"Those who cannot be cured by medicine can be cured by surgery. Those who cannot be cured by surgery can be cured by heat. Those who cannot be cured by heat are probably incurable"

Hippocrates -470-377 B.C. The Father of Medicine
1.1. Introduction

Cancer is a disease, which is one of the leading causes of death in the present world. Even five years into the 21st millennium, cancer continues to torment humanity as the second leading cause of death with 12.7 million newly diagnosed cases worldwide in the year 2008 alone, which equates to around 188 cases for every 1,00,000 people. Out of the 12.7 million cases of cancer, 6.6 million cases were in men and in women it is about 6.0 million. This number is expected to increase upto 21 million by 2030 [1]. Despite new discoveries of drugs and treatment combinations as evidenced by reports of close to 200,000 experimental studies on mice, two million scientific publications and an annual spending of around 15 billion US dollars worldwide, the deaths due to cancer did not change in the past five to six decades [2]. Therefore, there is a still strong need of a model shift in the approach to cancer diagnosis and therapy.

Till today, cancer treatments have been performed on the basis of clinical and pathologic staging that is determined using morphologic diagnostic tools, such as radiological and histopathological examinations and these are conventional techniques. The most common cancer treatments are restricted to chemotherapy, radiation and surgery [3]. Chemotherapy is a major therapeutic approach for the treatment of localized and metastasized cancers. Chemotherapy involves in the treatment of cancer by the injection of free drug into the blood stream. The selective increase in tumor tissue uptake of anticancer agents would be of great interest in cancer chemotherapy since anticancer drugs are not specific to cancer cells. Cancer therapy is still far from optimal because the drugs used for chemotherapy are strong and thus they kill any cell in the body that is growing fast; no matter what it is a cancer cell or a healthy cell. Current diagnostic and prognostic classifications are insufficient to make predictions for successful treatment and patient outcome. Thus, there is an urgent need and major thrust to develop new and innovative technologies that could destroy the complete tumour and help to determine whether a tumor has been completely removed.

In order to improve the Radiation and Chemotherapy use of localized heating along with these therapies has been reported. The treatment which makes localized heating of
cancer tumour is called hyperthermia treatment. As a result the heat treatment of cancer gained a lot of attention not only as a modality by itself, but it was also demonstrated that it gives significant results when used in combination with other modalities such as radiotherapy and chemotherapy. Thus, the preferred hyperthermia system will need to have the ability to localize the heating at the tumor site without generating a spot overheating as well as ability to couple with other modalities of treatment.

Recently magnetic nanoparticles (MNPs) have been studied for localized heating. Cancer hyperthermia treatment includes rise in temperature of tumour in between 42-46 °C. The cancerous cells are completely killed at this temperature, where normal cells are alive. Self-control heating of the particles by limiting their Curie temperature provides a safeguard against cell death and can be utilized in the hyperthermia treatment [4-6]. Magnetic fluid hyperthermia (MFH) for cancer treatment involves injecting a fluid containing magnetic nanoparticles directly into tumors. When MNPs are placed in an alternating magnetic field with frequencies similar to those of FM radio signals, these MNPs can generate heat and destroy the tumors. This is a minimally insidious procedure and distinct from conventional laser, microwave, and ultrasound hyperthermia, which prevents unnecessary heating of surrounding healthy tissues as the localized MNPs only absorb the magnetic field. This integrated system of self controlled magnetic hyperthermia therapy has a great potential in cancer treatment. However, the research on different components of the system is still evolving.

1.2. An overview on cancer

Cancer is a group of diseases of higher multicellular organisms. It is depicted by alterations in the expression of multiple genes, leading to dysregulation of the normal cellular program for cell division and cell differentiation. This results into an imbalance of cell replication and cell death that favors growth of a tumor cell population. While cancer is clearly associated with an increase in cell number, change in the mechanisms regulating new cell birth, or cell proliferation. Decreased rates of cell death or apoptosis are now known to contribute to certain types of cancer. Cancer is distinct from other tumor-forming processes because of its ability to invade surrounding tissues. Typically, tumor cells differ from normal cells in that they exhibit uncontrolled growth. Because of features that distinguish tumor from normal cells may be key to understand neoplastic cell behavior and may ultimately lead
to therapies that can target tumor cells [5]. These orderly processes help to keep the body healthy. In many times cells keep dividing when new cells are not needed. These extra cells form an accumulation of tissue at the same place of organ, called a growth or tumor. Tumors are mainly of two types benign or malignant tumor.

![Characteristics of Cancer and Normal Cells](image)

**Figure 1.1.** Characteristic features of normal and cancerous cells.

(a) **Benign tumors** are not cancerous tumors. They can be frequently removed and, in most cases, they can remove permanently. Cells or tissues from benign tumors do not spread to other parts of the body. Most important, benign tumors are infrequently a threat to life.

