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Bioactive glasses and glass–ceramics for hyperthermia treatment of cancer: state-of-art, challenges, and future perspectives

S.S. Danewalia [a], K. Singh [b,*]

[a] Division of Research and Development, Lovely Professional University, Phagwara, 144411, India
[b] School of Physics & Materials Science, Thapar Institute of Engineering and Technology, Patiala, 147004, India

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ABSTRACT

Bioactive glasses and glass-ceramics are well-proven potential biomaterials for bone-tissue engineering applications because of their compositional flexibility. Many research groups have been focused to explore the utility of bioactive glass–ceramics beyond bone engineering to hyperthermia treatment of cancer. Hyperthermia refers to raising the temperature of tumor close to 44°C at which malignant cells perish with negligible harm to normal cells. Hyperthermia can be employed by many means such as by ultrasonic waves, electromagnetic waves, infrared radiations, alternating magnetic fields, etc. Magnetic bioactive glass–ceramics are advantageous over other potential candidates for thermoseeds such as nanofluids, superparamagnetic nanoparticles because they can bond not only to the natural bone but also with soft tissues in few cases, which helps regenerating the affected part due to its bioactive nature. Strict restrictions on clinical settings ($H \times f < 5 \times 10^9$) force the research activities to be more focused on material characteristics to raise the implant temperature to required ranges. Lots of efforts have been made in past years to tackle these challenges and design best-suited glass–ceramics for hyperthermia treatment. This review aims to provide essential information on the concept of hyperthermia treatment of cancer and recent developments in the field of bioactive glass–ceramics for cancer treatment. The advantages and disadvantages of magnetic glass–ceramics over other potential thermoseed materials are highlighted. In this field, the major challenges are to develop magnetic glasses, which have fast and bulk crystallization with optimized magnetic phases with lower Curie and Neel temperatures.

1. Introduction

Cancer is a generic term used to represent a large group of diseases affecting human body [1]. It is one of the deadly and fearsome diseases that causes a large number of deaths worldwide, irrespective of developed or developing countries [2]. Over 1.7 million new cancer cases were estimated in the USA in 2018, causing an estimate of more than 0.6 million deaths [3] Worldwide research efforts have shown extraordinary progress to understand the complex nature of cancer. A decline of 26% was observed in the death rate from 1991 to 2015 because of the improvement in early detection techniques as well as reduction in various types of smoking [4]. This decline saved more than 2.3 million lives all over the world. Despite of all these efforts, the current medical practices to encounter cancer are incomplete.

There is no single mechanism to cure cancer; instead, a combination of various modalities is to be involved for better results [5–8]. Mostly used techniques for cancer treatment include radiotherapy (to treat cancer cells with radiation), chemotherapy (to treat cancer cells with chemicals/drugs), and hyperthermia (to treat cancer cells with heat) along with other recently developed techniques, as given in Fig. 1. All these techniques have their own advantages and disadvantages [7,9]. Hyperthermia is one of the promising techniques that has shown great potential to perish cancer cells via heat generation [10]. So many materials have been developed and tested to check their efficiency to cure cancer via hyperthermia. Among these materials, bioactive glass–ceramics have been proved to be quite useful materials [11–14]. Besides their heat generation ability, suitably selected glass compositions are also able to exhibit bioactive response toward the natural bone and even soft tissues in some cases as a result of exchange reactions with physiological fluids [15,16]. This way, along with the elimination of the cancer cells, bioactive glass–ceramics may also help in regeneration of the affected bone parts.

Glasses and glass–ceramics having transition metal (TM) oxides in their compositions have been widely studied for their magnetic and

* Corresponding author.
E-mail address: kusingh@thapar.edu (K. Singh).

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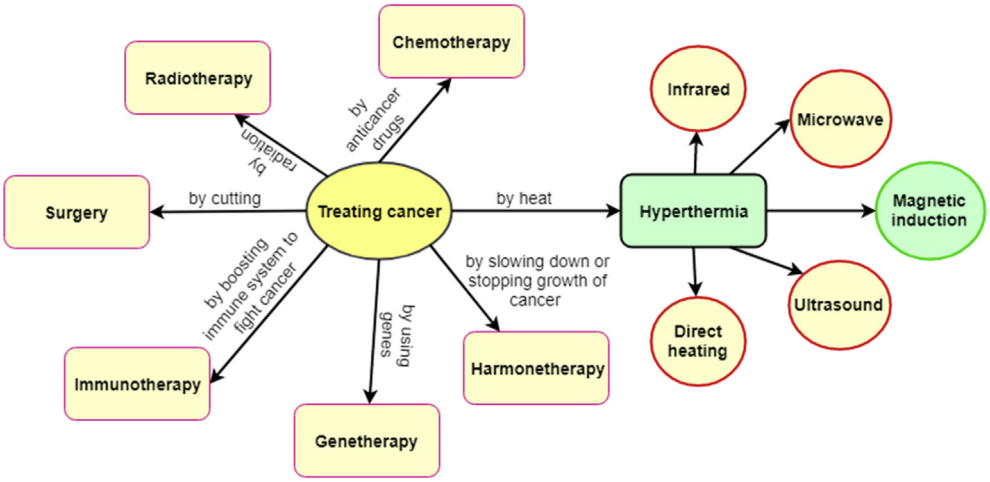

Fig. 1. Various techniques for the treatment of cancer.

bioactive nature. Lot of research has been carried out to address the challenges to design better and more suitable materials, which can act as thermoseeds for hyperthermia treatment of cancer. After decades of research on glasses and glass–ceramics, it is worthwhile to look at the overall perspective and outline the major findings and crucial points for effective future development of the glasses and glass–ceramics for cancer treatment. Because of the very fast growing field and advent in technology, there is need to have a comprehensive and state-of-the-art review articles frequently on magnetic glass–ceramics for hyperthermia treatment of cancer, even having some good review articles on similar topics [13,17]. In a recent review article, Miola et al. have reviewed the magnetic and structural features of sol-gel, as well as melt-quenched glasses [17]. The present article not only reviews the glasses and glass–ceramics for magnetic induction hyperthermia (MIH) treatment of cancer but also their bioactivity and influence of heat treatment and composition on both the properties. This review encompasses a wide range of published literature on glasses and glass–ceramics targeting heat generation in alternating magnetic fields. The present review article starts with a formal introduction to hyperthermia, its variants, advantages, and disadvantages. The structural, magnetic, and bioactive characteristic of the magnetic glasses are reviewed. Finally, some of the aspects are discussed from the material science's point of view that can be explored in near future to best utilize the full potential of magnetic bioactive glass–ceramics for the cancer treatment.

2. Concept of hyperthermia treatment of cancer

The word hyperthermia originates from Greek words *hyper,* i.e. raising, and *therme,* i.e. heat. Technically, the term hyperthermia refers to the elevation of temperature of a part of the body at a temperature more than that of the normal body temperature and maintaining it for a specific time duration [18]. It involves the heating the malignant cells to high temperatures (close to 43°C) by external or internal means with minimum harm to normal cells of human body in its neighborhood. Within temperature ranges 42–46°C, the cell apoptosis takes place. While at even higher temperatures, i.e. around 48°C, cell necrosis occurs. Both these mechanisms lead to the cell death [19].

Actually, cancer is the uncontrolled growth of the cells, which spreads in the adjoining body parts [20] and ends up to be fatal for the patient if not treated on time. Mostly, another word *tumor* is frequently used as a synonym to cancer cells, but it must be stressed that tumor may and may not be cancerous. If a tumor remains intact at a certain part of the body, it is not cancerous. However, if it spreads in other body parts with time, it is definitely cancerous. The present article is concerned about cancerous tumor cells. Cancer cells need lots of nutrients to grow, which they intake by developing a large network of blood vessels. Usually, blood vessels associated with cancer cells are of large size, which may create a misconception in reader's mind that the cancer blood vessel system is superior than that of normal cells. However, the blood vessel system in cancer cells is more likely a one-way traffic system rather than a two-way system as in normal cells. That means blood circulation (blood flow) through cancer cells is significantly lesser as compared to that in normal cells. A detailed discussion on the blood vessel system of tumor cells is reported by Nagy et al. [21]. The blood vessel system of cancer cells is insufficient to take away any heat provided during hyperthermia treatment. Therefore, cancer cells cannot withstand temperatures exceeding 41–42°C. By contrast, healthy cells owing to their better blood vessel system can survive even few degrees above this temperature. Thus, controlling the temperature near the cancer cells around 43°C is key for their successful elimination, without affecting the neighboring healthy cells to much extent [6].

Hyperthermia is usually employed in combination with other treatment therapies such as radiotherapy and chemotherapy of cancer cells. It is reported that the temperature elevation due to the hyperthermia process increases the sensitivity of the cells toward radiotherapy and chemotherapy [6]. It happens due to shrinkage of the cells by the damage of proteins and structures upon heating above the certain temperature [6, 22]. For simplicity, the biology of these events is not discussed in detail in the present article. The interested readers are suggested to refer to the available review article for deeper understanding [23].

Hyperthermia is practiced in the clinical usage for many years [24, 25]. It is advantageous over conventional radiotherapy and chemotherapy in particular cases where solid tumors are the most difficult to eliminate [26]. Some tumors are drug-resistant as well as radiation-resistant. Such tumors cannot be eliminated by chemotherapy and/or radiation therapy. In such cases, hyperthermia is more useful. Other than increasing the cytotoxicity to the tumor cells, hyperthermia also triggers certain anti-tumor immune responses that helps preventing the growth of tumor cells [27].

Depending on the size/spreading of the tumor cells and their location within the body, there are commonly three clinical methods of hyperthermia treatment:

- Local hyperthermia;
- Regional hyperthermia;
- Whole-body hyperthermia.

Local hyperthermia is meant for small tumors (up to 5–6 cm) [7]. Mostly, radio waves, microwaves, ultrasound waves are used to produce required heat of this type of tumor. The method of treatment can be both

invasive or non-invasive. For an invasive treatment, a specially designed probe is inserted inside the tumor, and the tip of this probe heats up the tumor. On the other hand, for the non-invasive treatment, waves carrying high energy are focused on the tumors using machines outside the body. Regional hyperthermia is employed for relatively large tumor cells where the whole limb or organ needs the treatment. One of the variants of regional hyperthermia is perfusion hyperthermia where blood from the targeted part of body is pumped out, heated, and pumped back into the targeted part. While pumping the blood back, the anti-cancer drugs can be loaded along with the blood. This way, chemotherapy and hyperthermia are employed in combination with each other [7]. Other method of regional hyperthermia includes heating the organ/body parts by placing some devices on the surface of body part and using focusing radio/microwaves onto the targeted area. Whole-body hyperthermia is used for metastatic cancer where the tumor cells are spread though the body. Body temperature in this modality can be raised by many ways such as using heating blankets, immersing the patient into warm water, or putting the patients into large thermal chambers. The body is heated to temperatures similar to that in high fever for a short time duration. General anesthesia or other drugs may be provided during the treatment to make the patient sleepy. Whole-body hyperthermia is also applied to assist chemotherapy. The heat treatment to the body makes certain immune cells more active to kill cancer cells effectively for few after--treatment hours [28].

