Materials Advances

ROYAL SOCIETY OF CHEMISTRY

REVIEW

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Cite this: *Mater. Adv.*, 2022, 3, 7425

Therapeutic applications of magnetic nanoparticles: recent advances

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Received 21st April 2022,
Accepted 5th August 2022

DOI: 10.1039/d2ma00444e

rsc.li/materials-advances

Magnetic nanoparticles (MNPs) show tremendous possibilities in the field of biomedicine, especially as therapeutic agents for use over a prolonged duration. Most notably, magnetic nanoparticles are widely used in magnetic hyperthermia, targeted drug delivery, photothermal therapy, photodynamic therapy and magnetofection for the treatment of cancer. The background of these applications relies mainly on interaction of the MNPs with an applied magnetic field, as well as light. The characteristics of the particles, such as size, crystal structure, shape, optical absorption, surface chemistry, magnetization and toxicity, have become important for building nanoparticles intended for various therapeutic applications. In this review advances in therapeutic MNPs for the field of biomedicine are highlighted, with a primary focus on synthetic methods, magnetic properties, therapeutic applications, challenges and future outlook.

1. Introduction

Magnetic nanoparticles (MNPs) are nanomaterials that consist of magnetic elements such as iron, cobalt, nickel and their alloys (Fig. 1), which show properties such as ferromagnetism and superparamagnetism.[1] The use of magnetic nanoparticles in therapeutic applications has been recorded since ancient times. Hippocrates, the father of medicine, used styptic iron oxide to stop bleeding and to control haemorrhages.[2] Currently, cellular labelling/repair, drug delivery, magnetic resonance imaging (MRI), tissue repair, magnetic hyperthermia therapy (MHT), photodynamic therapy (PDT), photothermal therapy (PTT) and magnetofection for gene delivery are some of the prominent examples of biomedical applications shown by MNPs.[3–12] Such a variety of biomedical applications demands a narrow size distribution, a high surface-to-volume ratio, high biocompatibility, low toxicity, a high magnetic moment and the high magnetization of nanoparticles.[13,14] Among the different MNPs, iron oxide nanoparticles (IONPs) have been the most widely studied nanomaterials for decades since they are safe, biocompatible, and have significant clinical utility. Different ways can be applied to initiate their therapeutic activity.[15,16] Cancer hyperthermia therapy and MRI contrast enhancement are applications that have already been shown by US Food and Drug Administration (FDA)-approved IONPs.[16,17] In addition, superparamagnetic iron oxide nanoparticles (SPIONs) are used as MRI contrast agents as they are non-toxic and have the ability to exhibit no residual magnetic force after the removal of the applied magnetic field.[3]

For more effective therapeutic treatments, transition metals (Fe, Co, Ni) or metal oxides (Fe_3O_4, γ-Fe_2O_3) are usually considered because of their high magnetic saturation.[18,19] Although pure metals possess a high magnetic saturation, their high toxicity and extreme sensitivity to oxidation make them largely inappropriate for therapeutic applications.[20] However, a stable magnetic response is given by iron oxide as it is less sensitive to oxidation. Nanoparticles of magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) show a wide range of biomedical applications, such as drug delivery, cancer treatment *via* MHT, contrast enhancement in MRI, immunoassays, *etc.*, as they are non-toxic, biocompatible, and relatively easy to functionalize with polymers such as polyethylene glycol (PEG), polyvinyl pyrrolidine (PVP), or functional groups such as thiols, carboxyls and amines.[21–28] For practical purposes, the nanoparticle (NP) surface must be functionalized to reduce agglomeration, improve biocompatibility, prevent protein absorption, reduce toxicity, and extend the NP time in blood circulation.[4] Without any surface modification, these MNPs that have a hydrophobic surface and a high surface-to-volume ratio agglomerate to form large clusters[17]

This review highlights the advances in MNPs for various therapeutic applications. Initially, a short description of the various synthetic procedures for MNPs is provided. Next, information about recent advances in the use of MNPs for various therapeutic applications, including MHT, targeted drug delivery, PTT, PDT and magnetofection for gene delivery, is discussed in detail. Finally, the challenges, future outlook and conclusions regarding MNPs in therapeutic applications are described.

2. Synthesis of magnetic nanoparticles

The synthesis of MNPs deserves critical attention because of their colloidal nature and the multistep procedure required.

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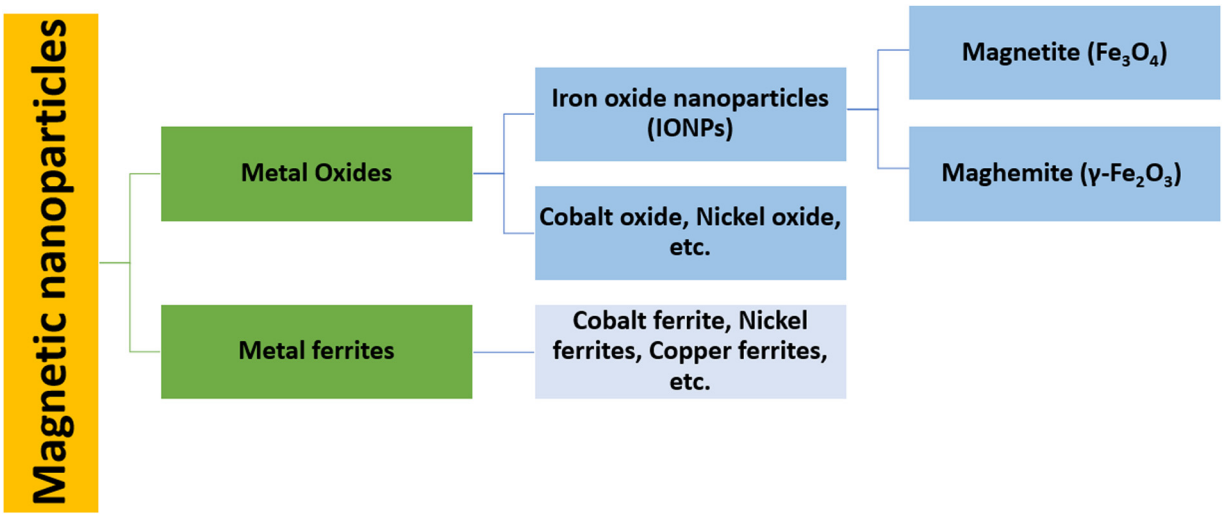

Fig. 1 Classification of biomedically useful magnetic nanoparticles.

Key demands in the synthesis of NPs include the experimental conditions, which define the size, shape and surface properties that can be reproduced without any complex purification method (such as magnetic filtration and size-exclusion chromatography).

Several chemical methods for MNP synthesis have been established, in which the most commonly used methods are co-precipitation, thermal decomposition and microemulsion-templated synthesis (Fig. 2). These methods lead to facile control over the size, shape and composition of MNPs, and are also effective and economical. On the other hand, some physical methods that lead to uncontrollable particle size include gas-phase decomposition and electron beam lithography. Whichever synthetic scheme is used, ideally, it should produce the highly crystalline nanoparticles with uniform dimensions and a high saturation magnetization. A summary of the various synthesis methods of MNP synthesis is also given in Table 1.

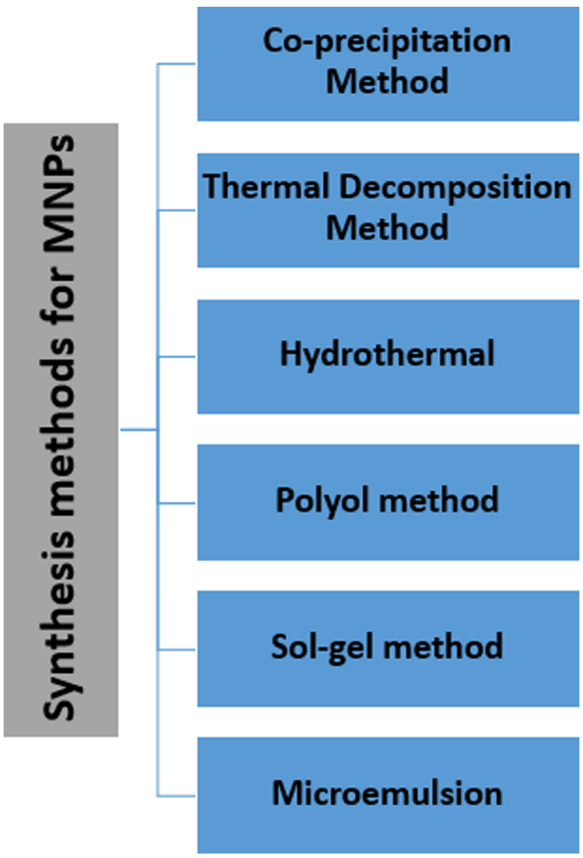

Fig. 2 Various synthetic methods for nanoparticle synthesis.

