REVIEW ARTICLE

# A review of the treatment of bone tumours by hyperthermia using magnetic nanoparticles

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**ARTICLE INFO**

***Article History:***
*Received 2021-11-13*
*Accepted 2022-05-03*
*Published 2022-09-30*

***Keywords:***
*Pharmaceuticals application,*
*Cancer Diagnosis,*
*Magnetic Resonance Imaging,*
*Magnetic Targeting.*

**ABSTRACT**

Cancer is a fatal disease that has long plagued and damaged people. In the last two decades, many researchers have been interested in the use of magnetic nanoparticles (MNPs) in medicine and pharmaceutical application particularly in the field of cancer diagnostics and treatment. The goal of this article is to provide an overview of MNPs as well as the principles of successful techniques for delivering these nanoparticles to cancer cells. According to an examination, there are two types of active and passive techniques for delivering MNPs to cancer cells. The targeted transfer of nanoparticles to the tumour happens in the active approach, which uses specific molecular ligands of tumour cells and irradiates an external magnetic field to the tumour area, whereas the passive method penetrates the tumour due to its permeability and nanoparticle retention. MNPs offer a variety of applications in biomedicine, including targeted medication delivery to tumours, magnetic resonance imaging, and cancer treatment with hyperthermia, due to their magnetic nature and capacity to carry pharmaceuticals. The use of MNPs in medicine has led to focus on the treatment of cancer. This review indicates that a reduction in the side effects and biological damage produced by chemotherapy in patients can be obtained using MNPs.

**How to cite this article**
*Ehsani A., Shrinivas Mahale R., Shaygan S., Attaeyan A., Ghorbani A., Vasanth S., Sharath P. C., Shahriari S., Asefnejad A., A review of the treatment of bone tumours by hyperthermia using magnetic nanoparticles. J. Nanoanalysis., 2022; 9(3): 206-217.*
*DOI: 10.22034/jna.2022.1944876.1278*

## INTRODUCTION

Using magnetic nanoparticles (MNPs) and the creation of targeted medication delivery techniques, nanotechnology has aided in the diagnosis and treatment of cancer diseases [1-2]. MNPs offer a lot of promise for diagnosing and treating cancer diseases. Recently, researchers have examined the potential of these MNPs as contrast enhancers in traditional magnetic resonance imaging as well as nanocarriers in current drug delivery systems (DDS) [3-6]. In the cancer treatment situation, targeted transfer of chemotherapeutic drugs to cancer cells with the use of MNPs has been explored, yielding valuable and desirable results. These particles have also been used in the treatment of cancer by

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heating absorption, heat release and in the transfer of nucleic acids, plasmids and RNA7 to cells [7-12]. It is critical to diagnose the disease early on to optimize treatment outcomes. Currently, cancer treatments are based on changes in cells and tissues, which can be detected through a doctor's clinical examination and traditional imaging techniques. Scientists are attempting to detect cancer based on the initial molecular changes [13-15]. Only iron oxide nanoparticles have been employed in clinical treatment as a contrast agent in magnetic resonance imaging and as a medication delivery carrier [16-17]. Experiments on iron oxide nanoparticles have shown that they have no immediate or long-term harmful effects in animals, although the inclusion of nanocarriers in some nanoparticles boosts their action on cancer cells [18-19]. These nanoparticles boost the efficacy of nanocarriers through a variety of techniques including increased oxidative stress and optimal drug accumulation in the cell [19-22]. The elimination of tumours using the magnetic hyperthermia treatment was discussed in this review article and a general conclusion and suggestions connected to the current topic are provided at the end.

## METHODOLOGY OF THIS RESEARCH IN MNPS

The approach to data collection in this review article is library-type, and it was done using Scopus, PubMed, and Web of Science databases. Keywords like MNPs, cancer, magnetic targeting and other related terms were used to search the publications. These articles featured Latin articles on the topic that were summarized after they were read. This article covers the basics of tumour targeting methods with MNPs for multiple uses in magnetic resonance imaging and targeted drug delivery, as well as the purpose of drug delivery and the essential properties of MNPs (especially the important properties of super-magnetic) for biomedical applications.