2.1. Side-effects and limitations of hyperthermia

Table 1 summarizes the limitations of different hyperthermia modalities [22,29]. One of the natural physiological consequence of hyperthermia is *thermotolerance*. The treated tissue may become susceptible to the heat effects after the removal of the heat provided. This thermotolerance can protect the treated tumor against further treatment. Another limitation with hyperthermia is related to its applicability. It cannot be used at all the affected sites in human body. At deep-seated sites of cancers such as bladder, brain, etc., hyperthermia is quite difficult to apply [30]. Most of the side-effects after hyperthermia treatment are temporary, except few cases. Side-effects of hyperthermia get worse depending on the stage of the cancer. Local hyperthermia is least hazardous relative to other modalities. Regional and whole-body hyperthermia have similar side-effects, where in certain cases, whole-body hyperthermia can have serious side-effects. These effects are lessening with technological advancement and deeper understanding of the treatment modalities [24].

3. Magnetic induction hyperthermia (MIH)

Heat can be produced in many ways as mentioned in previous sections. Based on earlier experiences to generate the heat in industrial applications, for the first time in 1957 (to best of our knowledge), magnetic hyperthermia was proposed on the basis of heat generation ability of iron oxide due to hysteresis losses [31]. When alternating magnetic fields are used to produce heat, it is named as MIH. Other similar phrases are also used in literature to indicate this type of hyperthermia such as magnetically induced hyperthermia, magnetically mediated hyperthermia, or simply magnetic hyperthermia. In this technique, ferrimagnetic/ferromagnetic/superparamagnetic materials (called thermoseeds) are injected into the tumor cells, and the system is subjected to externally applied alternating magnetic fields. These thermoseeds produce heat under alternating magnetic field via different mechanisms. Fig. 2 represents schematic of MIH treatment. Ferrimagnetic/ferromagnetic thermoseeds experience magnetic hysteresis under the alternating magnetic field. Magnetic moments of these materials try to orient in the direction of magnetic field. However, on reversal of direction of the magnetic field, complete reversal of magnetic moments does not occur. Thus, magnetization versus applied magnetic field graph is characterized by a hysteresis loop. The area of the hysteresis loop signifies the work done during reversal of the magnetic moments with the changing magnetic field. This work is manifested as thermal energy, which is dissipated to the surrounding and tumor cell is killed due to this heat. By contrast, superparamagnetic materials induce the heating effect under alternating magnetic fields by Brownian relaxation or Neel's spin relaxation, which is ascribed to the rotation of magnetic particles or magnetic moments, respectively [32]. Superparamagnetic systems are also favorable, as they exhibit zero remanence after the alternating magnetic field is removed [33].

Generally, the heat generation capacity of a material is measured in terms of the specific absorption rate (SAR). It represents the amount of energy converted into heat per unit mass and time:

$$SAR = C\frac{\Delta T}{\Delta t}\frac{1}{m}$$

Here, C denotes the specific heat of the material, $\Delta T/\Delta t$ denotes the initial slope of the time-dependent temperature curve, and m denotes the mass of the magnetic material.

Table 1
Side-effects of different hyperthermia modalities.

Modality	Area	Side-effects	Nature of side-effect
Local hyperthermia	A small part of human body	Local site pain, swelling, blood clotting, infection, burns, skin damage, nerves, and muscles in vicinity of tumor site	Temporary
Regional hyperthermia	Limb, organ, or body cavity	Diarrhea, nausea, and vomiting	Common
Whole-body hyperthermia	Whole human body (metastatic stage)	Serious side-effects may include cardiac and vascular disorders/ diarrhea, nausea, and vomiting	Rare/ common

3.1. Controlling the heat generation

Among other hyperthermia modalities, MIH is better known for its better control on the temperature. Heat generation by a material during hyperthermia can be controlled by the many factors, namely material's characteristics, its dosage, clinical settings, etc. [34]. Fig. 3 depicts the dependence of heat generation on various factors.

The heat dissipated in ferrimagnetic and ferromagnetic materials primarily depends on their magnetic parameters, i.e. saturation magnetization (M_s), coercive field (H_c), and shape of the hysteresis curve. A larger hysteresis area signifies larger heat generation under alternating fields. Moreover, the dosage of the material injected into the tumor directly affects the heat generation. To minimize the sufficient dose of heat mediator, material with high SAR is required. The size and size distribution of the magnetic particles also affect the heat generation [32,35]. In general, homogeneously distributed fine particles generate more heat than that of coarser particles. Clinical settings, for instance, the magnetic field strength and the frequency at which the magnetic field is alternating can also affect the heat generation of a material [36]. However, due to biomedical reasons, there is a strict limit on clinical settings ($H \times f < 5 \times 10^9$) [37,38]. With these conditions imposed, the treatment outcomes have to rely up on thermal conversion efficiency of the thermoseeds [38]. For superparamagnetic nanoparticles, heat generation is mostly dependent on their size, as indicated by Fig. 4. Ma et al. [39] found that Fe_3O_4 superparamagnetic nanoparticles generate more heat up to 46 nm. However, above 46 nm, heat generation reduced with the growth of Fe_3O_4 nanoparticles. This is because of apparent hysteresis losses for larger particles. Conversely, smaller particles exhibit heat generation due to Neel's relaxation and Brownian rotation.

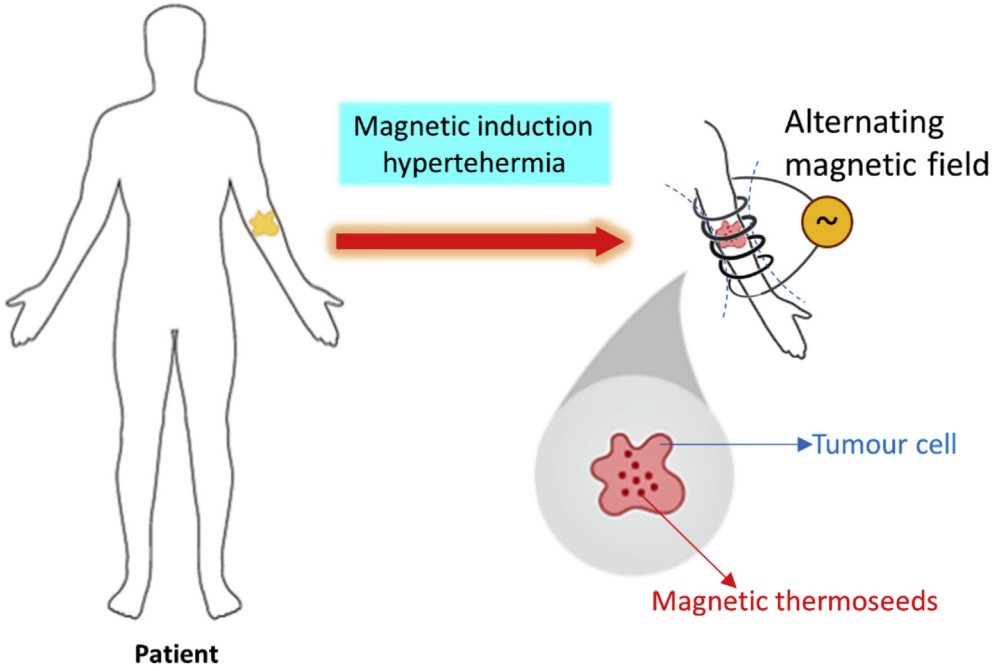

Fig. 2. Treating cancer cells via MIH. Magnetic particles injected at the tumor site are heated up due to hysteresis losses/Brownian motion/Neel's relaxation under alternating magnetic fields. The heat so produced kills the cancer cells.

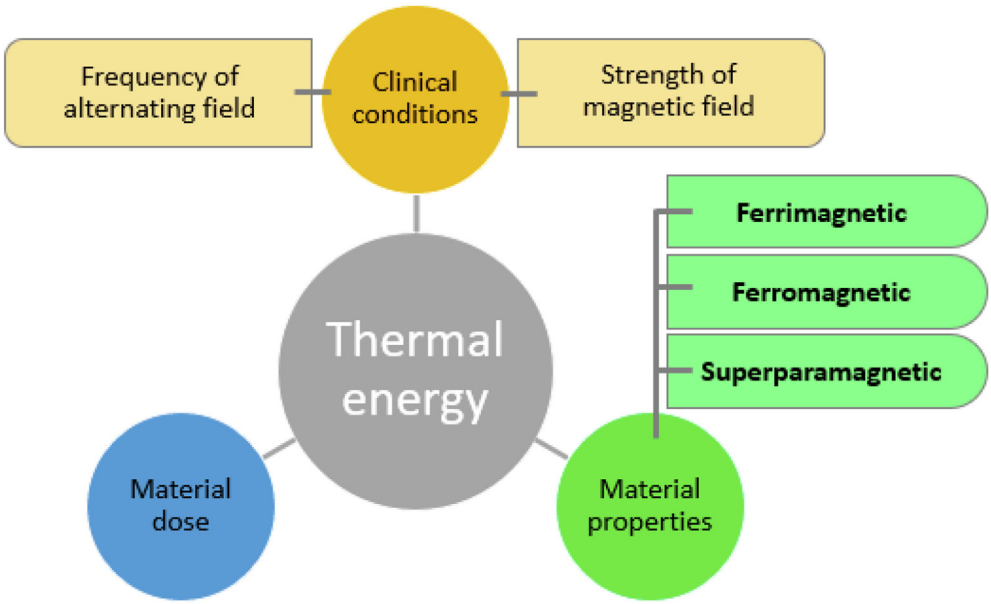

Fig. 3. Factors affecting heat generation in hyperthermia treatment.