2.1 Co-precipitation method

In biomedical applications, co-precipitation is the most commonly used method because the particles produced are comparatively less harmful and easy to prepare.[29] In addition, this method is safe, cost-effective and requires a low synthesis temperature compared with other conventional methods.[30,31] As an example, a one-step co-precipitation reaction of ferrous (Fe^{2+}) and ferric (Fe^{3+}) salts in an alkaline solution is shown in Fig. 3.

The general composition used for the method is a 2 : 1 ratio of Fe^{2+} and Fe^{3+} salts at either room temperature or an elevated temperature (80–85 °C). Upon completion of the reaction, a precipitate of Fe_3O_4 is formed at the bottom of the reactor, which can be recovered through centrifugation or magnetic isolation. The expected pH of the precipitate formed should be between 7.5 and 14. The general reaction can be given as:

$$Fe^{2+} + 2Fe^{3+} + 8OH^- \rightarrow Fe_3O_4 + 4H_2O.$$

If the molar ratio and pH of the precipitate are maintained properly then it may be oxidized to $Fe(OH)_3$, which will drastically affect the physical and chemical properties of the NPs. The process can be described with the following reaction:

$$4Fe_3O_4 + O_2 + 18H_2O \rightarrow 12Fe(OH)_3.$$

To prevent the imminent oxidation, inert or alkaline conditions are required during the synthesis of Fe_3O_4 nanoparticles.

Table 1 Summary of various synthesis methods for magnetic nanoparticles

Method	Conditions	Reaction temperature (°C)	Solvent	Advantages	Disadvantages	Ref.
Co-precipitation	Very simple, ambient condition	25–85	Water	Safe, cost-effective, requires low synthesis temperature.	Surface oxidation, poor size distribution	29–31
Thermal decomposition	Inert atmosphere	100–320	Organic compounds	High-quality monodisperse particles, small size.	Complicated, time-consuming, low production rate, demands protracted purification.	33–41
Hydrothermal	High pressure	220	Water–ethanol	Simple, eco-friendly, cost-effective, versatile.	High pressure and temperature, longer synthesis time.	42–45
Polyol	Simple	25 up to boiling point	Ethylene, PEG	Precise control over the size and shape, cost-effective, low-cost industrial method.	Difficult to synthesise small particles.	41,47,48
Sol–gel	Ambient conditions	10–30	Water	High purity, homogeneity	Impurities hard to remove.	49,50
Microemulsion	Ambient conditions	20–50	Organic	High magnetization value.	Complicated, slow reaction kinetics.	51–53

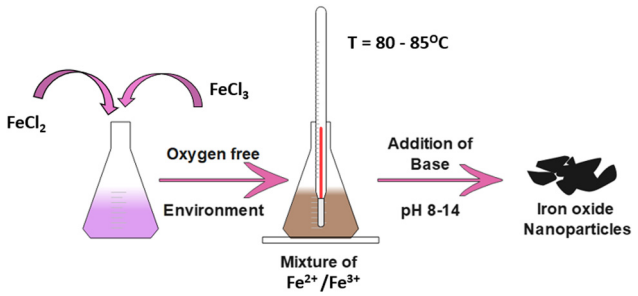

Fig. 3 Steps to synthesize IONPs through the co-precipitation method. Fe^{2+} and Fe^{3+} are added in a 2 : 1 molar ratio in an oxygen-free environment and heated to 80–85 °C followed by the addition of base. The precipitated particles are then centrifuged or magnetically separated.

Moreover, during the precipitation process, the NPs are usually coated with organic or inorganic molecules such as detergents, proteins, starch, polyelectrolytes, *etc.* Other reaction parameters, such as the dropping speed of the basic solution and the stirring rate, also affect the quality of the nanoparticles. Despite the nanoparticles being produced having a polydisperse nature, the pH value of the reaction mixture needs to be regulated during both the synthesis and purification steps. In addition, nanoparticles have a high surface-to-volume ratio, and they tend to form aggregates in solution to reduce their surface energy.[32] Thus, other methods have been developed with better surface characteristics and more uniform dimensions.

2.2 Thermal decomposition method

The thermal decomposition method, also known as pyrolysis, has been used to synthesise highly crystalline and monodisperse MNPs.[33] It is carried out at high temperatures, commonly using organometallic precursors.[1,34,35] To overcome the limitations of the co-precipitation method, this method was developed using non-aqueous solvents with a high boiling point, as depicted in Fig. 4.[36] NPs produced using this method are reproducible, monodisperse and monocrystalline and generally of better quality.[1] Any residual surfactants present may affect the efficiency of surface modification. Oleic acid, hexadecylamine and fatty acids are the most frequently used surfactants in this method. To attain a high degree of uniformity and a size of 4–30 nm, the optimum temperature should be within 100–350 °C.[37,38]

Thermal decomposition is advantageous for the MRI process since the nanoparticle size is a critical parameter and the size can easily be controlled using this method.[39] Other advantages provided by this method include high crystallinity, dispersibility, uniformity and a fine particle size distribution.[40] Despite having tremendous advantages, this method demands protracted purification steps before it can be used for biomedical applications.[41] Furthermore, this method is time-consuming, has a low production rate, and requires costly and hazardous organic solvents.[33]

2.3 Hydrothermal method

The hydrothermal method is a commonly used method for preparing NPs in autoclaves or reactors over a wide range of temperatures and pressures, resulting in the fast nucleation and growth of newly synthesized MNPs.[42] The particles produced by this method are pure with a controlled morphology.[41] This method is considered to be eco-friendly, cost-effective and versatile as it does not use any organic solvent, thus eliminating the need for further treatment after synthesis.[43,44] The main drawbacks of this method are that it fails to synthesize particles smaller than 10 nm, and at high temperatures it shows slow reaction kinetics. There are, however, some noteworthy advantages of the hydrothermal method over others, for example, it offers magnetic controllability, and a greater control over the size, shape and dispersion.[45]

2.4 Polyol method

The polyol method is used for synthesizing inorganic compounds from NPs to alloys, sulphides, oxides, fluorides, *etc.*[46] In this method, the polyols act as a polar organic solvent for metal precursors, as a reducing agent, and in some cases as a complexation agent for metal cations. For the synthesis of metal and alloy nanoparticles, this method is versatile for controlling the size and shape of the particles. In addition, by varying the precursor concentration, the shape and size can be

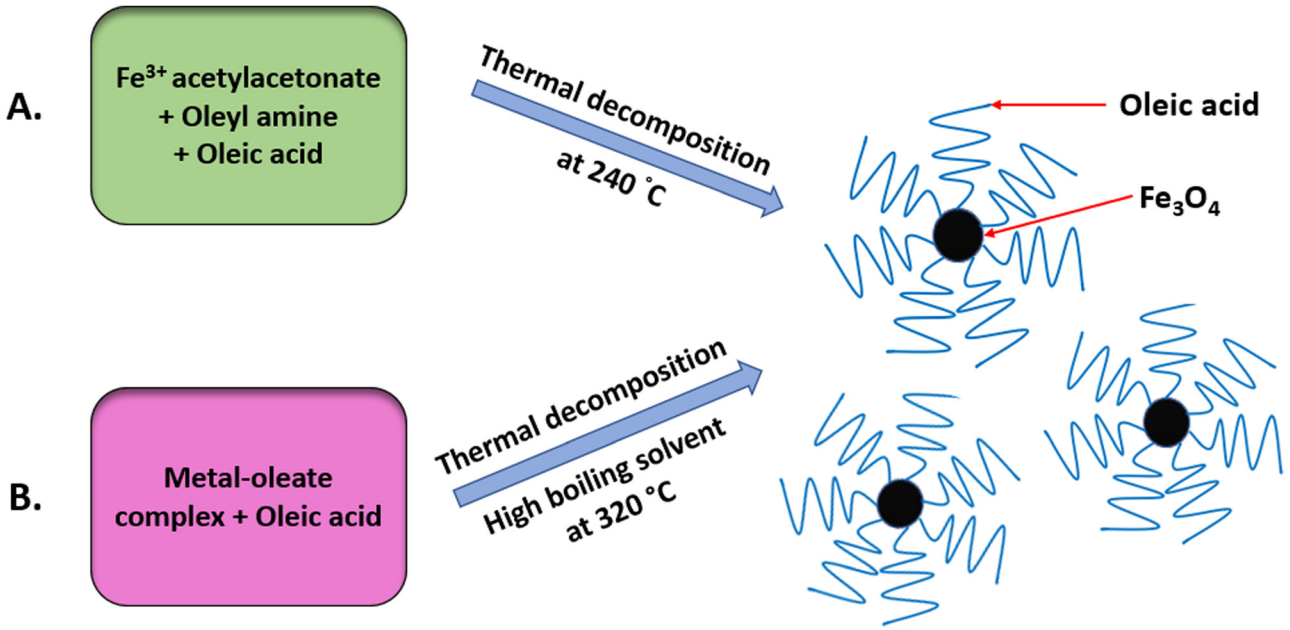

Fig. 4 Widely used methods for the synthesis of monodisperse IONPs *via* thermal decomposition: (A) using an iron precursor in surfactants oleyl amine and oleic acid; and (B) using a metal oleate complex in oleic acid.