### *Physical properties of magnetic nanoparticles for targeted transfer*

The main challenge in cancer treatment is to target and kill cancer cells with a little effect on healthy cells. Targeted drug delivery is one of the goals of nanotechnology, which involves mounting medications on nanoparticles carriers and then sending and releasing them into the target cell. The medicine can be intelligently delivered to the intended tissue and improved without harming other tissues by employing MNPs and establishing a magnetic field [23-28]. Furthermore, magnetic residues in these materials can cause them to coagulate, resulting in blood clots in the arteries. As a result, substances having superparamagnetic characteristics are required for such applications [21-29]. A sort of magnetic property found in small ferromagnetic or ferromagnetic nanoparticles is known as superparamagnetic property. Under the effect of temperature, the magnetic of tiny particles can change direction at random. As the duration employed to assess the magnetic susceptibility of nanoparticles is significantly longer than the indigo's comfort time, their average magnetization is zero, indicating that the particles are super paramagnetic as can be seen in Fig. 1.

When a group of superparamagnetic nanoparticles is exposed to an external magnetic field, their magnetic moments tend to align with the external field. These particles in the field behave similarly to paramagnetic matter, but with a much higher magnetic moment. As a result, their magnetism may be significantly higher than the paramagnetic condition. Iron oxide nanoparticles are the only magnetic materials that have qualities that are suitable for application in biomedicine [29-36]. These particles dissolve quickly and may be non-toxic to humans, making them useful in nanomedicine. Experiments on iron oxide nanoparticles undertaken over several years have shown that these particles have no immediate or long-term harmful consequences in the body. The absorption of biological materials such as plasma proteins on the hydrophobic surface of the particles causes the particles to leave the bloodstream fast. One of the most essential characteristics of nanoparticles can be used in medical applications is their size and size distribution. MNPs with the right form, size, and surface qualities can be used to target malignancies. MNPs are non-cytotoxic and stable in water, as well as at the normal pH and physiological conditions of the human body, are employed in biological and medical diagnostic applications. It is feasible to bind medicines, proteins, and genetic elements to the surface of these molecules by creating the required surface changes as shown in Fig. 2. The influence of an external magnetic field may allow for selective transmission of these chemicals in this fashion [37-41].

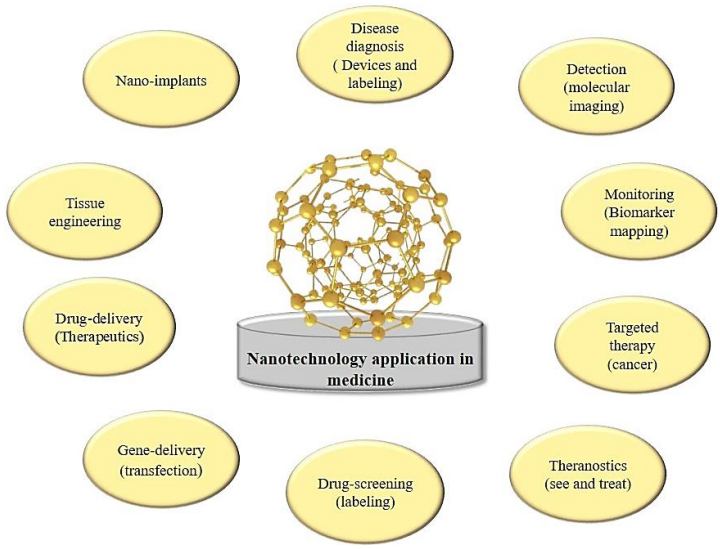


Fig. 1: Nanotechnology application in medicine

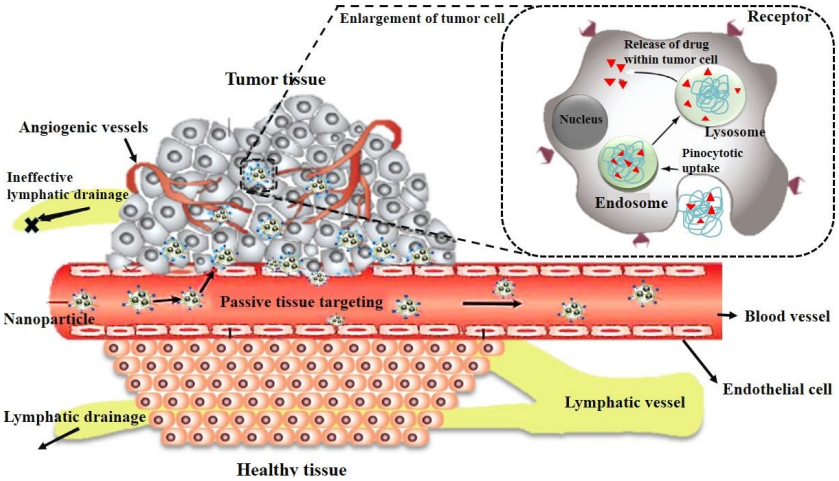


Fig. 2: Schematic illustration of the EPR effect (Nanocarriers can pass through the gaps between endothelial cells and accumulate at the tumour site due to poor lymphatic drainage)