3.2. Advantages of MIH

Using magnetic fields to induce heat is advantageous over other hyperthermia modalities. Magnetic interactions are realized as action at a distance. No wires need to be there in connection with the thermoseeds. Properties of the thermoseeds can be optimized to enable a self-control over temperature. For example, if the thermoseeds have a Curie temperature close to 43°C, then at temperatures exceeding 43°C, the material will turn into a paramagnetic material. As paramagnetic materials do not produce heat under alternating magnetic fields, such a system will not increase the temperature anymore. Body cells do not get excessively heated up under alternating magnetic fields. As thermoseeds are non-radiative, it is easier for physicians to implant the thermoseeds without any special attention, such as in brachytherapy [40]. Brachytherapy is a kind of internal radiation therapy that allows to provide higher radiation doses to the cancer sites by placing the radioactive sources inside the tumor itself. It has fewer side-effects than that of externally provided radiation in conventional radiotherapy. Similar to brachytherapy, MIH can also be used to impart local heating effects with minimum harm to neighboring healthy cells.

4. Materials as thermoseeds for MIH

As mentioned in Section 3, materials must be ferrimagnetic, ferromagnetic, or superparamagnetic in nature to induce any heating effect. Various materials proposed as thermoseeds include metallic compounds,

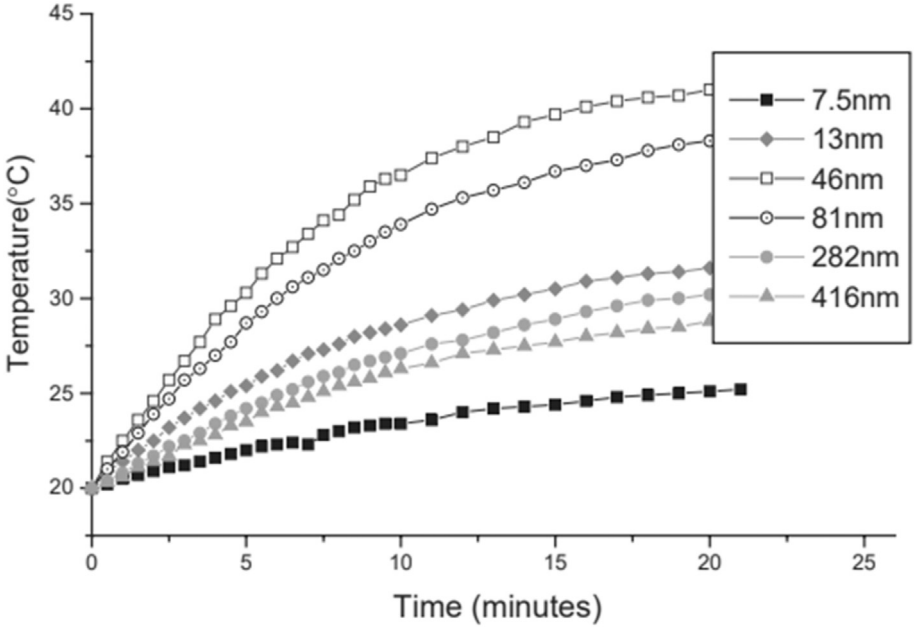

Fig. 4. Influence of size of magnetic nanoparticles on the heat generation in alternating magnetic field for different time durations [39].

magnetic fluids, nanomaterials, glasses, glass–ceramics, etc. [29,41–43]. Various materials tested for hyperthermia applications have their advantages and limits as summarized in Table 3. Metallic alloys for instance Fe–Pt, Ni–Si, Ni–Cu are found to be of great interest as their Curie temperature can be modified to be in the optimal ranges [41]. However, such materials suffer with problems like corrosion, bio-inert nature, and instability within the sites in human body. It limits their uses in hyperthermia treatment of cancer. However, metallic alloys otherwise are extensively used as biomaterials for various applications [44].

Instead of using metals or alloys, use of oxides of magnetic elements such as iron have been proved to be of great significance. Iron oxide is the most widely studied and clinically used compound among others magnetic oxides like nickel oxide and cobalt oxide. This is because of its notable magnetic properties along with biocompatible nature. Nevertheless, all the phases of iron oxide are not of magnetic significance. Magnetic fluids have shown a great potential as thermoseeds in hyperthermia applications [29,33]. Magnetic fluids are generally magnetic nanoparticles dispersed in aqueous media or some hydrocarbon. When the particle size approaches 20 nm or less, the iron oxide nanoparticles become superparamagnetic. That is why, these particles are abbreviated as SPIONS (superparamagnetic iron oxide nanoparticles). SPIONS have shown a great potential as thermoseeds [41]. SPIONS can also act as contrast agents for MRI purposes [45]. Additionally, SPIONS can be guided to the targeted site via external magnetic fields. Being superparamagnetic, SPIONS exhibit zero coercivity and zero remanence. Thus,

Table 2
Commercially available materials/systems useful for hyperthermia therapy.

S. No.	Material/ System	Manufacturer	Salient feature	Reference
1	Nanomag-D-SPIO	micomod Partikeltechnologie GmbH	SAR 90 W/g, for $H = 5.7$ kA/m and $f = 900$ kHz	[52]
2	FluidMag-D	Chemicell GmbH, Germany	SAR 80 W/g, for $H = 5.7$ kA/m and $f = 900$ kHz	[52]
3	FluidMag-CT	Chemicell GmbH, Germany	SAR 1,350 W/g, for $H = 12.0$ kA/m and $f = 950$ kHz	[52]
5	Magno	NanoScale Biomagnetics	SAR>210 W/g, for 23.877 kA/m and $f = 580$ KHz	–
4	Ferucarbotran	Meito Sangyo Inc., Japan	SAR 90 W/g, for $H = 5.7$ kA/m and $f = 900$ kHz	[52]
6	MP25 Series	Nanocs	Superparamagnetic nanoparticles coated with biocompatible polymers, size ~ 25–45 nm	–

Table 3
Comparison of the advantages and disadvantages of potential thermoseed materials.

Thermoseed material	Major advantages	Major disadvantages
Metallic alloys **Examples:** Fe–Pt, Ni–Si, Ni–Cu	• Controlled temperature in alternating fields • Optimal Curie temperature	• Corrosion • Bioinert nature • Biocompatibility issues • Instability at application site
Magnetic nanoparticles **Examples:** SPIONS, silica coated-Fe_3O_4, HAp-coated-iron oxide nanoparticles	• No remanence of magnetism after removal of external alternating field • Effective drug delivery • Can be exploited for simultaneous MRI, drug delivery, and hyperthermia	• Agglomeration of nanoparticles during AC field application • Colloidal instability • Dissolution of SPIONs and possible release of iron which can promote cancer growth • Lower magnetic characteristics as compared to bulk materials
Magnetic bioactive glasses **Examples: Glass system with compositions** SiO_2–Na_2O–CaO–P_2O_5–Fe_3O_4	• Compositional flexibility • Biocompatibility • Bone bonding nature • Regeneration of affected bones after treatment • Possible treatment without surgery in case of recurrence of tumor	• Compromise between magnetic and bioactive properties • Phase transformation during heat treatment • High Curie temperatures

no magnetic interactions are observed after the removal of the external magnetic fields. However, certain issues limit the uses of SPIONs as thermoseeds in the anti-cancer therapies. Dissolution of the SPIONS is a major concern, which leads to the possible release of iron particles in the body. It may have adverse effects such as promoting the growth of the tumors. Secondly, SPIONs are prone to agglomeration during the application of alternating fields. SPIONS have high surface energy due to their high surface area to volume ratio. Furthermore, there exist attractive magnetic and van der Waals forces due to which individual particles tend to agglomerate [46]. Such problems can be reduced to some extent with effectively coating SPIONs with some biocompatible materials such as silica, small organic molecules, hydroxyapatite (HAp), etc. [47–51]. These coatings may reduce the release of iron species and the dipole interactions of the magnetic particles. However, this approach has limited success only. To completely eliminate dipole interactions, the coating must be thick enough. This may lead to an instability of colloidal solution of the SPIONS. Also, SPIONS possess insufficient thermal conversion efficiency due to their degraded magnetic susceptibility. Further, iron oxide shows different magnetic parameters (M_s, H_c etc.) in its crystalline, nanoparticle, and composite form. In the bulk form, magnetite (Fe_3O_4) has M_s~92 emu g^{-1}, while maghemite (γ-Fe_2O_3) has M_s~76 emu g^{-1}. Relatively lower values of M_s are observed in their nanoparticles, as the degree of crystallinity differs in the core and on the surface. Bulk and nanoparticles of these materials also differ in coercivity. In contrast to bulk forms, nanoparticles of these magnetic phases are superparamagnetic and show nearly zero H_c at the physiological temperature, i.e. ~37 °C. Based on their structure and magnetic characteristics, different materials have different clinical applications. Some of the commercially available materials/systems useful for hyperthermia therapy are given in Table 2.

Magnetic bioactive glass–ceramics are another potential candidate as thermoseeds for hyperthermia treatment of cancer. Some of the issues with SPIONs are avoided in case of magnetic bioactive glass–ceramics due to their inherent characteristics. In bioactive glass–ceramics, the magnetic phase is encapsulated within the bioactive glass matrix, which prevents any leaching of metal ions in the body environments, which otherwise might be harmful [53]. Agglomeration of the magnetic species (here embedded in solid matrix) is not an issue with the magnetic bioactive glass ceramics. As discussed later in the next sections, magnetic bioactive glass–ceramics can bond to the natural bone. So, thermoseed once implanted would stay at the application site. Thus, hyperthermia heat cycles can be repeated whenever needed at a later stage of the treatment (if required). In case of bone cancer, the bone is damaged and becomes weaker after removal of the tumor. SPIONs do not have any ability to regenerate damaged bone tissues. However, the bioactive glass–ceramics can also help in regenerating such affected bone parts. These properties make magnetic bioactive glasses advantageous over other materials as thermoseeds. A glass matrix can also be used to control the growth of the nanocrystallites of magnetic phases. However, glass–ceramics meet a problem having high a Curie temperature. To the best of our knowledge, the glass–ceramics with Curie temperature close to 44°C have not been reported yet. Other ceramics such as certain manganates have been reported for their Curie temperature in ranges close to that required for hyperthermia [54]. Advantages and disadvantages of different materials/systems for hyperthermia are summarized in Table 3.