(b) **Malignant tumors** are cancerous tumors. Cells in these tumors are abnormal, the division of cells is uncontrolled or not in order. They can occupy and damage nearby tissues and organs. Also, cancer cells can rupture away from a malignant tumor and enter the bloodstream or the lymphatic system. This is how cancer spreads from original cancer site to form new tumors in other organs.

Figure 1.1 represents the difference between normal and cancer cells. In the normal cells mitoses is negligible, however, mitosis is predominant in cancerous cells. From the study it is observed that, cancerous cells losses contact inhibition, increases growth factor secretion, increases oncogene expression and losses tumour suppression genes. In the normal cells oncogene expression is rare, growth factor secretion is rare and tumour suppressor genes are present.
The data published for the year 2008 by International Agency for Research on Cancer and World Health Organization (WHO), following are the most commonly diagnosed cancers worldwide in male and females.

(i) Lung Cancer  
(ii) Breast cancer  
(iii) Colorectal cancer  
(iv) Stomach cancer  
(v) Prostate cancer  
(vi) Liver cancer  
(vii) Cervical cancer  
(viii) Esophageal cancer

The lung, stomach and liver cancers are common in male and female. In the year 2008 WHO formulated a project named GLOBOCAN to estimate the data for deaths and new cases of cancer patients. The aim of the project is to provide contemporary estimates of the incidence of, mortality, prevalence and disability-adjusted life years from main type of cancers, at national level, for 184 countries of the world. The data published by GLOBOCAN is presented in table no. 1 and 2 for males and females, respectively.
Table 1.1. Estimated new cancer cases and deaths worldwide for leading cancer sites by level of economic development, 2008 (in Male). Source: GLOBOCAN 2008 [7].

<table>
<thead>
<tr>
<th>Types of cancer</th>
<th>Worldwide</th>
<th>Developed countries</th>
<th>Developing countries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated deaths</td>
<td>Estimated new cases</td>
<td>Estimated deaths</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>9,51,000</td>
<td>10,95,200</td>
<td>4,12,000</td>
</tr>
<tr>
<td>Prostate</td>
<td>4,78,300</td>
<td>9,03,500</td>
<td>1,36,500</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>4,64,400</td>
<td>6,63,600</td>
<td>1,66,200</td>
</tr>
<tr>
<td>Stomach</td>
<td>3,20,600</td>
<td>6,40,600</td>
<td>1,10,900</td>
</tr>
<tr>
<td>Liver</td>
<td>2,76,100</td>
<td>5,22,400</td>
<td>75,400</td>
</tr>
<tr>
<td>Esophagus</td>
<td>2,58,400</td>
<td>3,26,600</td>
<td>53,100</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>1,43,700</td>
<td>2,97,300</td>
<td>55,400</td>
</tr>
<tr>
<td>Non-hodgkin lymphoma</td>
<td>1,38,100</td>
<td>1,99,600</td>
<td>-----</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1,12,300</td>
<td>1,95,900</td>
<td>48,600</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>1,09,500</td>
<td>1,70,900</td>
<td>-----</td>
</tr>
<tr>
<td>All sites but skin</td>
<td>42,25,700</td>
<td>66,29,100</td>
<td>15,28,200</td>
</tr>
</tbody>
</table>

Table 1.2. Estimated new cancer cases and deaths worldwide for leading cancer sites by level of economic development, 2008 (in Female). Source: GLOBOCAN 2008 [7].

<table>
<thead>
<tr>
<th>Types of cancer</th>
<th>Worldwide</th>
<th>Developed countries</th>
<th>Developing countries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated deaths</td>
<td>Estimated new cases</td>
<td>Estimated deaths</td>
</tr>
<tr>
<td>Breast</td>
<td>4,58,400</td>
<td>13,83,500</td>
<td>1,89,500</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>2,88,100</td>
<td>5,70,100</td>
<td>1,53,900</td>
</tr>
<tr>
<td>Cervix Uteri</td>
<td>2,75,100</td>
<td>5,29,800</td>
<td>-----</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>4,27,400</td>
<td>5,13,600</td>
<td>1,88,400</td>
</tr>
<tr>
<td>Stomach</td>
<td>2,73,600</td>
<td>3,49,600</td>
<td>70,800</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>-----</td>
<td>2,87,100</td>
<td>33,200</td>
</tr>
<tr>
<td>Liver</td>
<td>2,17,600</td>
<td>2,25,900</td>
<td>39,900</td>
</tr>
<tr>
<td>Ovary</td>
<td>1,40,200</td>
<td>2,25,500</td>
<td>64,500</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1,30,700</td>
<td>2,10,200</td>
<td>-----</td>
</tr>
<tr>
<td>Non-hodgkin lymphoma</td>
<td>-----</td>
<td>1,56,300</td>
<td>33,500</td>
</tr>
<tr>
<td>All sites but skin</td>
<td>33,45,800</td>
<td>60,38,400</td>
<td>12,23,200</td>
</tr>
</tbody>
</table>