*Approaches of using magnetic nanoparticles in targeting the tumours*

Inactive targeting, which directs nanoparticles to tumours based on the EPR phenomenon, and active targeting, which conducts magnetic nanoparticles to tumours using an external magnetic field and molecular ligands that bind specifically to cancer cells, are the two methods used to target tumours with magnetic nanoparticles [32-44].

*Passive targeting based on EPR phenomenon*

The ideas of passive targeting are based on the transmission system's features as well as the disease pathophysiology. MNPs are amplified based on the effect of permeability and retention; accumulate in the tumour due to their small size at the nanoscale. This mechanism separates MNPs from the bloodstream and travels via the vascular pores of the tumour due to its big holes, wide and leaky strength as can be seen in Fig. 3.

These MNPs are retained in the tumour tissue due to the lack of lymphatic outflow around the tumour [38-47]. Particles small as 1 μm (micrometres) have been found to penetrate the tumour space in some cancers. The results of investigations in this field demonstrate that the EPR phenomenon in solid tumours of model

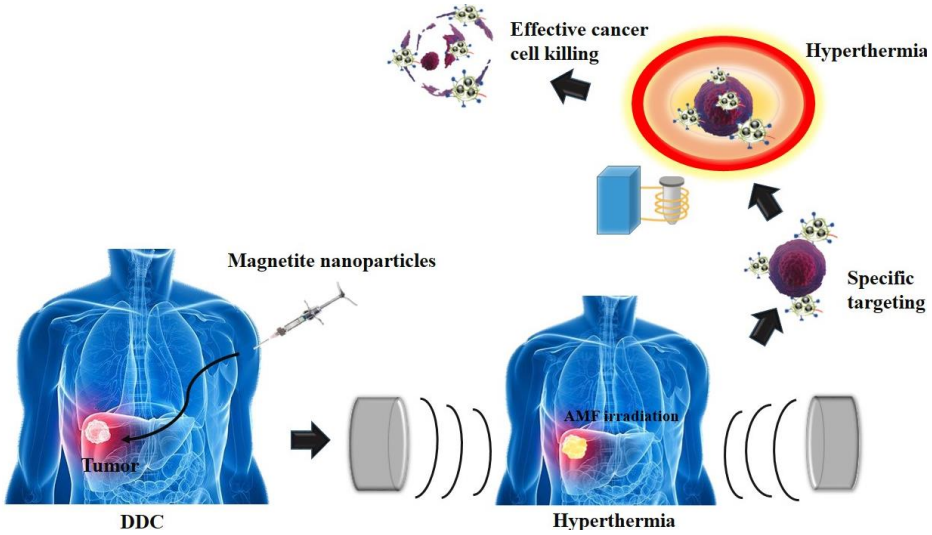


Fig. 3: Hyperthermia effect that a fluid containing MNPs is injected into the cancerous tissue.

mice generates high nanoparticle adsorption at the tumour site in a reinforced manner [48-51]. Pores that are larger and wider play a bigger impact in nanoparticle uptake and retention in tumour tissue. Shayan et al. [14] found that when loaded on nanoparticles 10 to 100 times greater than the free form of the drug, the anti-cancer medication cisplatin is absorbed into solid tumours of model mice. A study investigated the role of molecular targeting in the genesis and progression of tumour selectors utilised in magnetic resonance imaging. The high cost of production of macromolecular ligands and the intricacy of the chemistry of their binding to MNPs have produced issues and restrictions in the use of these agents in clinical and laboratory stages. Furthermore, peptides infiltrating cell expand cationic characteristics into MNPs, reducing their time in plasma and eliminating them. To ensure tumour selectivity and pharmacokinetic preservation, measures that modulate cationic activity must be considered when selecting this sort of material in the platform design [52-57].