5. Bioactive glasses and glass–ceramics

Successful use of any material for biomedical applications is restricted by its biocompatible properties. Hench et al. synthesized *Bioglass*®, which were able to bond with the natural bone [55]. The chemical composition of the Bioglass® (also called 45S5 glass) is $45SiO_2$–$24.5CaO$-$24.5Na_2O$-$6P_2O_5$. When this glass is immersed in body fluids, after some time (depending on various factors discussed later), a layer of HAp is developed over its surface, which helps it to bind with the bone. Later, Ohura et al. suggested that artificial implants can make bond with the living bone if they can form HAp on their surfaces in the body environments [56]. Moreover, the phenomenon of development of HAp can be reproduced using simulated body fluid (SBF) having the ionic concentrations close to that of human blood plasma [57–59]. While, SBF cannot replicate every aspect of the physiological environments and should not be considered as a single criterion to rate the biological performance of a material. Rather, an *in vitro* test using SBF can be regarded as a preliminary tool or initial indicator of *in vivo* bioactivity of the material [60]. The SBF tests are economic, fast, risk-free, and reproducible prior to the *in vivo* studies. These days, the bone bonding glasses/glass–ceramics are usually termed as *bioactive glasses/glass–ceramics*. In the following sections, structural, magnetic, and bioactive characteristics of such bioactive glasses prepared for MIH are reviewed.

6. Structure–property relationship

Materials can be categorized on the basis of their structure–properties relationship. The properties of materials are either structure-insensitive or structure-sensitive, for instance Young's modulus and ultimate tensile strength, respectively. For high-performance materials, knowledge of these properties and their variation with atomic structure is essential. Therefore, in the following section, the properties relevant to the present review are discussed.

6.1. Structural and magnetic properties

Glass is an amorphous solid material that lacks long-range atomic periodicity. Above 10 Å, the periodicity of the structural units is absent in these substances. By definition, a material is said to be glass if it exhibits glass transition (T_g) on heating or cooling [61]. During this transition, glass loses its brittleness. On the other hand, a material is termed as a glass–ceramic if it contains crystalline phase(s) grown into the glass matrix [62]. Glass–ceramics are usually obtained after synthesis processing of the base glass. The base glass is subjected to heat treatment at appropriate temperatures for sufficient time duration. This controlled heat treatment leads to the formation of nuclei in the glass matrix. The crystallization is induced then with the growth of these nuclei within glassy phases. Besides this, sometimes the glass–ceramics are formed even during the quenching of glass [63]. Such *in situ* crystallization is observed when certain components of the glasses such as TM metal oxides are immiscible with other glasses ingredients [64]. Phase separation is the consequence of presence of such oxides, where different phases have different local chemical compositions and structures. Further, some of the TM oxides, for instance TiO_2, Fe_2O_3, are found to be good nucleating agents [65–68]. These nucleating agents speed up the nucleation process and result in easier crystallization in a glassy matrix. The properties of the final material are dependent on the type and volume fraction of the crystalline phases embedded in the glassy matrix. Sometimes, crystallization makes the glass–ceramics more durable to acid and base attacks and reduces its dissolution [69,70]. However, formation of the crystalline phases may also prove to be detrimental for chemical durability for certain compositions [71,72]. In general, the mechanical properties of the glass–ceramics are superior to their glass counterparts [73,74]. Suitable heat treatment given to glasses containing magnetic ions such as iron gives rise to glass–ceramics with better magnetic properties. For example, crystallization of Fe_3O_4 in the glass matrix shows ferrimagnetic behavior of the glasses [75,76].

In order to formulate glasses and glass–ceramics for MIH treatment of cancer, it is very important to understand their magnetic and bioactive properties with respect to composition. The choice of selecting ferromagnetic elements is very much limited. In the elemental form of TMs, only three elements (iron, nickel, cobalt) are ferromagnetic; chromium is anti-ferromagnetic, while other elements are either diamagnetic or paramagnetic. Hence, most of the elements are not of much use for MIH treatment particularly in their elemental form. Further, nickel and cobalt

cannot be used owing to their toxic nature [77]. Thus, most important choice for the MIH is iron and its compounds [78]. However, the magnetic properties of the elements differ from their compounds. Iron is generally incorporated in the glasses and glass–ceramics in its oxide form. It should crystallize either as magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3) for hyperthermia. There is another possibility that iron oxide crystallizes as α-Fe_2O_3, which is non-magnetic. Fe_3O_4 and γ-Fe_2O_3 are approved for the medicinal use [79,80]. Ferrite particles coated with biocompatible phases, i.e. HAp has been reported to be useful for hyperthermia treatment [81]. Unstable calcium hexaferrite phase was stabilized by doping lanthanum in place of some of the calcium ions. Magnetic measurements showed that such materials could generate appropriate heat for the destruction of tumor cells via hysteresis losses. Gadolinium-based compounds (Gd_5Si_4) have also been developed and investigated for the hyperthermia treatment [82]. Many compounds exhibit superparamagnetic nature at nanoscale regime, which allows using them for MIH applications. In fact, iron oxide also gives interesting magnetic properties at nanoscale, which affects their use for aforementioned applications [83–85].

First experimental studies describing the feasibility of hyperthermia treatments using magnetic materials were carried out by Gilchrist et al. [31]. Ferrimagnetic materials got special attention when Stauffer et al. [86,87] reported that ferrimagnetic materials can be used as localized heat sources at the targeted sites inside the human body kept under alternating magnetic fields. The idea of using magnetic glass–ceramics for hyperthermia treatment of cancer appeared after a report by Luderer et al. [88]. They showed that non-bioactive glass–ceramics containing lithium ferrite were useful as thermoseeds for hysteric hyperthermia. Afterward, so many reports followed with various designs and materials that can be used for the MIH in a better way. Ikenaga et al. [89] performed hyperthermia treatment using an animal with metastatic bone tumors, where ferromagnetic ceramic pins were used as the source of heat under magnetic field. Almost all the tumor cells implanted in the bone marrow were killed upon the given treatment. Ohura et al. [90] reported the magnetic and bioactive properties of SiO_2–B_2O_3–P_2O_5–CaO–Fe_2O_3 glasses and subsequently heat treated at 1,050°C to obtain glass–ceramics. Magnetite and wollastonite were the major crystalline phases formed, which are considered to be desirable for good bioactivity [91,92]. The addition of iron oxide enhanced the chemical durability of the glasses and retarded the Ca–P-rich layer during *in vitro* tests. Higher iron oxide content ($\geq$3 wt %) completely prevented the HAp layer formation. Interestingly, heat-treated glass–ceramics formed Ca–P-rich layer after 8 days of implantation. Ebisawa et al. [93] studied ferrimagnetic glass–ceramics obtained by heat treating SiO_2–CaO–FeO–Fe_2O_3 glasses. The glass–ceramic contained 36 wt% of magnetite. Due to some amount of iron oxide remaining in the glass matrix, the glass–ceramics did not show any bioactivity. However, addition of Na_2O to above composition accelerated the apatite formation of the samples in SBF. The addition of B_2O_3 retarded, while P_2O_5 accelerated, the apatite layer formation. Simultaneous addition of P_2O_5 and B_2O_3 resulted in good magnetic properties and most effective apatite layer formation. However, the mechanism of the apatite layer formation process was not clear. Jagadish et al. [94] explored the formation of bioactive glass–ceramics with calcium ferrite crystalline phase. Upon heat treatment, α-Fe_2O_3 and $CaFe_4O_7$ phases were grown within the glass matrix. The presence of iron in the glass compositions increased the chemical durability of the glass. No direct evidence was found for the formation of apatite layer on the surface of the glass–ceramics even after 30 days of immersion in SBF. Only the formation of silica-rich layer indicated the initial stage of apatite layer formation. These glass–ceramics exhibited the absorption of microwave power, indicating their possibility to be used for microwave hyperthermia. Singh et al. [42] studied the effect of glass composition on the crystallization, *in vitro* bioactivity and magnetic properties of SiO_2–Na_2O–Fe_2O_3–CaO–P_2O_5–B_2O_3 glasses. $Na_3CaSi_3O_8$ and $Na_{3-x}Fe_xPO_4$ were identified as the major crystalline phases formed in the glass–ceramics. Magnetic moments did not saturate even up to 12 kOe. Glass–ceramics exhibited low hysteresis area with random variation in coercivity with change in iron oxide content. Ca–P-rich layer on the surface of the glass–ceramics was observed after 36 days of immersion in SBF. Lee et al. [53] used higher amount of iron oxide to prepare ferrite-based glass–ceramics for hyperthermia treatments. They demonstrated by *in vitro* as well as *in vivo* tests that these glass–ceramics could kill the cancer cells locally after keeping in alternating magnetic field for 9 min. Carcinoma cells in the vicinity of ferrimagnetic material were killed; on the other hand, cells 5 cm apart from ferrimagnetic material were not affected much (Fig. 5). It shows the advantage of MIH in local heat generation without any harm to the cells lying apart. However, the researchers also recommended long-term studies to further confirm the results.

Similarly, high iron-containing calcium-silica-phosphate glasses were studied for the magnetic and structural properties. In this glass, silica was replaced by Fe_2O_3 up to 30 mol% [95]. Glass stability was higher for higher iron oxide-containing samples. Glass–ceramics were obtained by heat treatment (1,000–1,200°C) of the as-quenched glasses. Magnetite was the major phase along with hematite (non-magnetic) and maghemite. Iron ions seem to form magnetic domains even in glasses. The samples were proposed for the hyperthermia treatment of cancer; however, their bioactivity was not reported.

In ferrite-based glasses, the formation of useful crystalline phases, i.e. magnetic Fe_3O_4 and γ-Fe_2O_3, is difficult to achieve mainly due to following reasons: first, low control over Fe^{2+}/Fe^{3+} ratio, and secondly, higher stability of non-magnetic α-Fe_2O_3 phase than γ-Fe_2O_3 and Fe_3O_4 phases [80]. Formation of simultaneous presence of α-Fe_2O_3 along with Fe_3O_4 leads to reduce the heat generation tendency of the sample during hysteresis losses. Bretcanu et al. [75] came up with the adjustment of the heat generation with the chemical composition, primarily by changing iron content. They investigated the effect of crystallized Fe_3O_4 on the magnetic properties of ferrimagnetic glass–ceramics. Nanometric magnetite crystals were found in as-quenched form of the glasses. Saturation magnetization increased, while coercivity decreased with the increase in iron oxide content in the composition. Smaller crystal size was found to generate more heat during hysteresis losses than that of bigger crystallites. They concluded that by controlling the composition (ratio of iron oxides), the generated heat can be controlled. In the subsequent year, they studied the effect of preparation parameters on the crystalline phase formation and its effect on magnetic properties [64]. Excess amount (45 wt%) of iron oxide in the composition resulted in the formation of glass–ceramics during the quenching of the melt. With increase in the melting temperature, the volume fraction of magnetic phase increased and consequently the saturation magnetization also increased (Table 4). Similar observations were also made by other research groups [96]. The glasses changed from pseudo-single domain to multi-domain glass–ceramics at 1,500 °C. Possibly due to same reason, coercive field for the glasses melted at 1,550°C was lowest among the series and with smaller hysteresis area than other glasses. The samples prepared by melting process were found to exhibit higher specific losses than that of prepared by co-precipitation method.