The data summarized in table 1 and 2 suggest that Lung & bronchus cancer is the major type of cancer in male and female. Prostate, Colon and rectum, Stomach and Liver cancers are the other type’s cancer, which is a major reason of deaths in male. Breast cancer
is a predominant over other types of cancers in female. Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females. Lung cancer is the leading cancer site in males. At the moment Breast cancer is also the leading cause of cancer death among females in economically developing countries. As compared to developed countries deaths due to cancer is higher in developing countries for male and female. This may due to lack of advanced medical facilities available and cost of the cancer treatment in developing countries. From the table 1 and 2 it is observed that the estimated new cases are becomes higher than the estimated deaths. The conclusion of above data is that the cancer is spreading very fast over its previous years. This may due to the change in the lifestyle of people, increased environmental pollution in both types of countries. To reduce the percentage of cancer, development in new medical treatments is necessary. In the following section overview on old and newly coming cancer treatments are discussed in detail.

1.3. An overview on cancer treatments

The treatments of cancers are classified in to conventional and nonconventional therapies. Currently, cancer treated with conventional therapies like, surgery, chemotherapy, radiation therapy hormonal therapy, and immunotherapy. They are used alone or in combination depending on the type of cancer and the stage of the disease. Surgery is the oldest and still most effective mainstream treatment for solid tumors, and is curative in several cases of localized cancer in which all or nearly all cancerous tissue can be removed. The aim of surgery is to remove as much tumor as possible without disabling the patient, so that the other treatments (chemotherapy and radiotherapy) have a greater chance of successfully eliminating the remaining tumor cells [8]. The hyperthermia treatment is a nonconventional therapy and currently it is used with combination of conventional therapies. The graphical representation of cancer treatments are presented in the figure 1.2.
Figure 1.2. Graphical representation of treatments used for treating the cancer.

Among the conventional treatments used for curing the cancer surgery, chemotherapy and radiation therapy are preferred on the basis of types and stage of cancer. The hormonal, monoclonal and radioactive material therapy is rarely used in combination with chemotherapy. The description on surgery, chemotherapy and radiation therapy used for cancer are as follows.

(a) Surgery

Surgery is a local treatment used to cure cancer. It is used to attempt a cure or to alleviate symptoms. At the moment surgery is effective for lung cancer. Lung cancer that has not spread can potentially be cured with surgery, which is often combined with chemotherapy and/or radiotherapy. Lobectomy is the removal (resection) of the lobe of the lung affected by cancer. This is the most common surgery performed for lung cancer. Pneumonectomy is the surgical elimination of the entire lung affected by cancer. All surgical procedures cause postoperative pain. The austerity of the pain depends on the surgical
technique used to perform the surgery the extent of the procedure, and your personal sensitivity to pain. Immediately after surgery, strong pain medicines are often needed.

(b) Chemotherapy

The use of chemotherapy to treat cancer began at the start of the 20th century for potential development in new drugs as well as for targeted treatments. Chemotherapy involves using any type of chemicals to kill cancer cell. Most chemotherapy agents target at fast dividing cells and impair cell mitosis. Since cancer cells divide much faster than most normal cells, they are more sensitive to chemotherapy agents because cell division events are more likely to happen at any time. Chemotherapy is administered with a variety of treatment schedules designed according to the intent and responsiveness of therapy. Cancer chemotherapy is *systemic therapy*, meaning the entire body is exposed to the treatment. Chemotherapy is used when there is clear evidence the cancer has spread beyond the original tumor or if there is reason to suspect there may be undetectable cancer cells (*micrometastasis*) in the body.

Many chemotherapy drugs must be given directly into the blood stream by an intravenous (IV) line. This route of administration (how a drug is given) is necessary for chemotherapy drugs that would be broken down and inactivated by the digestive processes of the stomach and intestines. Some chemotherapy drugs can be taken by mouth without any loss of anti-cancer activity. Chemotherapy can cause a wide range of side-effects. Several side-effects are related to the fact that these drugs do not selectively destroy cancer cells, but interfere with the processes of any rapidly dividing cell. Therefore, tissues in the body that normally grow and divide rapidly can be damaged as a side-effect of chemotherapy.