After reviewing a variety of sources and studies, it can be determined that putting anti-cancer medications onto MNPs enhances the drug action and kills cancer cells [52-56]. According to studies, MNPs stimulate the generation of reactive oxygen species or other undiscovered mechanisms that help anti-cancer medications (such as doxorubicin and cisplatin) kill cancer cells. The inclusion of MNPs in this technology has improved its sensitivity and accuracy in cancer diagnosis, allowing cancer to be discovered early and effective therapeutic measures to be applied for its definitive treatment. MNPs unique magnetic properties can also be exploited for targeted medicine delivery. Due to their potential to contain anti-cancer medications, high biocompatibility and low biotoxicity, as well as their propensity to concentrate in tumours, particularly iron oxide can be employed as nanocarriers in drug delivery.

According to the findings of the current study, new and optimal multifunctional DDS based on MNPs can be designed in the future that have high capability in drug delivery to the tumour area while also being used as contrast agents in magnetic resonance imaging and the process of magnetic hyperthermia for the definitive treatment of cancer. In other studies, nanoparticles are classified into two groups based on the materials that make up their composition [51-58]. Organic molecules, which are the main component of nanoparticles, are separated into organic and inorganic categories. Many polymers have been employed as drug transporters, including polyamide, polyamine acid, polyalkylation-Alpha-cyanoacrylate, polyester, polyurethane, polyurethane, polyacrylic Amide, and polycaprolactone. Between them thermoplastic aliphatic polyesters (thermoplastics) such as Polylactic Acid (PLA), Polyglycolic Acid (PGA) and a copolymer of these two polymers called Polylactic Glycolic Acid (PLGA) due to its biocompatibility properties high and excellent biodegradability as well as chitosan due to their properties, biocompatibility and compatibility

were highly regarded [55-61].

This activity achieves and improves the release system of anti-inflammatory medications for Polymer-based Nanoparticles became a good tool for cancer patients, as shown by macromolecules through polymers. The presence of these medications in these nanoparticles improves the pharmaceutical solubility and shelf life. The fundamental goal is to give the drug to the patient at a specific concentration and during the therapeutic window, resulting in patient satisfaction. Polymeric carriers have gained a lot of interest in recent decades due to their numerous functionalities and functional ability [62-64]. Getting to know the polymer nanoparticles are tiny colloidal solid systems in general. The medicine is chemically linked to their primary polymer chain or physically dispersed or dissolved in them. When polymer nanoparticles are used as drug nanocarriers, drug solubility and stability improve. As a result, polymer nanoparticles are one of the most used available drug delivery technologies. The influence of nanotechnology-based delivery methods on cancer release is significant [65-71]. Nanotechnology in the DDS has a significant impact on cancer cell detection, drug release targeting, and overcoming the limits of traditional chemotherapy. Although the loading of hydrophilic substances is still limited, different molecules can be encapsulated due to the diversity of nanoparticle shapes [72-76].

*Magnetite nanoparticles synthesize technique*

Although MNPs are produced by methods such as polyol, laser pyrolysis techniques, electrochemical and microorganisms and bacteria, the most common methods used for synthesis of MNPs is gel, solvent-free synthesis, hydrothermal, thermal decomposition and microemulsion mentioned, which may explain in the following sections [51-59].

**Homolysis method**

Co-precipitation method is a simple and common method for synthesizing MNPs from aqueous solution of their salts. The advantages of this method include the use of water as a solvent, high efficiency and purity, and the ease of adjusting reaction conditions. The precipitation reaction takes place in a neutral atmosphere with an increase in the base of the iron salt solution at room temperature or higher. Magnetite deposition is obtained in an environment with a pH range of 8-14 and a stoichiometric ratio of 2: 1 ($Fe^{3+}/Fe^{2+}$). The size, shape and composition of the resulting MNPs depend on the $Fe^{2+}/Fe^{3+}$ ratio, the reaction temperature, the base type used, the stirring speed, and so on.

**Sonochemical method**

Ultrasonic physicochemical effects are caused by sound cavities. In this process, sound cavities are created as a result of the formation, growth and collapse of internal bubbles in the solution. Internal collapse of bubbles produces hotspots through adiabatic compaction or shock wave formation within the gas phase of the collapse bubble. The conditions of these hot spots are transition temperature 5000 K, 18000 atm pressure and cooling speed. This condition is not only beneficial for the formation of a new phase, but also affects the breaking of clots. Other advantages of the chemical method include the high crystalline and magnetic properties of the product compared to the co-precipitation method [77-79].