It is still a big challenge to obtain a glass–ceramic with simultaneously good magnetic and bioactive properties. Magnetic species containing crystalline phase are required for good magnetic properties, while bioactivity decreases at the same time due to lower dissolution rate of glass–ceramics, which led to lower physiological reactions between sample and SBF. In an attempt to resolve such problems, Arcos et al. [97] introduced new biphasic material prepared by the mixture of sol-gel-derived glass for good bioactivity and a melt-quench-derived ferrimagnetic glass for magnetic properties. This biphasic material exhibited good *in vitro* bioactivity after 15 days of immersion in SBF. Due to dissolution of sol-gel glass during immersion in SBF, the saturation magnetization of the residual composition is increased. On the other hand, coercivity decreased drastically (400–250 Oe) due to stress relaxation of the crystalline part, which can affect the performance of the materials implanted for longer times. Similar biphasic materials were also studied by Ruiz-Hernandez et al. [98] and they found that apatite

Table 4
Influence of melting temperature on magnetic characteristics of SiO_2–CaO–Na_2O–P_2O_5–FeO–Fe_2O_3 glasses [64].

Melting temperature (°C)	Crystallite size (nm)	Magnetic phase (wt.%)	Saturation magnetization (emu/g)	Coercivity (Oe)	Interpolated hysteresis area±10 kOe (erg/g)	Power loss (W/g)
1,400	56	20	18.6	83	4,900	40
1,450	59	22	20.5	122	7,400	41
1,500	79	24	22.3	180	9,100	87
1,550	83	34	31.5	35	4,200	27

phase could not grow on the iron-containing glass–ceramic individually. Mixing of sol-gel glass improved the hyperthermia performance of the parent glass by modulating its coercive field. Saturation magnetization increased with increase in the glass–ceramic content. However, coercivity showed a random trend with the composition of the system. The SAR varied in accordance with the coercive field rather than with iron content. Biocompatible nature of biphasic materials was indicated by the *in vitro* experiments.

Shah et al. [99] presented another approach to optimize magnetic characteristics of the glasses. They prepared SiO_2–CaO–P_2O_5–Na_2O–Fe_2O_3–ZnO glass system followed by heat treatment at 600°C and cooled under the aligning magnetic field of 10 kOe. It helped the magnetic domains to set in their easy axis (the axis along which even small magnetic field is sufficient to reach saturation magnetization), which caused the saturation magnetization and coercivity to increase. Thus, the heat generation capacity of these field-cooled glass–ceramics enhanced as compared to that of normally cooled glass–ceramics. These glass–ceramics exhibited growth of HAp after 3 weeks of immersion in SBF [100]. It has been seen that Fe_3O_4 and calcium-based silicates are mostly formed crystalline phases in such heat-treated glass–ceramics [101]. The former is responsible mainly for magnetic properties, while the latter is reported to be bioactive in nature. Jiang et al. [102] also found such phases in silicon oxide composite containing zinc and iron oxide prepared by sol-gel method. Calorimetric measurements indicated lower specific power loss and increase in the temperature of the composite as compared to that of zinc ferrite glass–ceramics. The observations of cell culture experiment revealed that these composites promoted osteoblast proliferation more visibly than zinc ferrite glass–ceramics and HAp. Singh et al. [103] examined the glass–ceramics having finely dispersed nano-crystallites of zinc ferrite obtained after controlled heat treatment of x (ZnO, Fe_2O_3) (65-x)SiO_2 20(CaO, P_2O_5) 15Na_2O ($6 \leq x \leq 21$ mol%) glasses. The zinc ferrite and calcium sodium phosphate crystallized as the main phases. The effect of zinc iron oxide content on the magnetic properties these glass–ceramics was observed. The glass–ceramics changed from paramagnetic to fully ferrimagnetic material at higher zinc iron oxide content. The samples showed good *in vitro* bioactivity in 30 days of immersion in SBF [104]. Magnetic properties of the borate glass–ceramics consisting of Fe_2O_3 and ZnO were investigated by Pascuta et al. [105]. Glass–ceramics containing 15 mol% Fe_2O_3 exhibited ferromagnetic interactions along with superparamagnetic contribution. The characteristics of both spin glass systems and superparamagnetic were present. It is interesting that non-interacting superparamagnetic particles exhibited magnetic hysteresis even at higher temperatures. There are some other similar reports on ferrimagnetic glass–ceramics containing zinc and iron oxides with similar observations [106]. Our group reported magneto-structural as well as bioactive properties of multicomponent glass–ceramics having different concentrations of titania [107]. After heat treatment, superparamagnetic glass–ceramics were obtained. Formation of HAp was observed on the surface of samples after 42 days in SBF. Gopi et al. [108] used the ultrasonic irradiation technique to functionalize the HAp with the magnetite

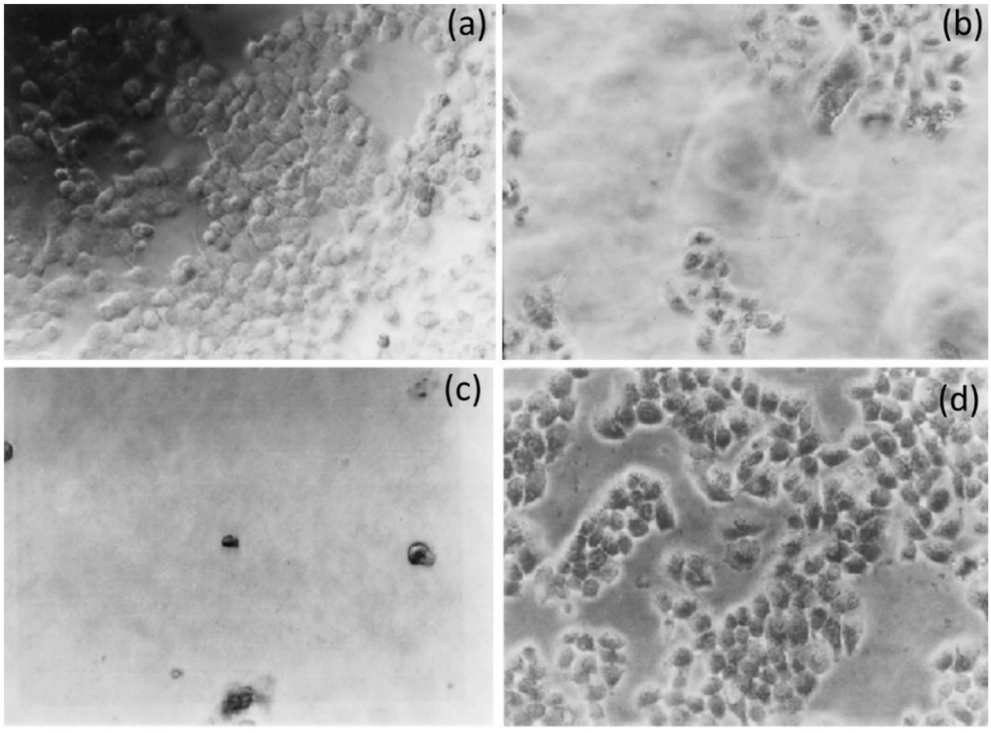

Fig. 5. Carcinoma cells, KB, around ferrimagnetic material under magnetic field after (a) 0 min (b) 5 min and (c) 9min (d) 9 min but cells are 5 cm apart from ferrimagnetic material. It is clear that with elapsing time, more and more carcinoma cells are destructed, and most of the cells have been eliminated after 9 min [53].

nanoparticles. The ultrasonic irradiation with two different frequencies of 28 and 35 kHz at the power of 150 and 320 W, respectively, was used for the synthesis purposes. The ultrasound irradiation of 35 kHz at 320 W showed the efficient diffusion of magnetic nanoparticles to the HAp host matrix, which was helpful for the formation of magnetic HAp. The samples showed superparamagnetic nature exhibiting very low coercivity (H_c). The saturation magnetization (M_s) value of magnetic HA was less than that of the magnetite nanoparticles. Sharma et al. [109] studied the biocompatibility and the magnetic properties of iron oxide/carbide nanocomposites encapsulated by carbon. Iron carbides are not bioactive in nature. However, the presence of iron oxide and the non-magnetic carbon shell improved the biocompatibility of the nanocomposite, which was confirmed by using different cell lines. Jayalekshmi et al. [110] prepared magnetic and degradable polymer/bioactive glass composite nanoparticles. The prepared composites showed soft ferrimagnetic behavior. Iron in Fe^{2+} state acted as a network modifier, while Fe^{3+} acted as an intermediate in glass. The structural and microstructural properties of the glasses/glass–ceramics with composition $34SiO_2$-(45-x)CaO–$16P_2O_5$-4.5MgO-0.5CaF_2-xFe_2O_3 have been reported by Sharma et al. [111] where iron oxide showed the network-modifying character. Apatite, hematite, wollastonite, and magnetite were the major crystalline phases formed. The further studies indicated that the glass–ceramics having 15 and 20 wt% iron oxide show good biocompatibility. CaF_2 in added to the glass compositions to control dissolution rate. It does not affect the bone bonding capability; however, fluorine ions retard the dissolution rate. Many researchers included CaF_2 in various amounts to their glass compositions for specific reasons [16,112–114]. Singh et al. [112] observed the crystallization and bioactivity of phosphosilicate glasses containing Fe_2O_3 converted to glass–ceramics at 1,050°C. The formation of nanocrystalline magnetite was strongly dependent on the initial iron oxide content. The samples exhibited better bioactivity at higher iron oxide content. It should be noted that though many reports claim that the presence of iron oxide decreases the *in vitro* bioactivity; there are some reports indicating that glasses containing Fe_2O_3 exhibit good bioactivity. Thus, there are conflicting reports in literature indicating variable influence of iron oxide on bioactivity of the glass. Manganese and its compounds are also being considered in glasses and glass–ceramics because of their importance from biological point of view. Mn^{2+}ions enhance the osteogenesis process, while their absence may cause several problems such as bone deformation, growth inhibition, or bone resorption [115]. Moreover, Mn^{2+}ions enhance the ligand-affinity of integrins, which in turn promotes the cell adhesion by mediating interactions between extracellular matrix and cell ligands [116,117]. Bigi et al. [118] reported that Mn-doped HAp coatings on etched Ti substrates exhibit better osteoblasts proliferation and activation of their metabolism. Manganese ions also have positive effects on proliferation in thin β-tricalcium phosphate film coatings on Ti substrates [119]. Thus, addition of manganese to the biomaterials may be useful for the integration of implants. Along with having good bioactive properties, manganese is of great interest for scientists because of its magnetic character. Manganese dioxide is anti-ferromagnetic in nature, but in ionic form manganese ions may give unique magnetic properties depending on their interaction between nearest neighbor ions. It leads to modify its *d*-orbital to atomic diameter ratio in such ways that tend to give positive exchange energy. In the presence of iron oxide, it forms manganese ferrite in glass compositions. Recently, many reports devoted to the application of Mn-ferrite for hyperthermia [35]. Li et al. [114] synthesized glass–ceramics with composition MgO–CaO–SiO_2–P_2O_5–CaF_2–MnO–ZnO–Fe_2O_3 and studied their *in vitro* surface bioactivity. After heat treatment at 1,200°C, apatite, fluorapatite, wollastonite, and $Zn_{0.75}Mn_{0.75}Fe_{1.5}O_4$ were the major crystalline phases present in the glass–ceramics. The bioactivity of glass–ceramics reduced with the doping of Mn–Zn ferrite, but a hydroxycarbonate apatite layer was found on the sample surface 14 days of immersion in the SBF. In another report, they prepared similar composition where they grew $MnFe_2O_4$ and Fe_3O_4 phases in the glassy matrix [120]. Along with the *in vitro* testing, cell culturing studies were also performed to observe the cell proliferation over the surface of glass–ceramics. The co-culturing experiments of samples with ROS17/2.8 cells indicated the successful attachment of the cells and good proliferation on the surface of samples. Magnetic glasses exhibited better cell affinity as compared to that parent glass matrix. The presence of manganese played important role in improving the cell affinity of the samples. Similar to iron oxides, manganese oxide may also act as an intermediate oxide because of its possibility to exist in higher oxidation states. The magnetic parameters of the glasses and glass–ceramics discussed above along with other similar reports [121–123] are given in Fig. 6.