(c) Radiation therapy

Radiation therapy uses particular equipment to deliver high doses of radiation to the cancer cells. The radiation damages cancer cells and causes them to die. Radiation therapy damage the DNA molecule inside the cancer cell and it keeps the cell from growing, dividing, and spreading. The normal cells nearby the tumour can be affected by radiation. Unlike chemotherapy, which exposes the whole body to anticancer drugs, radiation therapy is usually a side specific treatment. It is aimed at and affects only the part of the body being treated, i.e. tumour. The target of radiation treatment is to damage as many cancer cells as possible without damage of nearby healthy tissue. Some radiation treatments involve radioactive substances that are given in to vein or by oral administration. In both cases, the
radiation does travel throughout the body. The treatment planning involves the radioactive substance collects in the area of the tumor so that there is little effect on the rest of the body. The goal of radiotherapy used in this way is to cure the cancer. Adjuvant radiotherapy can be used to: shrink a tumor before surgery increase the response of cancer cells to treatment by administering it along with or following chemotherapy destroy any remaining cancer cells that may be left behind after cancer surgery [9, 10].

Till today the treatments mentioned above are used to treat cancer efficiently. However, all of these techniques have the major side-effects on cancer patients. Some of the most common include: bleeding, hair loss, high pain and infection. The briefing on side-effects of surgery, chemotherapy and radiation therapy is represented in figure 1.3.

![Side effects of Cancer treatments](image)

**Figure 1.3.** Side-effects of conventional cancer treatments used to treat the cancer.
1.4. Hyperthermia treatment for cancer

By definition, hyperthermia is an elevation in the temperature of either the entire body or a region of it to above the normal body temperature of 37 °C. Increasing the temperature of tissue results in a number of physical and physiological changes which depend on the magnitude of the temperature increase as well as the length of time for which the elevated temperature is maintained. These changes provide several routes for the application of hyperthermia as part of the treatment of cancer. Hyperthermia produces an enhancement of apoptosis within tissue when the temperature is increased to above approximately 42 °C for periods of 30 minutes or more. The value of this threshold temperature may vary depending on the tissue type, but the cytotoxicity changes sharply as the threshold is exceeded, with cytotoxic and non-cytotoxic temperatures differing by as little as 0.2 °C. Hyperthermia produces an enhancement of necrosis when tissue is heated to temperatures 46 °C for periods of 30 minutes or more. The required time of heating decreases with increasing temperature, and when temperatures of about 60 °C are applied coagulative necrosis occurs within 1-2 seconds [11].

In line with current trends for multimodality treatments, hyperthermia is also applied in a three modality option for cervical cancer, where the potential of radiotherapy + chemotherapy + hyperthermia is tested in phase III settings against radiotherapy + hyperthermia. Extensive biological research has shown that hyperthermia is one of the most modifiers of radiation known today. The main mechanism for cell death by hyperthermia is probably protein denaturation, observed at temperatures > 40 °C, which leads to among other things, alterations in multi-molecular structures like cytoskeleton and membranes, and changes in enzyme complexes for DNA synthesis and repair. Most normal tissues are undamaged by treatment for 1h at a temperature of up to 44 °C [12].

1.4.1. Types of hyperthermia treatments

The classification of hyperthermia treatments for cancer is based on the position tumour and type of the cancer. In general, local, whole body, regional and extracellular is the main types of hyperthermia treatments. The further sub classification of each hyperthermia treatment is graphically presented in the figure 1.4.
**Figure 1.4.** Classification of hyperthermia treatments used for treating the cancer.

In local hyperthermia, the aim is to increase mainly the tumor temperature while sparing surrounding normal tissue, using either external or interstitial modalities. Heat is applied to a small area, such as a tumor, using various techniques that can deliver energy to heat the tumor. Local hyperthermia treatment is a well-established cancer treatment method with a simple basic principle, namely, if a rise in temperature to 42 °C can be obtained for one hour within a cancer tumor, the cancer cells will be destroyed. The success of hyperthermia as a treatment modality lies in the localization of the heat inside the cancerous tumor without causing thermal damage to surrounding normal tissues. The local hyperthermia treatment is again divided into three types, external local hyperthermia, intraluminal or endocavitary hyperthermia, and interstitial hyperthermia.

Whole-body hyperthermia is used to treat metastatic cancer that has spread throughout the body. This can be accomplished by several techniques that raise the body temperature to 107–108 °F, including the use of thermal chambers (similar to large incubators) or hot water blankets. It is used to treat metastatic cancer that has spread throughout the body. To ensure that the desired temperature is reached, but not exceeded, the temperature of the tumor and surrounding tissue is monitored throughout hyperthermia treatment.
treatment. Heating can be accomplished with thermal conduction heat sources such as immersion in heated fluids, heated air, wrapping the patient in heated blankets, or using thermal chambers (similar to large incubators) [14].

Regional heating is indicated for patients with locally advanced deep-seated tumors such as those in the pelvis or abdomen. The application of regional hyperthermia is, however, more complex than local heating, particularly because of the wide variation in physical and physiological properties of body tissues. It requires more sophisticated planning, thermometry, and quality assurance. In regional hyperthermia, various approaches may be used to heat large areas of tissue, such as a body cavity, organ, or limb. Deep regional, regional perfusion and peritoneal perfusion are the main types of regional hyperthermia.