**Sol-gel method**

The sol-gel process is a chemical process for the synthesis of nanoparticles from mineral raw materials or a combination of organic-mineral matter. The structure and composition of nano-oxides prepared by the sol-gel method depend on the synthesis conditions, the nature of the precursor, solvent, temperature and pH concentration. The advantages of this method are suitable materials due to the ability to control the synthesis process. The existence of homogeneous multi-component systems is due to mixing in a liquid environment and low temperature to process the materials. The mechanism of the method is based on hydroxylation and concentration of molecular precursors in the liquid. Higher density and mineral polymerization lead to the formation of a 3D network called a gel [80-84]. This method is a non-toxic and economical method to produce magnetite nanoparticles that use iron salts ($FeCl_2.4H_2O$) or ($FeCl_3.6H_2O$) and a solid base (NaOH).

**Hydro-thermal method**

In this method, for the synthesis of iron oxide, metallic organic precursors such as iron carbonates or long carbon chain iron acetone, with a carboxylic or amine functional group, are used. The hydrothermal reaction takes place in the presence of a surfactant at a temperature above 200 ° C and

a pressure of more than 14 bar. The advantages of this method are the narrow range of particle size distribution, non-clotting of crystals due to the presence of stabilizing agents, very high purity and density [13].

**Reverse microemulsion or micelles**

Microemulsion can be described as the dispersion of two immiscible liquids with thermodynamic stability. Microemulsions are classified into two categories: oil in water and water in oil. As a surfactant is added to a mixture of water and oil, a complete microemulsion system is obtained. The surfactant is substituted as a surfactant at the boundary between the two phases and reduces the oil-water tension considerably. In reverse micelles, the reaction takes place inside the water and then the growth of particles stops and their size is limited.

**Magnetite surface correction**

MNPs have many hydroxyl groups on their surface. Hydroxyl groups adsorbed on the surface of MNPs are active components that can react with acid or base. Therefore, the surface chemistry of MNPs is strongly dependent on the pH of the environment (Fig. 1-b). Hydroxyl groups also react with other inorganic and organic anions. The stability of the colloidal suspension is due to the protective agents, due to the balance between repulsive and gravitational forces [14]. Fig. 1 shows the application of MNPs in nanotechnology, which is widely used in the treatment of cancer, drug delivery, nano implants and biomarkers. These nanoparticles also show special application in medical science and treatment of hyperthermia. Fig. 2 schematic illustration of the EPR effect (Nanocarriers can pass through the gaps between endothelial cells and accumulate at the tumour site due to poor lymphatic drainage).

**Organic coatings**

Surfactants [17] and polymers [18] are the most common organic preservatives. These materials can be added during or after the synthesis of magnetite nanoparticles. Binding of these protective agents to the surface can be done physically or chemically. In fact, surfactants and polymers often prevent particles from clotting by increasing the spatial amplitude between particles.

**Surfactants applications**

Surfactants are dual-molecules that have both hydrophilic and hydrophobic components. As two immiscible phases are mixed with surfactant at a concentration higher than the critical concentration of micelles, the surfactants become structures called micelles. In this structure, the hydrophobic end of the molecule is oriented towards the organic phase and the hydrophilic end is oriented towards the aqueous phase. This phenomenon can be used to protect metals or metal oxide nanoclusters by trapping them in micelles [64-68].

*Surface modification based on polymerization*

Despite the various polymerization methods to modify the surface of nanoparticles, radical polymerization and ionic polymerization are the most suitable options for the modification of nanoparticles by polymers. Solvent, primer, monomer to primer ratio and surface structure are some of the factors that can affect polymerization. The use of polymers as protective agents depends on the intended purpose. In general, there are two methods for modifying the surface of nanoparticles with a polymer coating as shown in Fig. 2. In method A, a pre-synthesized polymer with a suitable end group is attached to the MNPs through a special reaction between the end group and the binding agent (Fig. 2 (a)). In method B, polymer chains begin to grow from the binding sites of MNPs through thermal or photochemical processes (Fig. 2(b)). Comparing these two methods, method B is preferred due to the ability to adjust the thickness of the polymer shell by controlling the conditions of polymer synthesis [65-72].