controlled, which can be a useful tool for biomedical applications.[47] The particle size can be increased by increasing the reaction temperature.[39] Moreover, particles of different morphologies, such as spheres, flowers, nanorods, *etc.*, can be obtained using the polyol method.[44] As this method does not require separate calcination and uses only polyol as the solvent, it is one of the easiest methods for synthesizing nanoparticles. Furthermore, polyols are considered to be green solvents and are cost-effective, and consequently are used extensively in industry.[48]

2.5 Sol–gel method

The sol–gel method uses condensation and hydrolysis reactions of metal alkoxides or their precursors to produce NPs. To secure NPs of high crystallinity, the intermediates need to be treated further.[49] In this method, to prepare the sol the precursors are dissolved in water, followed by a series of stirring and heating steps; and for preparing the gel the MNPs are dried. The solvent is removed to achieve the desired MNP. Although the MNPs produced *via* the sol–gel method are of high purity and homogeneity, this method leads to the formation of impurities that are hard to remove. Like other methods, it provides a high level of control over the particle size and composition.[50]

2.6 Microemulsion method

Microemulsions are thermodynamically stable isotropic liquid mixtures of oil, water and surfactant.[51] MNPs are produced through a series of emulsion steps and give high magnetization values. The MNPs synthesized *via* this method are larger in size. Moreover, the reaction kinetics are slow, even though the method requires a high temperature for synthesis.[45,52] By controlling the water-to-surfactant ratio, concentration of the reactants, and surfactant film flexibility, one can control the size of the MNP microdroplets. The advantage of using the microemulsion method is that one can achieve precise control over the size, shape, and composition of the nanoparticles.[53]

2.7 Other methods

For synthesizing MNPs, other methods such as sonolysis, flow-injection techniques, electrochemical, aerosol/vapour methods, *etc.*, have also been used.[54] In sonolysis, by decomposing organometallic precursors, SPIONs can be produced at very high temperatures using ultrasound. Structural hosts, polymers, and organic capping agents are used to control the particle growth. In addition, these ultrasonic effects cause cavitation in the solution, which can thereby be used to modulate the nucleation, growth and formation of the MNPs.[55] Sonolysis is a simple, green process that offers a narrow size distribution and diverse applications in biomedicine.[56] Flow-injection techniques are carried out under a laminar flow system in a capillary reactor, which involves continuous or segmented mixing of the reagents. High reproducibility due to the plug-flow operation, high mixing homogeneity, accurate external control over the process and laminar conditions are a few benefits of this technique. The electrochemical method is an eco-friendly 'green' method that provides high selectivity at low cost, and includes diverse applications in biomedical and electronic fields.[55,56] Under oxidizing conditions, aqueous solutions of dimethylformamide and cationic surfactants are used to synthesize <8 nm IONPs using iron electrodes by simply altering the current or applied potential. The disadvantages of this method include poor reproducibility and a high number of confounding factors. By contrast, the aerosol method gives a high-quality output, high purity and a comparatively straightforward process, although

large aggregates are formed in this process, reducing the quality and leading to difficulty in scaling up.[55,57]

3. The basic magnetic properties of MNPs

Ferromagnetism and superparamagnetism are the two main types of magnetic behaviour displayed by MNPs, and they are governed primarily by the MNP size. Typically, bulk magnetic materials are ferromagnetic, where the magnetic moments remain aligned even after the withdrawal of the external magnetic field. Therefore, these 'permanent magnets' show high remanent magnetisation (*i.e.*, net magnetisation at zero external magnetic fields) and coercivity (*i.e.*, require a high magnetic field strength in the reverse direction to bring the net magnetisation to zero). Large, multidomain MNPs also display ferromagnetism; however, when their size is reduced further (approach single-domain dimensions), their coercivity increases, reaches a maximum, and then falls sharply to zero. At this stage, the magnetic behaviour converts to superparamagnetism, where the magnetic moments revert to the non-aligned (random) state from the aligned state once the external field is withdrawn. These 'temporary magnets', therefore, have negligible remanent magnetisation and coercivity. This size-dependent magnetic behaviour is depicted in Fig. 5.[58]

A Weiss domain or magnetic domain, which describes the volume of magnetic material where the magnetization is in a uniform direction, is used to differentiate between ferromagnetism and paramagnetism. The size-dependent variation can be determined by the domain structure of ferromagnetic material (also shown in Fig. 5). Frenkel and Dorfman first predicted that when the particle size is lower than a critical value (<15 nm), it becomes a single domain.[59] In accordance with magnetic domain theory, the magnetic saturation, exchange forces, surface energy and the shape of particles are several factors that affect the critical size of a single domain.

While ferromagnetic nanoparticles are advantageous in certain applications, such as in magnetic data storage, superparamagnetic nanoparticles are highly preferred for biomedical applications due to their negligible remanent magnetisation, which enables exquisite control of their magnetic behaviour using an external magnetic field. For example, superparamagnetic iron oxide nanoparticles (SPIONs) have been used widely in all classes of biological applications.[60] In general, MNPs with a size range of around 10–20 nm are usually preferred in most medical applications, not only because of their superparamagnetism but also due to their low toxicity and agglomeration, high circulation time, better pharmacokinetics/pharmacodynamics, ability to diffuse across tissues and biological barriers, and feasibility of targeting tumours *via* the enhanced permeability and retentivity (EPR) effect, among other factors.

4. Therapeutic applications of magnetic nanoparticles

The various types of therapeutic applications of magnetic nanoparticles are depicted in Fig. 6. We discuss these applications with an emphasis on recent advances.

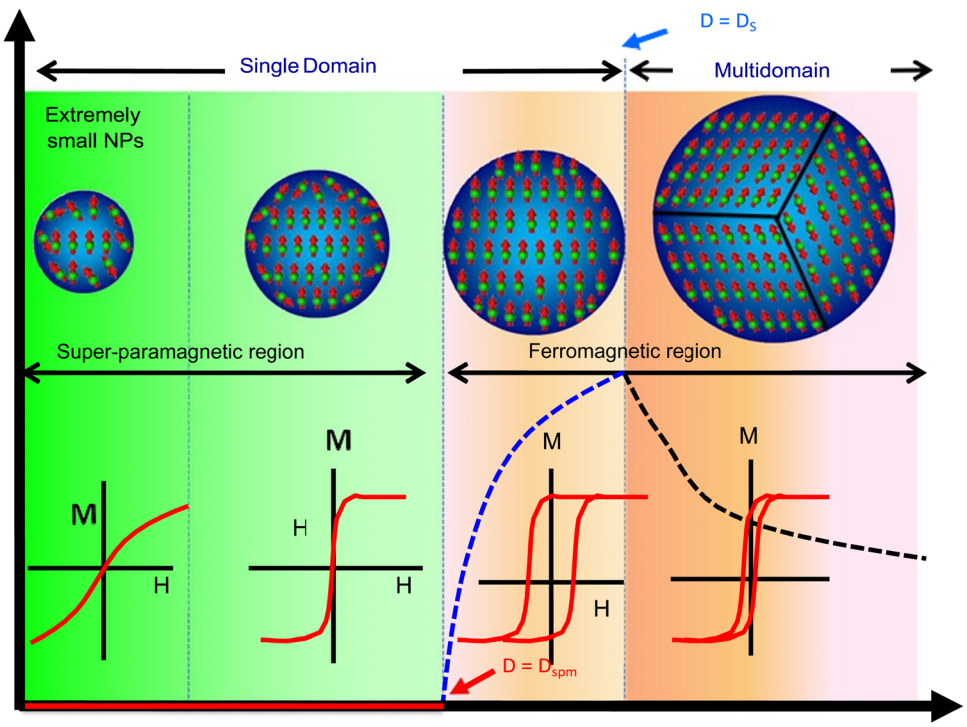

Fig. 5 Size-dependent variation of magnetism in MNPs.[58] Copyright 2018, Elsevier.