The main idea of the extracellular hyperthermia (or electrohyperthermia, oncothermia) is to heat up the targeted tissue by means of electric field, keeping the energy absorption within the extracellular liquid. Extracellular hyperthermia is devoted to enhancing the efficiency of conventional hyperthermia by additional, nonequilibrium thermal effects with the aim of suppressing the existing disadvantages of the classical thermal treatments. Extracellular hyperthermia is based on a capacitive coupled energy transfer applied at a frequency that is primarily absorbed in the extracellular matrix due to its inability to penetrate the cell membrane. Since the energy absorption for these effects is more significant than the temperature, it is important to characterize the hyperthermia by thermal dose and not by temperature. Thermal dose changes many energetic processes in the tissue and in their physiology. Most of the desired changes (structural and chemical) involve energy consumption.

1.4.2. Hyperthermia and Chemotherapy

The hyperthermia can improve the efficacy of chemotherapy: the three most important of these concern [i] its role as a chemo-sensitising agent, [ii] the role it can play in the delivery of drugs and [iii] its impact on drug resistance. Firstly, hyperthermia can act as a sensitising agent, improving the efficacy of drugs in much the same way as it acts as a radio-sensitizer, since the effects caused by chemotherapeutic drugs are similar to those produced by ionising radiation. Both systemic and localized hyperthermia can be of benefit when applied in conjunction with chemotherapy. Localized heating which enhances the sensitivity only within the tumour, is often particularly advantageous since chemotherapy is generally
delivered systemically. The second way in which hyperthermia can be benefit chemotherapy is drug delivery mechanism. Malignant tumours can be poorly perfused, and this can impede chemotherapeutic treatment since drug delivery comes via the blood. One of the primary physiological responses to mild hyperthermia (at temperatures 42 °C) is an increase in perfusion as the body attempts to regulate the temperature of the heated region. Localised hyperthermia is therefore, beneficial since it increases the perfusion within the tumour, and therefore also increases the drug uptake relative to the normothermal tissue.

1.4.3. Hyperthermia and Radiotherapy

Combined hyperthermia and radiation offers potential clinical advantages for treatment of tumors. Importantly, the synergy between radiation and heat is highly dependent on the order of application and highest when given simultaneously. It has been reported by many clinical trials that hyperthermia therapy has been shown to substantially improve local control of cancer, tumor clinical response, and survival rates when added to radiation treatments. It yields considerable therapeutic gain compared to radiation alone in treating various cancerous tumors. The synergistic effects of hyperthermia combined with radiation have been investigated and reported to yield higher complete and durable responses than radiation alone in superficial tumors. Hyperthermia may cause an increased blood flow, this can results into improvement in tissue oxygenation, which then consequences in a temporally increased radiosensitivity. Biologically, hyperthermia has special types of interactions with radiation. Primarily heat has a radiosensitizing effect and this is most prominent with simultaneous application. However, it results into same magnitude in both tumor and normal tissue. This will not improve the therapeutic ratio unless the tumor is heated to a higher temperature than the normal tissue. In the second case hyperthermia exhibits a direct cytotoxic effect, and a sensible heat treatment alone can almost selectively destroy tumor cells in a nutritionally removed chronically hypoxic and acidic environment. Since such cells are the most radioresistant, a minor radiation dose is needed to control the remaining more radiosensitive cells [13].
1.4.4. Hyperthermia and Radiochemotherapy

Radiochemotherapy is a widely used means of treatment for patients suffering from primary, locally advanced, or periodic rectal cancer. The efficacy of treatment can be enhanced by additional application of regional hyperthermia to this conventional therapy regime. Several scientists conducted investigations on the effectiveness of hyperthermia combined with radiochemotherapy in the treatment of cancer [14].

1.4.5. Hyperthermia and Gene Therapy

Gene therapy may be defined as the treatment in which genetic material is introduced in a cell to enhance or modify its function. This result in the manufacture of protein(s) that are either directly therapeutic or interact with other substances to exert a therapeutic effect. To treat the cancer effectively, the genetic material inside the body must exert its effect only on tumor or tumor-associated cells. The normal cells must be safe from this genetic material. The genetic material also must not eliminate the body’s immune response that is so critical in fighting cancer. In order to achieve these goals, an approach must be developed that combines fever-range WBH with a gene that only affects tumor cells spliced with additional genetic material designed to cause the suicide gene to be expressed predominantly in tumor cells. Hyperthermia is expected to help in opening the pores of tumor blood vessels so that more liposomes reach the tumors and deliver their DNA content to tumor cells. It also increases the amount of protein created by the incorporated DNA and boosts the immune system so that it sends specialized cells into the tumors to help kill them [15].