Recently, a new class of materials called mesoporous materials with high surface area has emerged as a promising platform for cancer therapeutic applications [124]. These materials differ from microporous and macroporous materials in their pore sizes (Fig. 7). Materials having pores of size in 2–50 nm range are referred to as mesoporous materials. Among various mesoporous materials, those based on silica have been the center of research for drug delivery applications. It is because of their similar biocompatible properties as that of conventional nanocarriers, low toxicity, and better understanding of their synthesis methodologies [125]. Moreover, their surface area, pore size, and shape can be controlled by compositional changes, heat treatments, changes in synthesis methodology, etc. [126–128].

Yan et al. used sol-gel and template synthesis method to prepare highly ordered mesoporous glasses, which exhibited high bioactivity because of high surface area [129]. Anand et al. prepared ternary glasses (SiO_2–CaO–P_2O_5) via the sol-gel method using three different surfactants [130]. *In vivo* studies indicate that all the prepared samples were biocompatible, biodegradable, as well as non-toxic. Among these samples, the one prepared with ionic surfactant, i.e. hexadecyltrimethylammonium bromide (CTAB), exhibited larger surface area than those prepared using non-ionic surfactants. All the samples exhibited bone regeneration tendency.

Mesoporous glasses can carry anti-cancer drugs [131,132]. The drug is loaded on the mesoporous material basically via the solvent evaporation method or via adsorption. Mesoporous carriers are dipped in the drug solution for sufficient time. During this time, drug penetrates into the pores of the carrier mesoporous material [133]. Kaya et al. found that silica-based mesoporous bioactive glasses exhibit a great potential to deliver antibiotics than the conventionally used method to prevent infections [134]. The path of mesoporous materials containing magnetic elements can also be controlled with externally applied magnetic field in addition to production of heat because of hyperthermia effects. Thus, in addition of being an effective drug delivery system, such materials can simultaneously be employed for chemotherapy as well has hyperthermia treatment of cancer. Such materials can also be triggered by the means of pH change, magnetic field, or heat effects to release the carried anti-cancer drug in the desired site at desired time [135–138]. Silica-based mesoporous nanospheres have shown a great potential for drug loading–deloading and bioactive properties [139–143]. Incorporation of various metallic ions and their influence on the characteristics of mesoporous host glasses are well known [144–148]. Magnetic mesoporous glass scaffolds were prepared by Zhu et al. in the system Fe_3O_4–CaO–SiO_2–P_2O_5 [149]. They reported that the replacement of CaO by Fe_2O_3 in the glasses reduced the dissolution rate in physiological environments. At the same time, it improved the osteoblast cell proliferation and differentiation. The glasses were loaded with gentamicin to check the drug loading and release. It was found that the magnetic mesoporous glasses exhibited sustained drug release capabilities. The superparamagnetic nature of some of these magnetic glass scaffolds indicated their potential for hyperthermia treatment of cancer. Li et al. observed that magnetic mesoporous silica nanocarriers have favorable selectivity among healthy and cancerous cells [150]. They studied cell

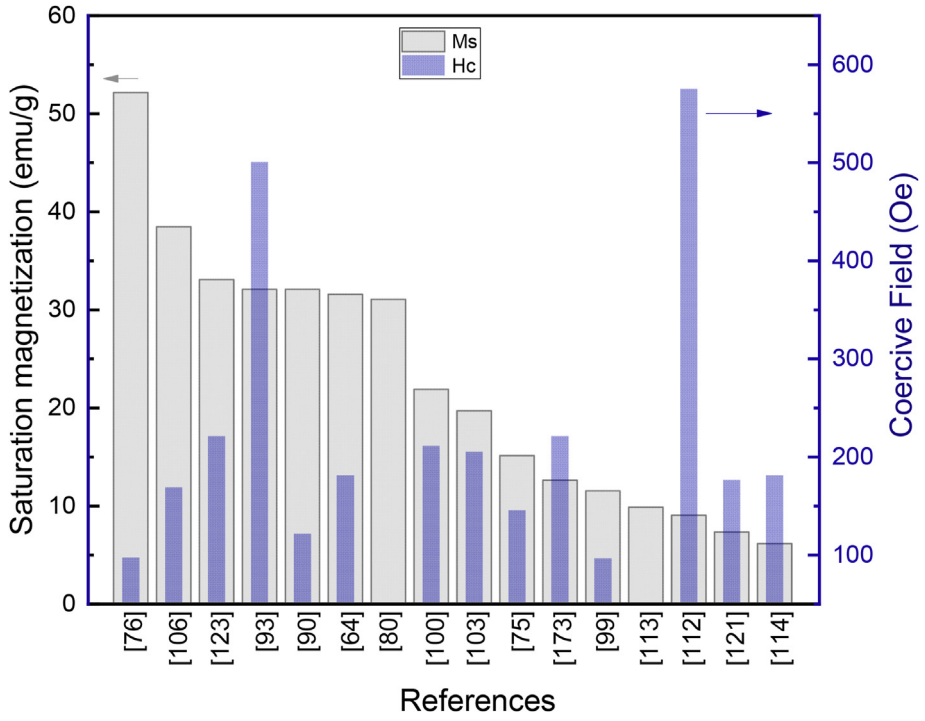

Fig. 6. Magnetic parameter of glasses reported by various research groups [64,75,76,80,90,93,99,100,103,106,112–114,121,123,173].

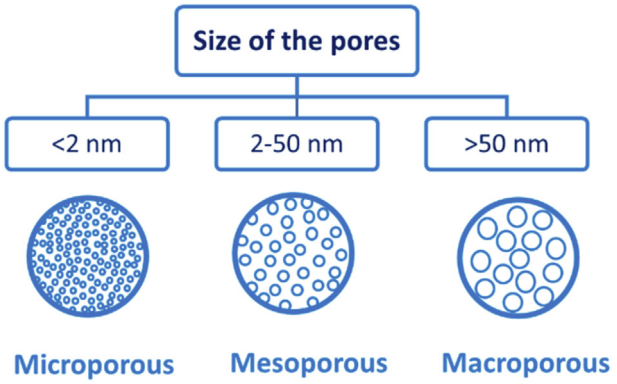

Fig. 7. Schematic representing difference between microporous, mesoporous, and macroporous materials based on their pore sizes.

viability of two kinds of cells, i.e. HT-1080 (which represented cancer cells) and NIH/3T3 (which represent normal cells). These cells were incubated for different time durations with anti-cancer drug DOX, Fe_3O_4 encapsulated with mesoporous silica nanoparticles (Fe_3O_4@MSNs) and peptide-Fe_3O_4@MSNs. It was found that for HT-1080 cells, when treated with DOX and peptide-Fe_3O_4@MSNs/DOX, the cell viability after 24 h was just 46 and 50%, respectively. On the other hand, cell viability was 80% for NIH/3T3 cells (Normal cells) treated with peptide--Fe_3O_4@MSNs/DOX (Fig. 8). It indicates the selective response of these particles toward normal and cancer cells.

Jafari et al. have reviewed structural, biocompatible, and drug loading capacity of mesoporous silica nanoparticles in their recent article [151]. They presented promising future of such materials along with the concern that such materials will take time to impact the clinical market. Similar conclusions are drawn by Albinali et al. who compared targeted drug delivery efficiency for various materials [152]. They concluded that mesoporous silica is a remarkable drug carrier. However, they found that it is challenging to bring the nano-drug carriers in clinical practices. Mass-scale synthesis of these materials, their quantitative assessment, detailed profiles in terms of toxicity, safety, immunogenicity, etc. are the major concerns to be addressed for the successful use of these materials. Kargozar et al. presented mesoporous bioactive glasses as remarkable

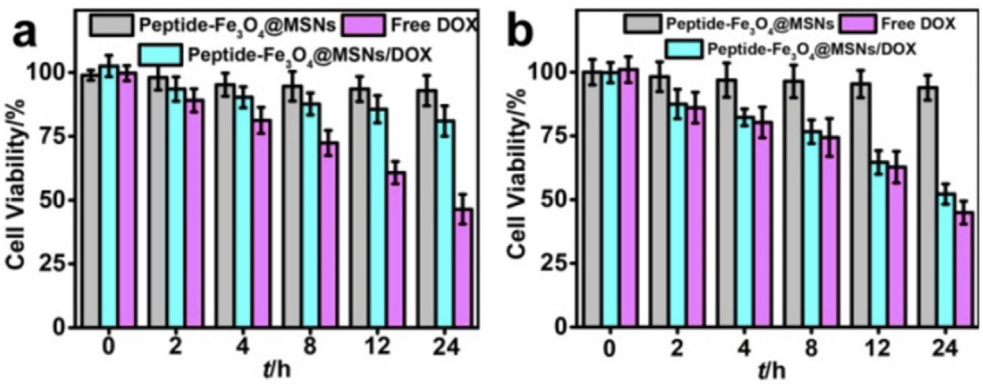

Fig. 8. Cell viability of (a) NIH/3T3 cells and (b) HT-1080 cells loaded with peptide-Fe_3O_4@MSNs, peptide-Fe_3O_4@MSNs/DOX and free DOX [150].

platforms for anti-bacterial strategies [153]. Extensive investigations on loading and release of various metal ions such as copper, cerium, silver, gallium, etc. on mesoporous glasses are compared. They identified that lengthy and expensive regulatory paths for approval of biomolecules and brittle nature of the pores are two major barriers for significant acceptance of mesoporous materials by the Food and Drug Administration (FDA).