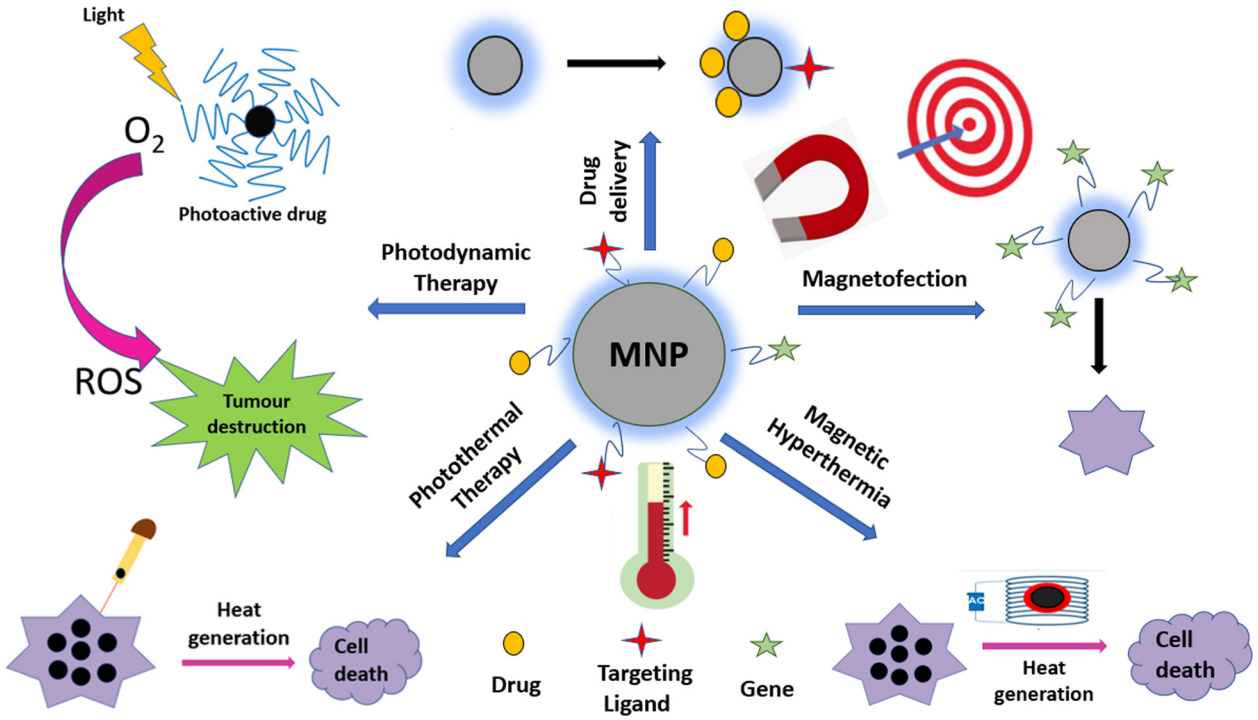

Fig. 6 Various therapeutic applications of magnetic nanoparticles.

4.1 Magnetic hyperthermia therapy (MHT)

The use of MHT has been identified since ancient times for the treatment of malignant tumours. The father of medicine Hippocrates proposed that hot iron can be used to treat surface tumours. Later, unconventional methods like hot water baths, magnetic hyperthermia and high-frequency radiation were used for the thermal ablation of tumours.[61] MHT uses MNPs to treat cancer through heat generation under the influence of an applied alternating (AC) magnetic field. It is a non-invasive method. The magnetic field can penetrate deep inside the body as it is not absorbed by living tissues. The working principle relies on increasing the temperature of the tumour to 41–47 °C to kill cancer cells, *via* either apoptosis or necrosis, as shown in Fig. 7.[62,63]

MNPs are first introduced inside the body by injecting a calculated amount of MNP solution, whereby they accumulate at the tumour site through passive or active targeting. MNPs are then subjected to an external magnetic field to produce heat that raises the temperature of cancerous cells more than that in non-cancerous cells.[64] The benefit of MHT over chemotherapy is that it specifically targets the tumour and does not damage the surrounding healthy tissues, thereby having an increased efficiency over chemotherapy. In addition, cancerous cells have a higher sensitivity to temperature than healthy cells, which is referred to as 'thermal ablation'. An increase in temperature during magnetic hyperthermia can be explained *via* Brownian relaxation (in which the entire NP domain rotates to reverse the direction of the magnetic moment), or Néel relaxation (which is the re-orientation of the MNP domain within the particle), during exposure to an alternating magnetic field (AMF).[65] The AMF can penetrate deep inside the tissues, which enables the treatment of tumours at different positions within patients.

The transfer of magnetic energy to thermal energy can be measured as the specific absorption rate (SAR), which is given in watts g^{-1} by the following equation:[66]

$$\mathrm{SAR} = C(\mathrm{d}T/\mathrm{d}t)(m_s/m_m)$$

where C is the specific heat capacity of the solvent, $\mathrm{d}T/\mathrm{d}t$ is the initial slope of the time-dependent heating curve, m_s is the mass of the solvent, and m_m is the mass of magnetic nanoparticles.

SAR is a crucial factor for the clinical application of MNPs and must be exploited because a higher SAR value requires only a small quantity of MNPs that must be injected inside the body of the patient, as well as a lower AMF exposure time.[67] The size, shape and magnetic properties greatly influence the hyperthermia properties of MNPs.[68] Normally, SPIONs are used for hyperthermia studies as they have a high magnetic saturation.[69]

For improving the SAR, significant research has been done for synthesising nanomaterials with a specific shape, size and surface modification. For effective treatment in a physiological environment, the MNPs must be stable at neutral pH (pH = 7). The stability of the MNPs is dictated by their size and surface charge density.[70] The size-dependent properties of MNPs are responsible for the localised heating of cells.[71] MNPs with a size larger than 200 nm are easily absorbed by the spleen and liver, whereas smaller MNPs with a size of around 10 nm are rapidly eliminated by renal clearance. This shows that the size of the MNPs plays an important role in their uptake by target cells and their removal from the body.[72]

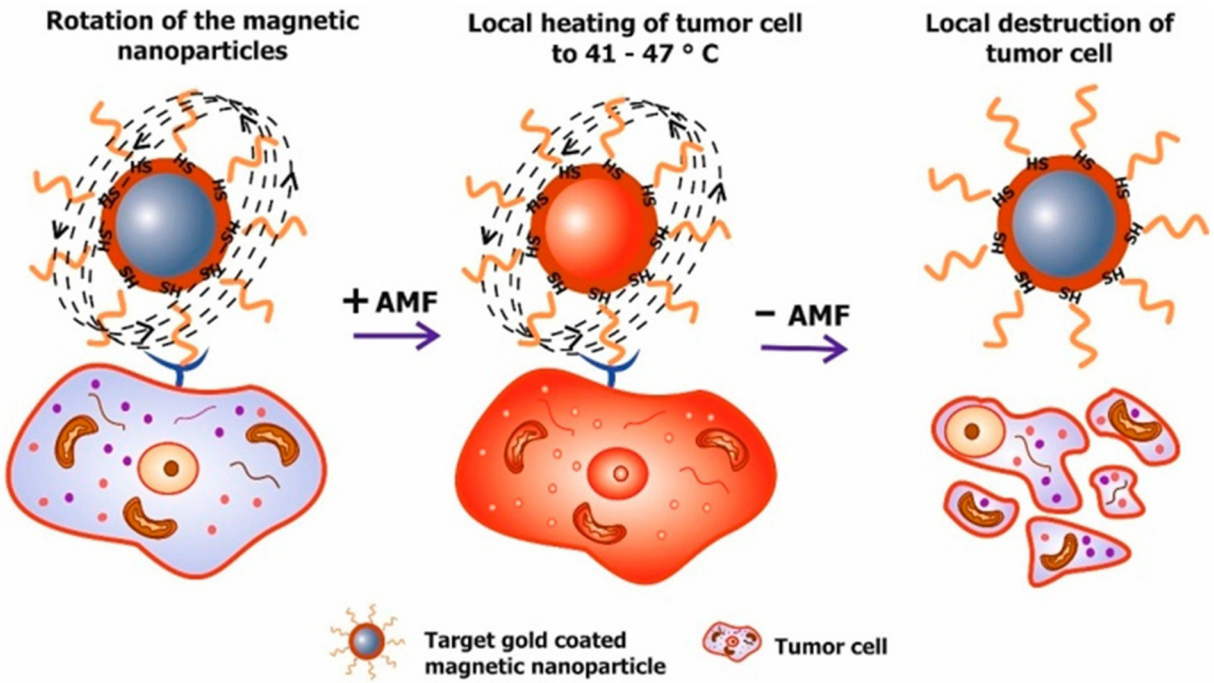

Fig. 7 Working principle of magnetic hyperthermia. Targeted MNPs delivered to a tumour site are exposed to an external magnetic field. Afterward, the increase of the tumour temperature to 41–47 °C is responsible for cell death.[63] Reprinted with permission under Creative Commons Attribution (CC BY). Copyright 2018, Multidisciplinary Digital Publishing Institute.