1.5. Hyperthermia using magnetic nanoparticles

Magnetic nanoparticles (MNPs) have been extensively used for generating heat for magnetic hyperthermia treatment (MHT) as a promising tool for therapeutics, particularly for cancer. With this, heat may be applied to tumor tissues with no systemic and side-effects compared to chemotherapy and radiotherapy. In this application, MNPs are used as effective heating mediator in the presence of an alternating current (AC) magnetic field. The possibility of treating cancer by artificially induced hyperthermia has led to the development of many different devices designed to heat malignant cells while sparing surrounding healthy tissue [16]. Experimental investigations of the application of magnetic materials for hyperthermia date back to 1957 when R. K. Gilchrist heated various tissue samples with
20–100 nm size particles of $\gamma$-Fe$_2$O$_3$ exposed to a 1.2 MHz magnetic field. The cancerous cell death mechanism by using MNPs with application of ac magnetic field is represented in figure 1.5. Figure represents the utilization of AC magnetic field for cancer treatment. Before injecting the MNPs at tumour site, there is no influence of applied field on tumour tissues. When field is applied along with MNPs the nonequilibrium steady structure of applied field is formed in the tumour and cancerous cells are killed.

![Diagram](image)

**Figure 1.5.** Cancerous cell death mechanism based on MNPs with the application of alternating magnetic field.

There have been numerous publications describing a variety of schemes using different types of magnetic materials, field strengths, field frequencies, methods of encapsulation and delivery of the particles for the possible application in hyperthermia treatment [17-44]. In broad terms, the procedure involves dispersing magnetic particles throughout the target tissue, and subsequently applying an AC magnetic field of sufficient strength and frequency to generate the heat from MNPs. This heat conducts into immediate surrounding diseased tissue, if the temperature can be maintained above the therapeutic threshold of 42 °C for 30 min or more, the cancer cells are destroyed. Whereas the majority of hyperthermia devices are restricted in their utility because of unacceptable coincidental heating of healthy tissue, magnetic particle hyperthermia is attractive because it offers a way to ensure only the intended target tissue is heated. The heating capacity of a magnetic material is quantified through the specific absorption rate (SAR), defined as the amount of
energy converted into heat in the unit time and mass. Many efforts have been devoted in the last 20 years to improve hyperthermia techniques for clinical applications. Development in the area of nanotechnology has contributed to the progress of magnetic fluid hyperthermia. Hyperthermia is a promising technique for cancer treatment because of ease in targeting the cancerous tissue and hence having fewer side-effects than chemotherapy and radiotherapy. It is remarkable that the results of current/ongoing clinical trials show significant reduction in side-effects.

1.5.1. Requirements of magnetic fluid hyperthermia

The use of hyperthermia to treat cancer has been a recent topic of research. Magnetic fluid hyperthermia offers particularly promising capabilities for treating several types of cancer. Following are the some requirements of hyperthermia treatment by using magnetic nanoparticles.

(a) Regional hyperthermia treatments can efficiently heat tumors. Nevertheless, healthy tissues also absorb ultrasound and microwave energy. Heating healthy tissues between the external energy source and tumor is therefore, unavoidable. Temperatures above 42 °C in healthy tissues can be burned. Necessarily, temperatures must be closely monitored during hyperthermia cancer treatment [49].

(b) In any case, the amount of nanoparticles injected in the tumour site should be as small as possible. In order to reach the therapy temperature with minimum particle concentration in tissue the specific heating power of the magnetic nanoparticles in magnetic AC fields should be as high as possible. There are numbers of known magnetic materials which, however, for biomedical applications are strongly restricted by the demand of biocompatibility [50].

(c) The fluid which consists of MNPs must have a neutral pH and physiological salinity. The particles should remain evenly dispersed throughout the fluid, and must therefore be small enough to avoid precipitation due to gravitational forces. In addition, the magnetic material should not be toxic, i.e. biocompatible.

The requirements of magnetic fluid hyperthermia mentioned above are discussed in brief in the following sections.
1.5.2. Superparamagnetism in nanoparticles for hyperthermia

Hyperthermia procedure with magnetic nanoparticles offers possibility of specific localized heating. The advantage of hyperthermia treatment with superparamagnetic nanoparticles is that the superparamagnetic nanoparticles could induce extra heat to local area through the oscillation of the magnetic moment inside the nanoparticles [45]. The specific absorption rate of superparamagnetic nanoparticles is higher than the ferromagnetic nanoparticles, which increases the efficiency of the hyperthermia and destroy the solid tumour at temperature 42- 46 °C. Due to this superior property of the superparamagnetic nanoparticles compared to ferromagnetic, recently more attention is paid to these types of nanoparticles as a mediator for hyperthermia. In a bulk ferromagnetic specimen the magnetization, \( M \), measured as a function of the applied field, \( H \), displays hysteresis loop at temperatures below its corresponding Curie temperature. The ferromagnetic materials consist of domains these domains are separated by domain walls and try to minimize the net energy of the system [46].

