kotoura, Y., et al., *J. Orthop. Res.* 11 (1993) 849.
99. Konaka, H., Miyaji, F., Kokubo, T., *J. Ceram. Soc. Japan* 105 (1997) 833-836.
100. Lee, Y.K., Kim, K.N., Choi, S.Y., *J. Mater. Sci: Mater. Med.* 11 (2000) 511-515.

101. Simon, S., Eniu, D., Pasca, A., et al., V., Modern Phy. Letters B 15 No. 21 (2001)921-928.
102. Arcos, D., del Real, R.P., Vallet-Reg, M., Biomaterials 23 (2002) 2151–2158.
103. Matsui, M., Shimizu, T., Kobayashi, T., Hyperthermic Oncology '86, Japan. (1986) 63–64.
104. Kobayashi, T., Tanaka, T., kida, Y., Matsui, M., et al., J. Neuro-Oncol. 7 (1989) 201–208.
105. Tohnai, I., Goto, Y., Hayashi, Y., Ueda, M., et al., Int. J. Hyperthrmia 12 (1996) 37–47.
106. Shimizu, T., Matsui, M., Science and Technology of Advanced Mater. 4 (2003) 469–473.
107. Shimizu, T., Matsui, M., Science and Technology of Advanced Mater. 4 (2003) 469–473.
108. Kawashita, M., Tanaka, M., Kokubo, T., Inoue, Y., Yao, T., Hamada, S., Shinjo, T., Biomaterials 26 (2005) 2231–2238.
109. Eniu, D., Caccina, D., Coldea, M., Valeanu, M., Simon, S., Journal of Magnetism and Magnetic Materials 293 (2005) 310–313.
110. Leventouri, Th., Kis, A.C., Thompson, J.R., et al., Biomaterials 26 (2005) 4924–4931.
111. Bretcanu, O., Spriano, S., Vitale, C.B., Verne, E., J. Mater. Sci. 41 (2006) 1029–1037.

112. Bretcanu, O., Spriano, S., Verne', E., Co'isson, M., Tiberto, P., Allia, P.,
Acta Biomaterialia 1 (2005) 421–429.
113. Bretcanu, O., Verne', E., Coisson, M., Tiberto, P., Allia, P., Journal of
Magnetism and Magnetic Materials 300 (2006) 412–417.
114. Bretcanu, O., Verne', E., Coisson, M., Tiberto, P., Allia, P., Journal of
Magnetism and Magnetic Materials 305 (2006) 529–533.