The shape is another important parameter that influences the heating performance of MNPs. The cubic shape is considered the best for magnetic hyperthermia applications.[73] The SAR values of iron oxide nanoparticles of different shapes follow the order $SAR_{nanocubes} > SAR_{nanoflowers} > SAR_{nano\text{-}octahedra} > SAR_{truncated\ MNPs} > SAR_{nanorods}$.[74]

The surface coating can also affect the heating efficacy of MNPs. Due to the direct connectivity between the surface coating and a biological system, it is assumed that the surface-functionalisation properties will be more important than the core properties of MNPs. Without any surface modification, MNPs with a hydrophobic surface and a high surface-to-volume ratio agglomerate to form large clusters, resulting in a larger particle size.[75] Therefore, it is important to coat MNPs with biocompatible materials. In addition, the thickness of the coating material can vary the heating rate.[76]

Manohar *et al.* prepared Ca-doped zinc ferrite NPs that can be used for the magnetic-hyperthermia treatment of cancer. Moreover, as the concentration of the dopant was increased, the SAR value decreased.[77] Gawali *et al.* showed that biocompatible BSA-conjugated IONPs have a higher heating efficacy than glutaric acid-coated MNPs and show considerable uptake in cancer cells, which makes them efficient for magnetic hyperthermia.[78] Using a modelling approach, Ali *et al.* showed that clustering can significantly decrease the thermal effects.[55]

Microwave-assisted nanocomposites of cubic SPION coated with PEG demonstrated heating efficiency for magnetic hyperthermia with a SAR value of 58.33 W g^{-1} in acidic solution. A toxicity assay revealed that after 48 hours the cell survival was 70%, which showed that the synthesized nanocomposite is a promising candidate for magnetic hyperthermia.[79] Nanoplates of copper ferrite fabricated with aromatic polyamide chains showed a maximum SAR at 1 mg mL^{-1} at different magnetic field frequencies for a time interval of 5–20 min.[80] Xing *et al.* reported that nanoparticles of iron carbide (Fe_5C_2) were used for multimodal hyperthermia treatment. Briefly, they showed *via* a comparative study of Fe_5C_2 nanoparticles with IONPs that Fe_5C_2 NPs have higher magnetization and SAR values than Fe_3O_4 nanoparticles at room temperature.[81]

Manganese-doped iron oxide showed promising results in both the MHT and photothermal therapy (PTT) of glioblastoma. A high SAR value of ~600 W g^{-1} achieved effective hyperthermia therapy along with photothermal therapy, which demonstrated their efficacy in glioma cell death.[82] Yang *et al.* synthesized Fe_3O_4 nanorods of different sizes (460, 350, and 250 nm) to study their effectiveness in magnetic hyperthermia using a mouse model. Among these three sizes, the 350 nm nanorods showed the highest SAR value of 1045 W g^{-1} at an Fe concentration of 0.2 mg mL^{-1}, which demonstrated a satisfactory reduction in tumour volume with the mouse model, along with decent biocompatibility *via* MTT assay.[83] Niclosamide is an FDA-approved drug that is used as an anticancer agent, which inhibits intercellular pathways when combined with hyperthermia to provide therapy against colorectal cancer cells; it can also be used to treat other cancer cells.[84]

Kaushik *et al.* reported a biosynthetic mechanism to produce MNPs that induce hyperthermia inside tumour cells. In short, they treated cancer cells with $FeCl_2$ and zinc gluconate, which thereby increased the Fe and Zn content inside the cells,

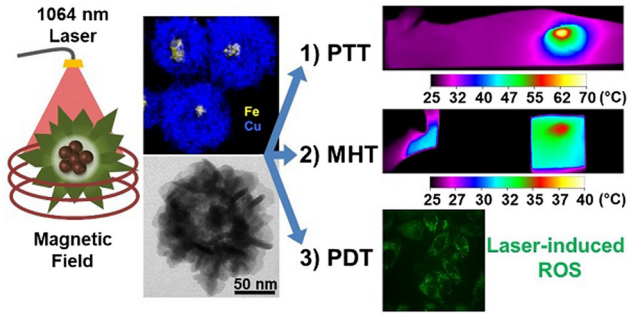

Fig. 8 Nanoflowers of iron oxide with a copper sulfide shell that show MHT, PDT and PTT suitability.[87] Reprinted with permission under Creative Commons Attribution (CC BY-NC). Copyright 2022, Ivyspring International Publisher.

leading to the *in situ* formation of the MNPs with the help of intracellular reactive oxygen species (ROS). As cancer cells have a higher ROS level than non-cancerous cells, the synthesis of the particles did not occur in healthy cells due to the lower ROS levels. Their exposure to AMF for 30 min resulted in a temperature increase of 4–5 °C within the cellular environment. Therefore, this mechanism targets only cancerous cells, and once the biosynthesis of the particles is complete, the particles can be used to induce cell death using magnetic hyperthermia.[85]

After injection, the rapid clearance of MNPs by the liver, bone marrow, spleen and kidneys must be avoided. The size, shape and surface charge greatly influence their mode of clearance. MNPs greater than 100 nm are excreted very quickly from the body; therefore, smaller particles are preferred as they favour protein adhesion due to their high surface-to-volume ratio. Macrophages easily recognize these protein adhesions, however, and MNPs are cleared through the spleen and liver. The circulation rate, retention time and heating performance of MNPs are also affected by their surface charge: a high surface charge usually leads to the adsorption of plasma proteins, with subsequent sequestration by macrophages, thus reducing their circulation time in the blood.[86]

Combination therapies have gained much interest from researchers as they offer a broader spectrum of clinical applications. Curcio *et al.* prepared iron oxide nanoflowers with a copper sulfide shell for tri-modal cancer therapy (Fig. 8).

Combining MHT, PDT and PTT indicates the use of NPs that show a response to light as well as to a magnetic field. Multi-therapeutic nanoparticles enable a lower dosage to be used for greater effectiveness, reduced exposure to laser power, and lower side effects, in contrast to conventional chemo- or radio-therapies used to treat cancer.[87]

4.2 Drug delivery

Another important therapeutic application of MNPs is as a carrier tool for targeted drug delivery. MNPs, using an external magnetic field, can be guided deep inside the tissue, which

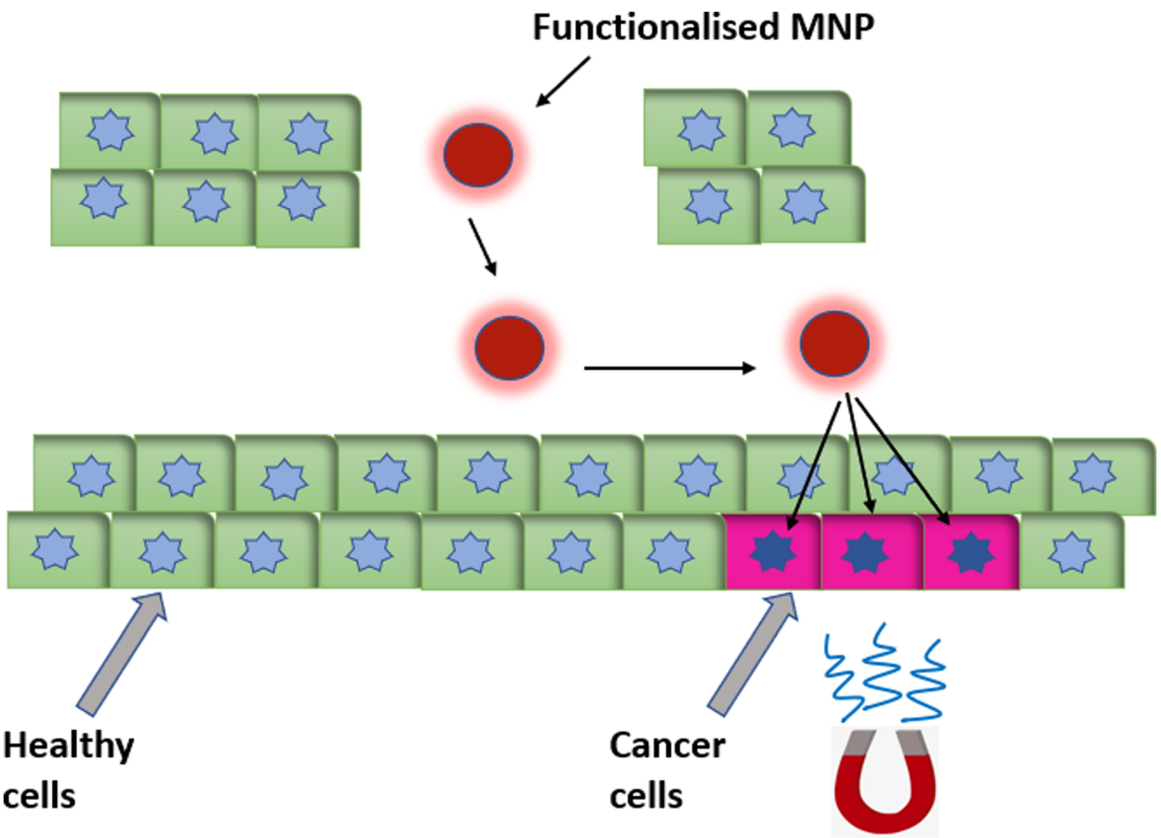

Fig. 9 Magnetic nanoparticles functionalized with a targeting fluorophore, therapeutic drugs or targeting ligands, *etc.*, for magnetically guided targeted drug delivery.