The magnetostatic energy increases proportionally to the volume of the material and the domain wall energy increases proportionally to the surface area of the material. Hence, a critical size may be reached, below which formation of domains may become energetically unfavourable due to the domain wall energy, such that the sample consists of a single uniformly magnetized domain. Afterward, the system is in a state of uniform magnetization and it behaves like a small permanent magnet, which is nothing but superparamagnetism.

1.5.3. Surface coating on magnetic nanoparticles for hyperthermia

Their application in biology, medical diagnosis and therapy require that the MNPs be stable in water at neutral pH and physiological salinity. Such colloidal stability depends on the dimensions of the particles; the size of the particles should be sufficiently small so that precipitation due to gravitation forces can be avoided. Another important factor is the charge and surface chemistry, which creates steric and coulombic repulsions. To control the surface properties of MNPs, they are coated with biocompatible materials during or after the synthesis processes in order to prevent the formation of bulky aggregates, transforms from the original structure and biodegradation when exposed to the biological system. In addition, biocompatible coating can also allow binding of drugs by covalent attachment, entrapment or adsorption on the particles [47]. Therefore, an integrative approach to advancing MNP
designs and understanding their interface with specific organs, by means of their application and security, are imperative to advancing nanomedicine.

Without a coating, MNPs have hydrophobic surfaces with large surface area to volume ratios and a propensity to agglomerate [48]. A proper surface coating allows iron oxide MNPs to be dispersed into homogenous ferrofluids and improve MNP stability. Several scientific communities working on this area preferred the following materials to modify MNPs surface chemistry:

a. Organic polymers, including natural (dextran, chitosan) and synthetic (PEG)
b. Organic surfactants, such as sodium oleate and dodecylamine
c. Inorganic metals, such as gold, silver
d. Inorganic oxides, such as silica, carbon, TiO₂
e. Bioactive molecules and structures, such as liposomes, peptides and ligands/receptors.

1.5.4. Biocompatibility issue of magnetic nanoparticles for hyperthermia

Biocompatibility is one of the most important considerations in the development of magnetic nanoparticles for hyperthermia Invivo. In the biomedical field, especially, nanoparticles are being used in diagnostic and therapeutic tools to better understand, detect, and treat human diseases. Exposure to nanoparticles for medical purposes involves intentional contact or administration; therefore, understanding the properties of nanoparticles and their effect on the body is crucial before clinical use can occur. The nanoparticles need to be encapsulated within biocompatible polymers/proteins to make them appear friendly to the body. The polymer/protein used to encapsulate the particles could be such that they melt and break open at 42 °C. These polymers/proteins are known as heat sensitive polymers/proteins. Also, a suitable drug (chemotherapy drug or radio sensitizer) can be loaded inside these coatings along with the magnetic nanoparticles. Thus, the Polymer/protein capsule acts as a carrier for the magnetic nanoparticles and a suitable drug [51].

1.6. Literature survey on MNPs used for hyperthermia

1.6.1 Ferrite MNPs

Until the last decade, magnetite Fe₃O₄ and maghemite γ-Fe₂O₃ were preferred for the MFH development because of their inherent biocompatibility, their easy synthesis in the form of stable aqueous magnetic fluids and their parallel development as contrast agents in
magnetic resonance imaging [52]. Their use is, however, associated with some inconveniences connected with a limited possibility to control magnetic properties in a desired way. First, they exhibit only medium heating efficiency, characterized by specific absorption rate (SAR), expressed in W/g of magnetic element. This factor is, however, crucial for clinical purposes because the higher value of SAR, the required dose injected to the patient is lower. A possible approach to solve this task is the use of complex magnetic oxides, whose magnetic properties can be properly tailored by various ways, like the modification of intrinsic properties depending on the composition and structure, or the modification of extrinsic properties like particle size depending on the synthesis procedure and alternatively employing multiphase materials [53].

1.6.2. Ferromagnetic spinels and derived phages

It possesses mixed, spinel structure of the formula (M₃Fe₁₋ₓ)ₐ[Mₓ₋₁Feₓ]B₄ where A and B indicate tetrahedral and octahedral sites, respectively and M= Co, Mn, Zn, Ni etc. The well studied spinel ferrite for the hyperthermia is CoFe₂O₄. The bulk CoFe₂O₄ is characterized by Curie temperature of Tc ~ 517 °C (790 K), saturated magnetization ~ 95 A m²/kg and a high magnetocrystalline anisotropy constant, K₁ = 270 × 10³ J m⁻³ at 20 °C, i.e. 293 K decreasing to K₁ = 90 × 10³ J m⁻³ at 90 °C, i.e. 363 K [53]. Its properties can be modified by a suitable compositional variation, e.g. by replacing cobalt cations by non-magnetic zinc cations which prefer the tetrahedral sites, it leads to increase the total moment. An attention should be paid to the influence of the magnetocrystalline anisotropy and shape anisotropy on the coercivity influencing significantly hysteresis losses. As a result, the combined influence of the outlined effects can thus offer a possibility to tune suitably the magnetic parameters, i.e. Curie temperature, magnetization and coercivity to the values assuring simultaneously a reasonable heating efficiency and the self-controlled heating mechanism in the range of 40-60 °C.