From the above discussion, it is inferred that glasses, glass–ceramics, and mesoporous materials have a great potential for hyperthermia treatment of cancer. However, these materials have their own advantages and disadvantages over each other as summarized in Fig. 9. So far, the structural and magnetic properties of various compositions are described. Various factors affecting bioactive properties of glasses and glass–ceramics are described in the next section.

6.2. Factors affecting bioactivity of glasses/glass–ceramics

An effective thermoseed for hyperthermia treatment of bone cancer (especially) is one with appropriate magnetic properties along with good bioactivity. Thus, it becomes essential to understand the response of glasses and glass–ceramics under bio-mimicking fluids. Various steps in the formation of the HAp layer over surface of the glasses are depicted in Fig. 10. The bioactivity process depends on the interaction of particles on the surface of glass and ions of SBF in contact with glass surface. Thus, all the factors affecting the ease of release of ions from glass surface and chemical environment at glass-SBF interface will also influence the rate of HAp formation on the surface of the glass. The bioactivity of the material mainly depends on material characteristics and immersion conditions in SBF, as shown in Fig. 11. In the next subsections, dependence of the bioactivity on these factors is elaborated.

6.2.1. Composition and structure of glass

The composition of the glasses/glass–ceramics has a marked impact on the formation of HAp in SBF. Application-specific bioglasses can be obtained because of the compositional sensitivity of their properties [154]. The nature and amount of network modifiers present in the system control the dissolution behavior of the glasses/glass–ceramics, and consequently, the rate of HAp formation. The addition of compounds that improve the strength of glass network delays the HAP formation. For example, the addition of intermediates such as MgO strengthens the network and delays the apatite layer formation [155,156]. On the other hand, the addition of network modifiers such as Na_2O, CaO, etc. breaks the network and makes the network more prone to ion leaching. However, excess leaching of the alkali ions is not favorable, as it may be cytotoxic and lead to cell death [157]. In contrast to these reports, Kapoor et al. [158] observed that there is no direct correlation between the dissolution of alkali-free glasses with their network connectivity. Rather, they found that the leaching behavior of the glasses was more sensitive to the specific chemistry of the glass constituents, i.e. their ionic radii, oxidation state, etc. Hoppe et al. [159] gave a brief review on the various therapeutic inorganic ions, which could show favorable impact in bone regeneration due to their release from bioactive glasses into the physiological environments.

In the glasses with composition similar to Bioglass®, bioactivity is very sensitive to the Ca/P ratio. Natural bone content hydroxyl apatite has Ca/P ratio 1.67 [103]. The glasses with Ca/P ratio ~1.67 show better bioactivity. The Ca/P ratio affects the structural and mechanical properties of the glasses too [160]. The bioactivity of the glasses is also affected by the amount and type of network formers in the glass. Many researchers studied the bioactivity of glasses with various amounts of B_2O_3 and SiO_2. It has been found that the degradation rate can be controlled by suitably choosing B_2O_3/SiO_2 ratio in the glass [157,161,162]. In the binary calcium borate glasses, boron forms poor three-dimensional network in comparison to silicate glasses. As a result, borate glasses exhibit higher dissolution rates [163]. However, with the increase in BO_4 units, formation of the HAp layer slows down because of better network connectivity. Phosphate glasses have also been studied for their bioactivity. However, phosphate glasses suffer excessive dissolution in comparison to silicate glasses [164]. Excessively soluble glasses suffer passive dissolution in the physiological environments and cannot be used for regeneration of the tissues. A balanced glass composition is, thus, required for active resorption to occur without detrimental effect on the cell activity. The faster dissolution of the phosphate glasses can be controlled by adding some intermediate oxides. For instance, addition of up to 3 mol% Al_2O_3 has been reported to remarkably reduce the dissolution of phosphate glasses [165]. However, higher amount (≥5 mol%) of Al_2O_3 had negative effects on the bioactive nature of the glasses [166]. The chemical durability of the glasses can be improved by befittingly incorporating other ions such as Ga^{3+}, Zn^{2+}, Fe^{3+}, Ti^{4+} and Al^{3+} [167–170]. Groh et al. [171] reported that the alkaline earth/alkali ions ratio is critical to design glasses to be processed easily at high temperatures. It is reported that by increasing the calcium content, partially replacing potassium with sodium, and incorporating small amount of fluoride increases the sintering behavior of the glasses. El Batal et al.

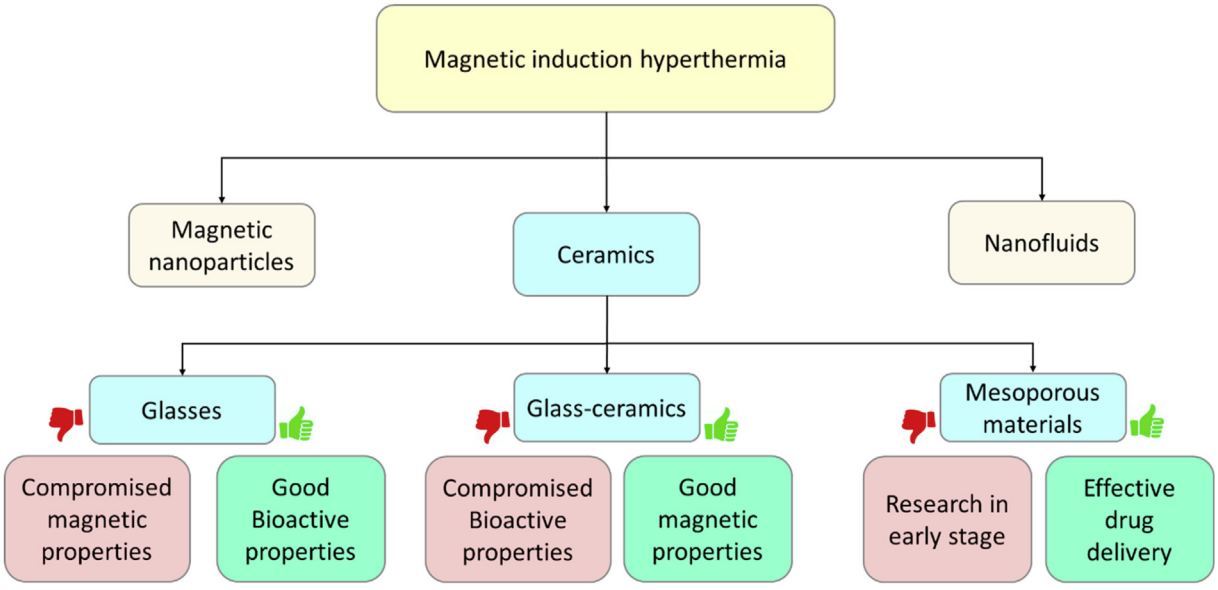

Fig. 9. Various materials used for MIH along with their advantages and disadvantages.

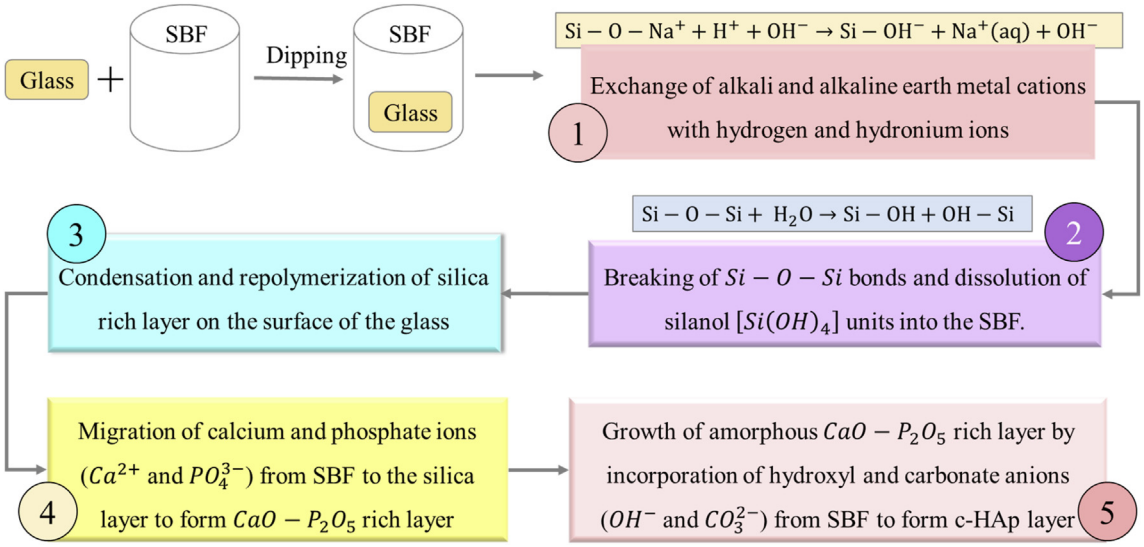

Fig. 10. Stages involved in development of the HAp layer on the glass surface immersed in SBF.