increases the bioavailability of the drug, and magnetic field control enables the precise targeting of the drug (Fig. 9). The main target of magnetically guided drug delivery is to deliver the drug directly to the diseased tissue, without having an impact on the rest of the body.[14] A pharmaceutical drug coated on a biocompatible MNP carrier that is delivered under an applied magnetic field to the targeted organ is also known as a nanoparticulate drug-delivery system (nano-DDS). Such a nano-DDS not only enhances delivery and controls release of the drug at pathogenic sites but also conquers the multidrug resistance (MDR) effect of cancer cells.[88,89] Targeted drug delivery overcomes the disadvantages of conventional therapies like chemotherapy and radiotherapy by providing precise targeting and enabling a reduced dosage, which thereby reduces the toxic side effects associated with it.

The rate of drug delivery at the site can be controlled *via* the intensity of the magnetic field. Numerous other factors, such as size, shape, and surface coating of the biocompatible nanoparticles, contribute to the effective use of MNPs for drug-delivery applications. The size of MNPs must be optimal so that they can easily enter into the bloodstream and escape from capture and elimination by the reticuloendothelial system (RES).[90]

The challenges associated with using MNPs as a drug carrier include drug-agglomeration, fast clearance by the RES, a low drug-carrying capacity, *etc.* However, these can be addressed by coating the MNPs with organic or inorganic multi-functional entities such as proteins, dendrimers, silica, *etc.*

Chitosan (CS)-coated IONPs conjugated with the anticancer drug telmisartan (TEL) were prepared for controlled and targeted drug delivery. Cytotoxicity studies were carried out on PC-3 human prostate cancer cells, which demonstrated a dose-dependent reduction of cell viability. Thus, in this study it was established that the MNP–CS–TEL nano-formulation showed potential as a nanocarrier for increasing the delivery of a poorly soluble drug (TEL) to cancer cells.[91]

4.3 Photothermal therapy (PTT)

PTT is another minimally invasive, localized therapy based on thermal energy, and has attracted the attention of researchers as an emerging tool for local cancer treatment. In PTT, malignant tissues loaded with nanoparticles are irradiated using a near-infrared (NIR) laser, leading to the generation of heat for the destruction of malignant tissues, as depicted in Fig. 10. This technique can be carried out using longer-wavelength light (700–1200 nm), which emits less energy and, hence, does not harm the surrounding non-malignant tissues.[92,93]

We can define a good photothermal agent as the one that has the ability to absorb NIR radiation, has high biocompatibility, low toxicity and a maximum light-to-heat conversion rate, *i.e.*, a high absorption cross-section.[94] Nowadays, gold-based compounds are the most commonly used photothermal agents, but their undefined toxicity is still the main cause of concern in the field of medicine. MNPs have become a viable alternative as photothermal probes for researchers because of their ability to combine with other photothermal agents, thus increasing the capacity of the therapeutic technique. Their downside of having a low molar absorption coefficient in the NIR region, however, can be resolved through controlled clustering.[95]

Several MNPs are also known to show optical absorption in the visible and NIR regions. It has been observed that when these MNPs are excited using visible or NIR light, localized heating (hyperthermia) is generated, which facilitates their use as agents for PTT. IONPs have higher biocompatibility, biodegradability and are relatively easy to functionalize, making them a promising candidate for PTT and other biomedical applications.[96,97] Bu *et al.* demonstrated that IONPs coated on

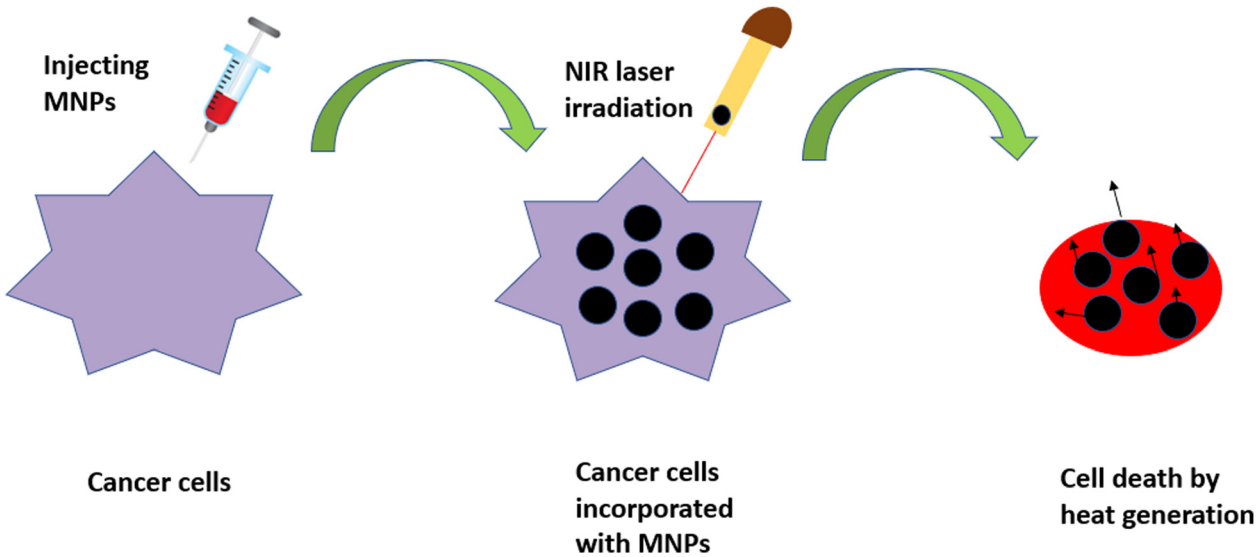

Fig. 10 Schematic representation of cell death *via* PTT for the treatment of cancer. MNPs injected into the cancerous cells followed by NIR laser irradiation result in the generation of heat, which is responsible for the death of the cancer cells.

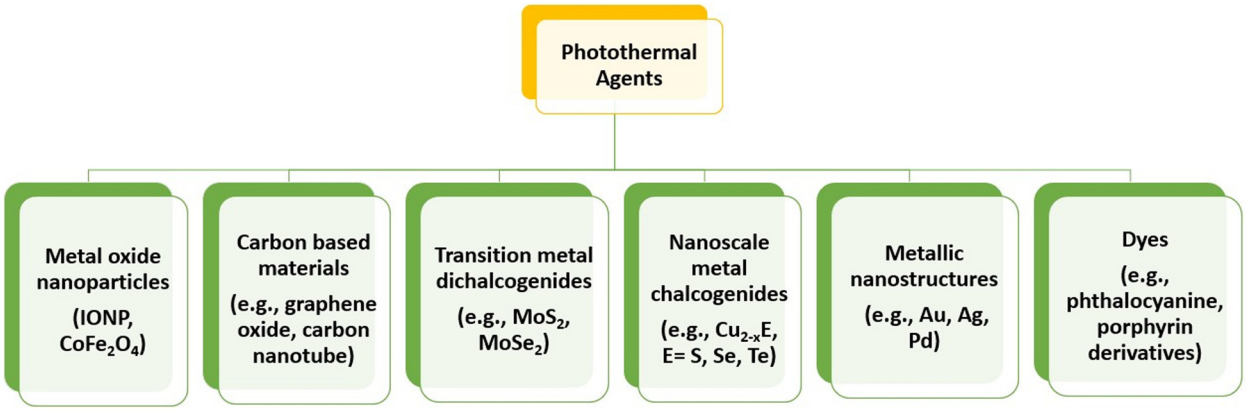

Fig. 11 Various photothermal agents for photothermal therapy.

platelet-cancer stem cells can enhance the PTT of head and neck squamous cell carcinoma.[98]