1.6.3. Ferrimagnetic SrFe₁₂O₁₉γ -Fe₂O₃ composites

The second entirely different approach to solve the outlined task is the use of multiphase materials. The combined contribution of considerable magnetically different phases make it possible to adjust the coercivity, remanence and thus the shape of the hysteresis loop to be appropriate for the magnetic fluid hyperthermia application. A
promising possibility thus appears in the use of composite materials consisting of maghemite spinel and Sr-hexaferrite phases employing simultaneously their structural similarity with difference of magnetic anisotropies. The values of anisotropy constant for such compounds are \( K_1 (\gamma-Fe_2O_3)_{283K} = -25 \times 10^3 \text{ J m}^{-3} \) and \( K_1 (\text{SrFe}_{12}\text{O}_{19})_{298K} = 380 \times 10^3 \text{ J m}^{-3} \) [52,53].

1.6.4. Ferromagnetic perovskite LSMO compounds

The perovskite manganese oxide compounds with composition ABO\(_3\) (A: La and Sr, B: Mn), most often called manganite, have received massive interest biomedical fields especially for hyperthermia because of their magnetic properties. A group of half-metallic ferromagnetic materials, such as manganite La\(_{1-x}\)Sr\(_x\)MnO\(_3\) (LSMO), are of interest due to the tuned transition temperature \( T_c \). The wide range of \( T_c \) from 283 to 380 K can be tuned by different divalent metal ions’ doping into La site. The substitution of divalent metal ion (Sr\(^{2+}\)) in the lanthanum (La\(^{3+}\)) at A-site creates the mixed valencies of the manganese ions in B-site (Mn\(^{3+}\) - Mn\(^{4+}\)) and significantly increases the magnetization of compound due to double exchange mechanism. This property rule out the drawbacks associated with ferrite composites for hyperthermia applications. The first possible application of LSMO for hyperthermia has been proposed by Vasseura et al. in the year 2006 [54]. On the basis of experimental results they proposed that the LSMO material is promising for hyperthermia as compared to other ferrites because the tunable \( T_c \) of LSMO can rule out the local overheating risk during treatment. The in-depth theoretical aspects of LSMO compounds for hyperthermia are presented in the chapter 2.

1.7. Statement of the problem

In order to successfully aid in constructing a magnetic fluid hyperthermia system based on MNPs there are two important fundamental problems that must be solved. The first one is the control on the heat generation by the nanoparticles around hyperthermia temperature range. Second, is the biocompatibility issue of the MNPs. In addition to these crisis there are several additional engineering challenges must be solved before magnetic hyperthermia can be implemented clinically. The first one is the improvement in specific absorption rate. The second is the ability to conduct site specific magnetic heating. The others include specific targeting, removal of MNPs from the body after treatment, etc.
Surface functionalization of MNPs with different ligands including, polymers, fatty acids, liposomes is the gentle way to overcome the problems mentioned above.

The main emphasis of the present work is to develop superparamagnetic material whose $T_c$ is in the range of 46-50 °C at the nanoscale for advanced bio-application such as magnetic fluid hyperthermia. With this aim an attempt has been made to prepare the La$_{0.7}$Sr$_{0.3}$MnO$_3$ (LSMO) nanoparticles with suitable heating characteristics in AC magnetic field for their use as potential heating mediator for magnetic fluid hyperthermia. This thesis is, also, focused on the surface functionalization of LSMO with biocompatible coatings to improve their colloidal, hyperthermia and biocompatible properties.

In light of this problem we carried out the work in this thesis with following objectives.

- To study the effect of fuel choice on structural, morphological, magnetic, colloidal and biocompatible properties of La$_{0.7}$Sr$_{0.3}$MnO$_3$ (LSMO) MNPs synthesized by solution combustion technique.
- To study the effect of polymeric and non-polymeric surface functionalization on structural, morphological, magnetic of La$_{0.7}$Sr$_{0.3}$MnO$_3$ (LSMO)
- To investigate the colloidal behavior of bare and functionalized LSMO nanofluid in different physiological conditions.
- To Study the biocompatible properties of bare and functionalized LSMO MNPs.
- To study the hyperthermia properties of bare and functionalized LSMO MNPs by applying AC magnetic field.
References


[15] ‘Magneto Hyperthermia and Cancer Therapy’ by A. Gopalakrishnan, A. Natarajan, A. Agarwal, M. D. Sanchan, G.S.Subramanya and V. V. Kumar,