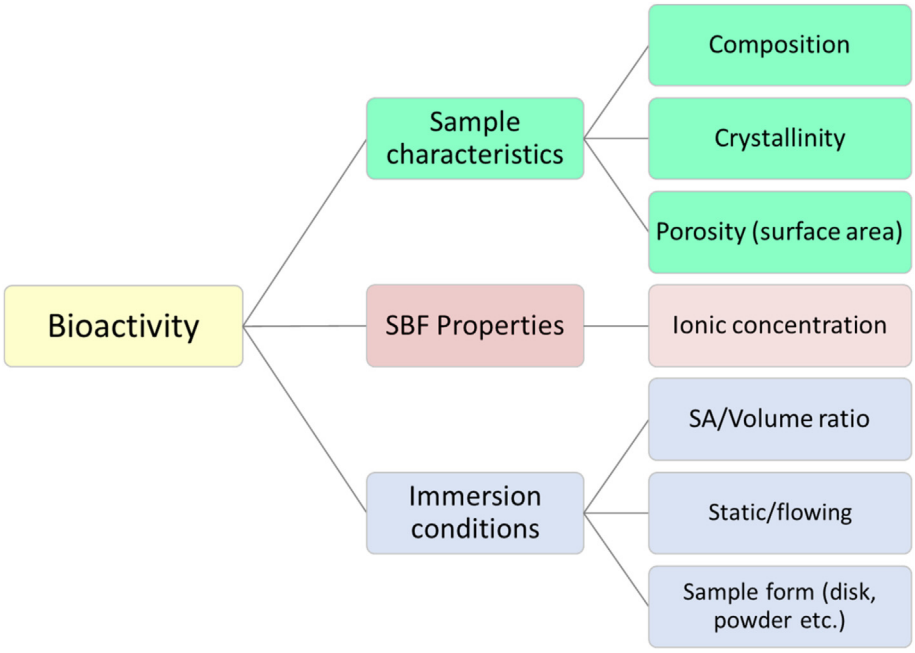

Fig. 11. Factors affecting *in vitro* bioactivity of the materials.

[172] studied the bioactivity rate of the glass–ceramics synthesized by the controlled heat treatment of phosphosilicate glasses. It was observed that sodium silicate-based crystalline phases were formed after heat treatment of the glasses, which slightly retarded the bioactivity rate of the glasses. There are many similar reports in literature where higher degree of crystallinity retarded the dissolution rate and bioactivity of the glass–ceramics [173–175]. In recent times, fluoride-based bioactive glasses gained interest, as these glasses favor the formation of the fluoro-apatite (FAp) layer when dipped in SBF, which is more stable than HAp or carbonated HAp layer [176,177]. Such glasses may be useful for dental applications. Oxygen and fluoride ions have similar ionic sizes and chemical properties. The incorporation of fluoride ions has been reported to reduce the phase separation of the glasses and improve network connectivity of the parent glass [178]. Similarly, TiO_2 is also found to enhance the bioactive and mechanical properties of glasses without harming their bioactive properties. It is lightweight and bioactive itself and has been extensively used in biomedical applications [179,180]. TiO_2 is a well-known nucleating agent and favors the devitrification of glass [65,66]. Also, glasses containing TiO_2 are observed to sinter effectively at lower temperatures as compared to TiO_2-free glasses [181]. It can be concluded that the composition of the glasses, their degree of crystallization, and type of crystalline phases affect the bioactivity. Hence, designing, preparation, and processing parameters need to be appropriately chosen to have a suitable material for biomedical applications.

6.2.2. *Role of sample's surface area*

The higher surface area to SBF volume (SA/V) or sample weight to volume (W/V) ratio provides large number of particles of the samples interacting with the SBF. The increased area for reaction leads to faster apatite layer formation rates. Therefore, same glass but different in shape, i.e. plate, particulate and powder exhibit different dissolution

rates in SBF [182]. There are ample reports on the bioactivity of the glasses and glass–ceramics using a range of SA/V or W/V ratios [183–186]. The high surface area and textural characteristics of mesoporous glasses have been reported to dominate their degradation properties and hence lead to good *in vitro* response in SBF studies [187]. Glasses with same composition but prepared via a different technique may exhibit different response to the bio-mimicking fluids [188]. The melt-derived glasses generally have non-porous surfaces with low intrinsic roughness and surface area. On the other hand, sol-gel-derived glasses have highly porous texture with large surface area [189]. The rate of formation and the thickness of the apatite layer vary with the morphological parameters, i.e. pore volume, pore size, surface area, etc. Consequently, sol-gel-derived glasses are more bioactive than the melt-quench-derived glasses [190].

Apart from the above-mentioned factors, immersion conditions such as SA/V ratio, flow or static arrangement, time duration, etc. are the factors that affect the realization of bioactivity of a glass. The reaction of the blood plasma with the implant will definitely be different to that of static conditions because, in circulating conditions, every time, fresh ions are available for reaction with the body part or implant [191,192]. However, in static solutions, the exchange reaction products are most likely to be stay in the vicinity of the implant–SBF interface, resulting in the drastic change in local pH of the solution and influencing the further reaction [185,193].

Some research groups have worked on the theoretical modeling of the bioactivity and dissolution of the bioactive glasses [194]. Computational tools such as *in-silico* studies are helpful in prediction and analysis of exchange interactions occurring at their interface of material and biological fluids and provide a useful structure–activity relationship [195–197]. Such computational techniques are time-saving, reproducible, risk-free, and can save lot of energy and cost to be invested in carrying out laboratory experiments. However, such computational results must be accompanied by the successive *in vitro*, *in vivo* and/or *in situ* experiments before clinical use.

7. Summary

MIH is a promising technique for cancer treatment with lesser side-effects as compared to other existing techniques for cancer treatment. Among various magnetic materials, glasses and glass–ceramics are fascinating materials because of their bioactive nature as well as great scope to tailor the properties as per requirement. Many of the properties of glasses and glass ceramics can be optimized via compositional and processing techniques. However, despite of lot of research carried out in the field of bioactive glasses, still there is a lot of scope of research for better understanding and knowing the true nature of different compounds to precisely design appropriate biomaterials for specific applications. Based on the literature reviewed above, the following conclusions are drawn and categorized as challenges and future scope as the following.

7.1. Challenges/gaps persisting in the field

- Despite enormous efforts dedicated to design suitable materials for hyperthermia, there are still many challenges faced in the translation of the concept to the clinical settings. One of the major challenges is the control of temperature during clinical practice. Ideally, the generated heat must not lead to temperatures exceeding 44°C because otherwise healthy cells would also be perished with excessive heat. However, the best known magnetic materials suitable for hyperthermia have sufficiently high Curie temperatures (e.g. magnetite has Tc ~577°C). A high Curie temperature allows the material to keep on heating up in alternating magnetic fields until the Curie temperature is reached. This makes temperature out of control at the clinical level. The glass–ceramics with a Curie temperature ~44°C need to be designed so that beyond this temperature, the material becomes paramagnetic, and no further heating is possible due to any hysteresis losses.
- It is desirable to design glass–ceramics that can generate sufficient heat with minimum dosage. It can be achieved if glass–ceramic has sufficient hysteresis area with high magnetic saturation. For hyperthermia, iron must crystallize as magnetite (Fe_3O_4, with M_s~92 emu g^{-1} in bulk form) or maghemite (γ-Fe_2O_3 with M_s~76 emu g^{-1} in the bulk form). A major challenge in optimizing the magnetic properties of bioactive glasses is the phase transformation during heat treatment. The glass–ceramic must be heat treated in order to improve volume fraction of magnetic content and consequently getting high magnetic saturation. However, magnetically important phases have strong chances to convert to other crystalline phases with no use. For example, magnetite changes to hematite during phase separation, which decreases the heat producing efficiency of the glass–ceramic.
- Available magnetic materials with non-toxic and suitable biocompatible properties are limited. Fe_2O_3 is highly used oxide among the limited range of materials. As mentioned above, higher amount of crystallized magnetic content is desired for better magnetic properties. However, in the melt-quench technique, only a small fraction (<5 mol%) of Fe_2O_3 takes part in the glass formation in usual. More studies are required to maximize the solubility of Fe_2O_3 using a chemical route like sol-gel and sputtering technique, and also, novel compositions need to be found to accommodate more Fe_2O_3 into the glass matrix.
- For biomedical reasons, there is a strict limitation on values of H and f so that $H \times f$ should be less than 5×10^9 [38]. In such circumstances, the efficiency of the treatment has to rely largely on the thermal conversion efficiency of the thermoseeds. Thus, magnetic material must invoke sufficient heat to raise the temperatures of surrounding up to desired values (~44°C). For this to happen, suitable magnetic phase must be crystallized to high enough volume fraction. Here, glass–ceramics meet another challenge, which is the balance between magnetic and bioactive properties. Lower magnetic content may fail to generate desired heat, while increasing magnetic content may hamper the bioactivity of the glass. Heat-treatment parameters (temperature, duration, heating rate, environment) and composition of glass–ceramics must be selected in such a way to achieve bulk and fast crystallization in the glass. This way, the retarded bioactivity due to surface crystallization can be avoided.
- As per the biocompatibility evaluation is concerned, only few reports appeared on simultaneous *in vivo* and *in vitro* studies of magnetic glasses/glass–ceramics. Under such circumstances, it is quite difficult to assess/compare performances of various glasses and glass–ceramics. For better understanding of the bioactive response of glasses and glass–ceramics, simultaneous *in vitro* and *in vivo* studies must be performed on large number of compositions in various circumstances such as in different chemical/biological environments.

7.2. Future scope

To meet the required material properties for hyperthermia treatment of cancer, new compositions of glasses/glass–ceramics must be designed with better blend of magnetic as well as bioactive properties.

- Mesoporous bioactive glasses can be potential candidates for combined hyperthermia and chemotherapy. More work has to be done in order to fully explore the potential of these fascinating materials. Synthesis methods need to be devised for mass-scale production of these materials. Also, various aspects of these mesoporous materials such as their toxicity, immunogenicity, biosafety, etc. need to be quantified.
- The binding nature of initial bioactive glass compositions was limited to the natural bones only. With the advent of new compositions of bioactive glasses, which are capable of binding with soft tissues too, the applications of hyperthermia treatment can be extended beyond

bone cancer. There is much scope of research in such kind of glass compositions to explore and optimize their properties to match application needs.

- Another perspective concerned with hyperthermia treatment is to develop bioresorbable magnetic bioglasses. These types of materials may be useful to avoid any need of surgery for removal of implanted material after successful treatment.
- Different approaches to synthesize glasses such as biphasic materials must be explored on wide range of compositions.
- The clinical settings have limits due to biomedical reasons. The efficiency of hyperthermia is, thus, dependent on the thermal conversion efficiency of the thermoseeds. Materials must be tested within clinically possible set of magnetic field parameters ($H \times f < 5 \times 10^9$). The magnetic material targeted for hyperthermia applications must be able to heat up to 44°C with these magnetic field settings.
- Efforts must be dedicated to produce biocompatible glass–ceramics with a low Curie temperature close to 44°C. Some ceramic materials such as manganates have been reported to have their Curie temperatures close to the required range. Glass–ceramics incorporating such phases in their compositions can be explored to combine the bioactive nature of glass–ceramics and suitable magnetic properties of manganates.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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