There are various types of photothermal agents that comprise inorganic and organic materials, as shown in Fig. 11. Organic compounds, mainly NIR dyes with good photophysical properties and large-scale chemical production compared with inorganic materials, have become attractive candidates for PTT.[99]

IONPs of various shapes (spherical, hexagonal and wire-like) irradiated using NIR laser light of wavelength 808 nm showed a strong photothermal effect. Using a human esophageal cancer model, Cu *et al.* demonstrated that spherical IONPs showed NIR-induced hyperthermia, which effectively inhibited the tumour growth compared with other IONP shapes. Thus, the photothermal effect of IONPs can be utilized in clinical cancer therapy applications.[100]

Recently, Deng *et al.* showed multifunctional magnetic nanoprobes for image-guided PTT. They demonstrated a seed-mediated growth method for the preparation of superparamagnetic Mn@Co MNPs, which were further functionalised with indocyanine green (photosensitiser) for MRI/NIR imaging and PTT. Using 808 nm laser irradiation in an MGC-803 tumour-bearing mouse model, these biocompatible nanoprobes exhibit good on-point targeting capability and photothermal therapeutic efficiency.[101] Iron-based nanoparticles also show magneto-thermal as well as photothermal effects when irradiated at 808 nm. Iron carbide (Fe_5C_2) nanoparticles were prepared using sol–gel and thermal decomposition methods. The carbon coating on Fe_5C_2 enhanced its optical absorption, which upon laser irradiation showed a rapid photothermal effect.[81]

Indocyanine green-loaded IONPs showed a synergistic effect in photothermal therapy and immunotherapy for ovarian cancer.[102] Similar work was shown by Zhang *et al.*, where indocyanine green (ICG)-loaded IONPs coated with polyphenols (MIRDs) were used for controlled cancer treatment *via* PTT/immunotherapy. After intravenous injection, the MIRDs showed a long blood-circulation time, magnetic targeting and acted as MRI guides. Using NIR irradiation, these MIRDs demonstrated potent tumour ablation, and further antigens

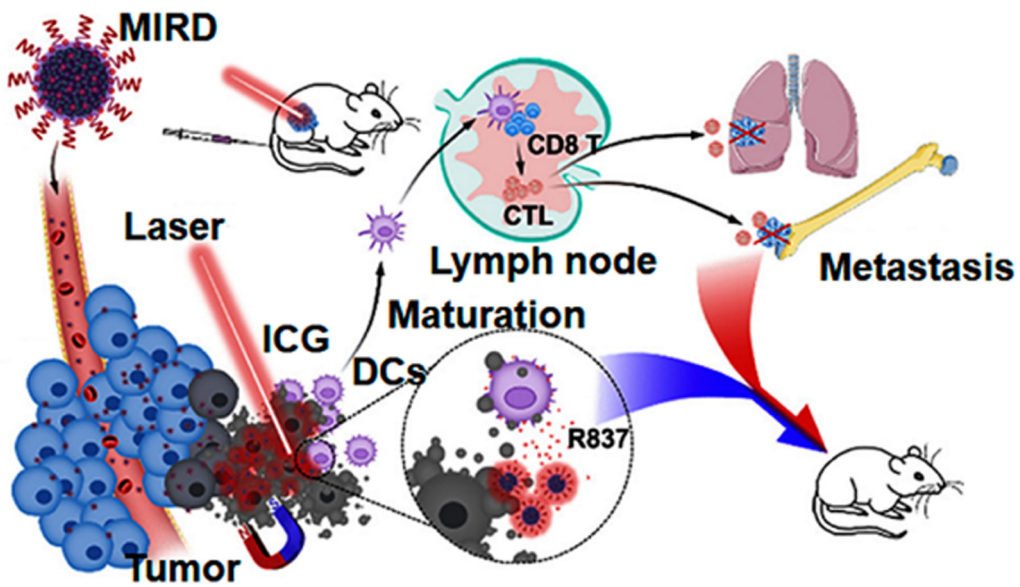

Fig. 12 Schematic representation of MIRDs for cancer treatment using combined PTT/immunotherapy.[103] Copyright 2020, Elsevier.

associated with the tumour induced an immunological response to the body. As a result, the synergism of PTT with immunotherapy caused tumour ablation, suppressed metastasis and prevented tumour recurrence, with fewer side effects (Fig. 12).[103]

In 2020, a comparative study on iron oxide (magnetite and maghemite) nanospheres and nanoflowers for PTT and MHT was demonstrated by Cabana *et al.* in the second optical biological window (NIR-II). In comparison with nanospheres, nanoflowers are known to be better nano-heaters and are largely used in biomedical applications. For PTT, the heating measurements were recorded at 0.3 and 1 W cm^{-2}, irradiated using a 1064 nm laser and MHT at 18 mT and a 470 kHz frequency (Fig. 13). For both therapies, magnetite nanoparticles were more effective, irrespective of their shape. Moreover, in cells, at a lower dosage of nanoparticles, PTT is

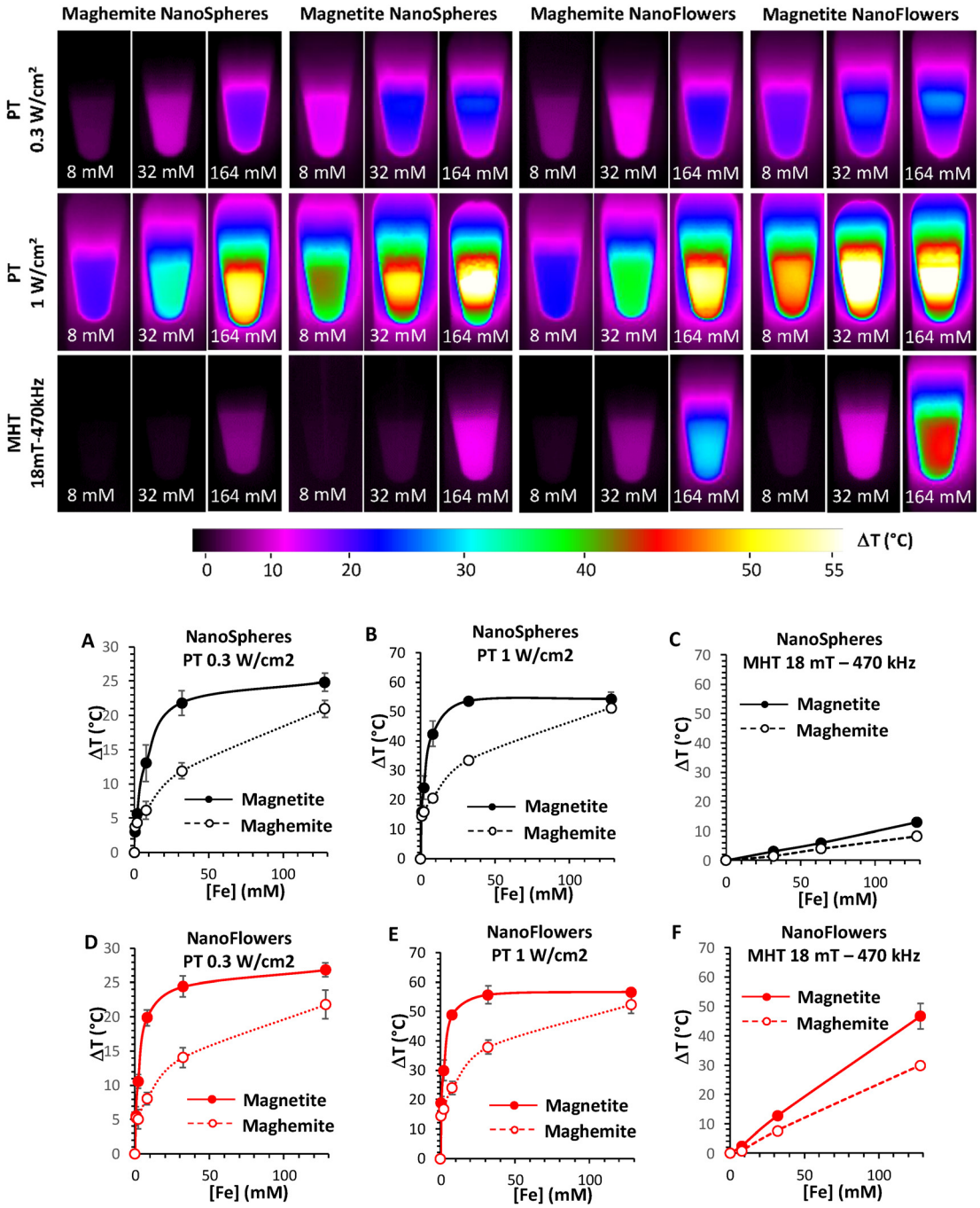

Fig. 13 (Upper images) Infrared images of 50 μL of magnetite and maghemite nanospheres and nanoflowers at different concentrations (8, 32 and 164 mM) for 10 min of exposure to different stimuli (Photothermal, or PT, at laser powers of 0.3 and 1 W cm^{-2}; and magnetothermal, or MHT, at magnetic fields of 18 mT-470 kHz). (Lower images) Elevated-temperature profiles of magnetite and maghemite nanospheres (Panels A, B and C) and nanoflowers (Panels D, E and F) for PTT (Panels A, B, D and E) and MHT (Panels C and F).[104] Reprinted with permission under Creative Common Attribution 4.0 International License. Copyright 2020, Multidisciplinary Digital Publishing Institute.