**Coating with minerals**

Numerous mineral compounds such as silica, carbon, precious metals and alumina are used to protect MNPs. Silica coating is the most common way to protect the surface of MNPs. This type of coating is especially useful in the field of catalysts and DDS. The process of coating MNPs with silica is a simple process due to the presence of hydroxyl groups on its surface. The sol-gel process is often used to coat MNPs with silica. Prior to coating with silica, it is necessary to select a low concentration of MNPs as well as expose it to ultrasound to prepare a typical core-shell structure. Otherwise, multi-core iron oxide is formed inside the silica shell. Coating MNPs by sol-gel process due to advantages such as ease of silica coating formation, the possibility

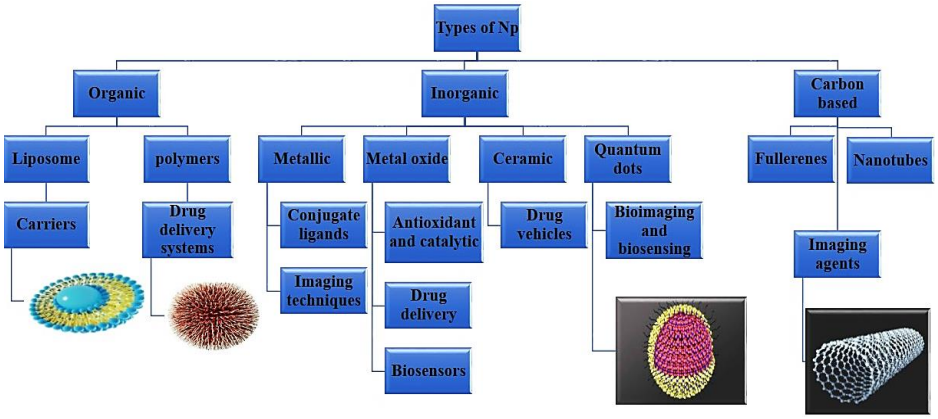


Fig. 4: Types of nanoparticles (based on chemical composition) and their main biomedical applications.

of controlling silica shell thickness by adjusting the concentration of silica modifying agent, ability to modify silica coated MNPs with other silane coupling agents or other compounds. Fig. 3 shows the application of nanoparticles in the treatment of body tumours that release heat into the magnetic field and hyperthermia environment. This heat released in the magnetic field reduces the size of the tumour and destroys the cancerous tumour. Fig. 4 shows a classification of nanoparticles with different applications, which identifies organic and inorganic materials.

**Coating with precious metals**

Precious metals can be deposited on magnetic nanoparticles in a variety of ways, thereby protecting them from oxidation. Among precious metals, the use of gold is more desirable due to its low reactivity, ability to act with thiol groups, and the ability to bind widely used ligands to the surface. In addition, by coating iron oxide nanoparticles with gold, this compound becomes stable in neutral and acidic conditions [27].

**Application of magnetite nanoparticles**

MNPs composed of a biocompatible iron oxide mineral nucleus can be recovered by cells using normal biochemical pathways. Due to the unique properties of MNPs, such as the ability to respond to external magnetic fields and the high surface-to-volume ratio, much attention has been paid to the feasibility of their application in many fields such as targeted drug delivery, cell imaging, catalyst design for organic reactions and water treatment. Fig. 5 also shows the effect of concentration changes on the formation of nanoparticles such as silica.

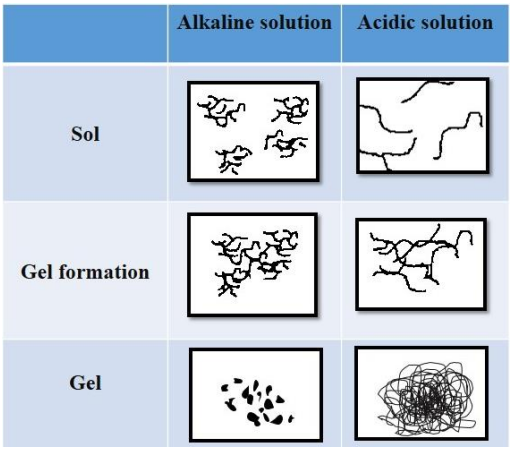


Fig. 5: The effect of pH on the appearance of the final silica gel

**Targeted drug delivery**

The low toxicity and high biocompatibility of MNPs have led to the widespread use of MNPs in targeted drug delivery. Using an external magnetic field, the nanoparticles can be directed to the target tissue and the drug. Iron oxides with different structures have been used in areas such as nanotechnology, biotechnology and the environment. Regarding the synthesis process and quality evaluation of nanoparticles, the researcher may purpose that MNPs were first synthesized by milling method. The salts used were iron (II) chloride, iron (III) chloride - soda, and industrial NaCl was used to prevent the destruction of the container and mill pellets. Then, different identification methods were used to study nanoparticles, and the optimal time for the synthesis process was obtained by mechanochemical method. In the next step, porphyrin was added to the synthesized nanoparticles to increase the surface efficiency of

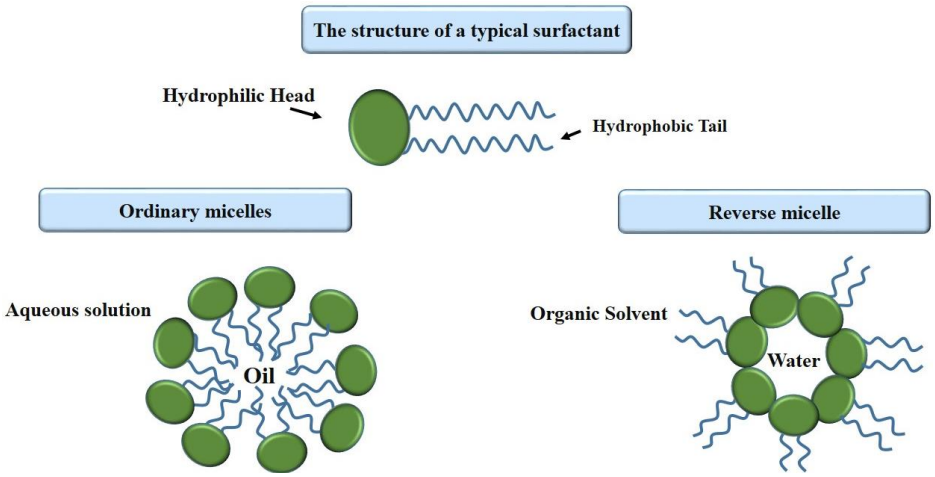


Fig. 6: Schematic illustration of normal and inverted micelles.

the nanoparticles in their photocatalytic activity in visible light. According to results which showed that the synthesized magnetite alone degrades a significant percentage of methylene blue in visible light, the presence of porphyrin enhances light absorption and methyl blue degradation to higher values. Fig. 6 shows the image of normal and inverted micelles, characterized by two heads such as hydrophobic tail and hydrophilic head.

## CONCLUSIONS

An overview of MNPs with the fundamentals of popular methods for conveying these nanoparticles to cancerous cells are discussed in this article. Magnetic nanocomposites have a broad array of applications in biomedical science, targeted delivery of medicine to tumours, magnetic resonance imaging, and cancer treatment with hyperthermia. The consumption of MNPs in medicine has resulted in the development of targeted and effective cancer treatments. The most difficult aspect of cancer treatment is identifying and killing cancer cells. One of the goals of nanotechnology is targeted drug delivery, which entails mounting drugs on carriers and afterwards transferring and releasing those into the target tissue. One of the most important properties of the MNPs that could be used in medicinal uses is that their own size and distribution are constrained. The two methods used to target tumours with MNPs are (1) inactive targeting-directs the nanoparticles to tumours EPR technique base, and (2) active targeting- external magnetic field is used and molecular ligands bind specifically to cancer cells. Even though there are tremendous possibilities of therapeutic applications in the future but the expenditure of generating macromolecular compounds, and also the chemistry of them bonding to MNPs has led in challenges and limitations in their application in clinical and laboratory settings. Furthermore, peptides that infiltrate tissues improve the cationic qualities of MNPs, limiting their presence in plasma and enabling them to be discarded. Polymer nanomaterials have emerged as superior groups in carriers of anti-cancer nanodrugs due to their ease of manufacture, biocompatibility, and biodegradability. Polyol, laser pyrolysis techniques, electrochemical, and synthesis by microorganisms and bacteria along with gel, solvent-free synthesis, hydrothermal, thermal decomposition, and microemulsion are the various methods that are used to generate MNPs that have been discussed. Because of MNPs properties, such as their ability to respond to external magnetic fields and their high surface to volume ratio, much emphasis has been placed to the practicability of their implementation in a variety of fields, including targeted drug delivery, cell imaging, catalyst design for organic reactions, and water treatment. This article puts bright light on all the aspects of use of MNPs in cancer treatment.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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