much more effective than MHT. In addition, the cellular uptake shown by the magnetite nanoflowers was higher than that of nanospheres. During antitumour therapy, complete cell death was observed at a power density of 0.3 W cm^{-2}.[104]

4.4 Photodynamic therapy (PDT)

PDT is a form of drug delivery that has gained much interest over the past few years as a new therapeutic tool for the treatment of cancer.[105] It is a light-activated therapy in which the drug/photosensitizer (PS) is targeted to the tumour. The photosensitizer is then irradiated with a specific wavelength at which the PS absorbs, resulting in the formation of cytotoxic reactive oxygen species that in turn are responsible for the death of cancer cells.

Due to its minimally invasive nature, low side effects, and high cure rates, it has become an alternative to conventional cancer treatments like chemotherapy and radiotherapy.[106,107] Warrier *et al.* also stated that these properties of PDT can also be used to control microbes in biofilms that do not respond to conventional antibiotic therapies as well as for treating infections caused by bacteria. Photosensitizer molecules used can be naturally occurring compounds to increase the efficiency of PDT.[108]

The mechanism of PDT can be explained through a Jablonski diagram, which gives the electronic states and their transitions as the basic requirement of light-activated therapeutic reagents.[109] When a PS is irradiated with light, it gets excited from the ground singlet state (S_o) to an excited singlet state (S_n). It may undergo internal conversion and relax to a lower energy level of (S_1). The PS can gain energy in two different ways: [1] the molecule in the S_1 state releases a photon of a higher wavelength than S_o; this process is called fluorescence; and [2] the molecule in the S_1 state undergoes intersystem crossing, leading to the transition from S_1 to the excited triplet state (T_1).[110,111] By releasing a photon, the molecule can relax from T_1 to the S_o state. This process is known as phosphorescence. Moreover, the excited triplet state can form radicals for two different types of PDT.[112,113]

In Type I reactions, the PS reacts directly to endogenous substrates that have an electron/hydrogen atom which subsequently produces superoxide or reactive oxygen species that destroy the cancer cells *via* oxidation.[114] A Type II process can

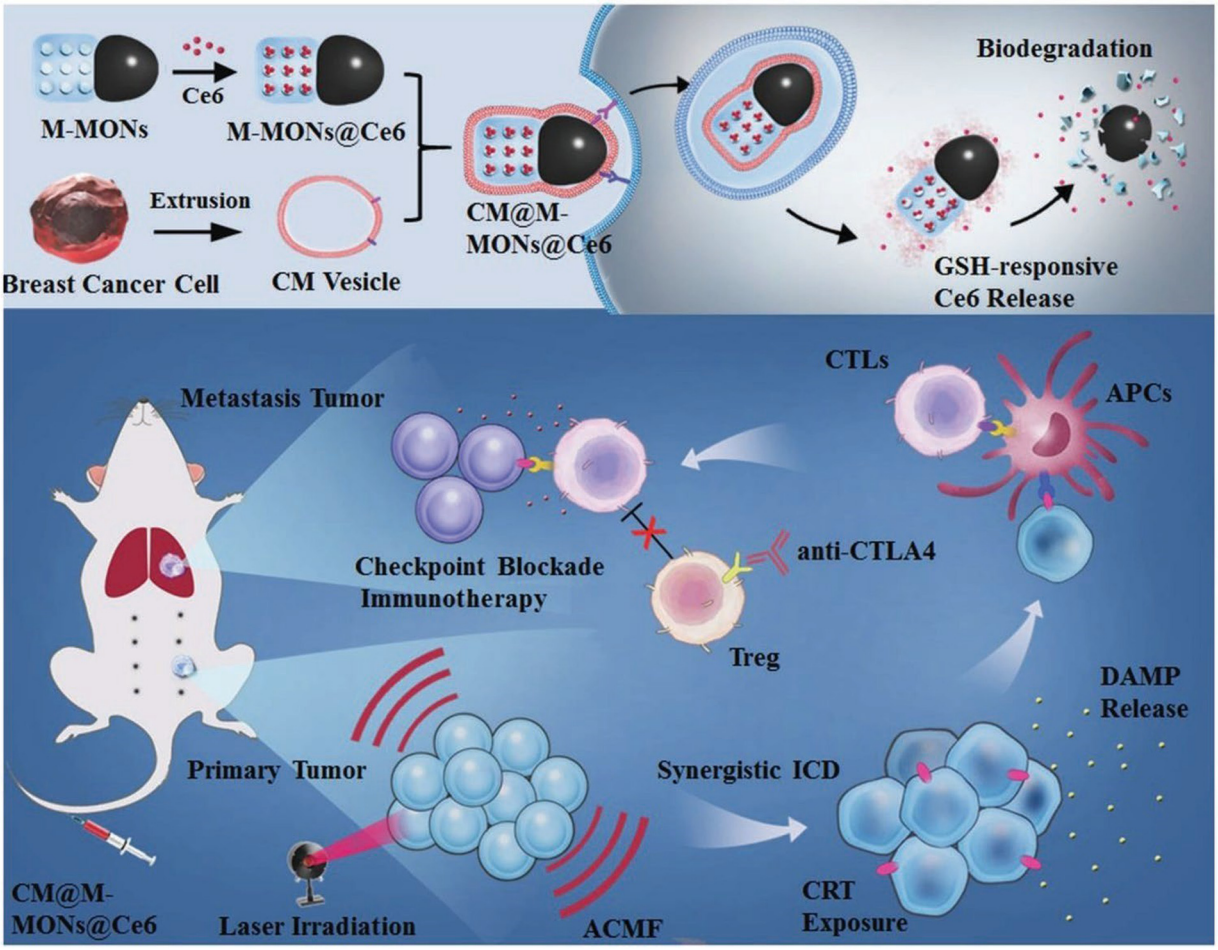

Fig. 14 Schematic representation of the synthetic procedure of Ce6-loaded Janus magnetic mesoporous nanoparticles (CM@M-MON@Ce6) for cancer cell membrane targeting. Combined PDT and MHT are shown to enhance the synergistic antitumour efficiency in combating cancer treatment.[117] Reprinted with permission under Creative Common Attribution 4.0 International License. Copyright 2019, Wiley and Co.

also occur in which the T_1 state directly transfers its energy to molecular oxygen ($^3O_2$) to generate highly cytotoxic singlet oxygen ($^1O_2$).[115]

In 2019, Amirshaghaghi *et al.* developed nanoclusters of chlorine e6 (Ce6)-coated SPIONs for dual-mode imaging and PDT. Briefly, the second-generation photosensitizer Ce6-coated SPIONs were synthesized *via* an oil-in-water emulsion system. The Ce6-SPOINs show high biocompatibility, solubility and significantly slowed down tumour growth in the murine tumour model due to the generation of ROS, making it a theranostic agent for clinical translation.[116]

The synergism of MHT with PDT demonstrated by Wang *et al.* showed an antitumor immune response when bullet-like organosilica-modified MNPs loaded with the photosensitizer Ce6 were used to treat breast cancer cells. Notably, these particles exhibited a high blood circulation time with homogenous targeting. The synthetic procedure with PDT and MHT application for an enhanced synergistic antitumor efficiency against tumour metastasis is shown in Fig. 14.[117] In addition, Ce6 and folic acid (FA)-formulated IONPs can be used as a therapeutic tool in photodynamic therapy (PDT).[118]

Recently, Yu and co-workers developed Ce6 loaded with PG functionalized IONPs linked with glucose, which can give both targeted photodynamic therapy and boosted immunogenicity of lung carcinoma.[119] Combining two therapies in one nanoparticle will increase its efficacy and decrease the side effects associated with it. This synergistic effect has been shown by many researchers. Ngen *et al.* combined PDT with magnetic hyperthermia for the treatment of prostate cancer.[120] Ashkbar *et al.* demonstrated an encouraging alternative to chemotherapy using PDT and PTT for the treatment of breast cancer. Briefly, iron oxide nanoparticles coated with silica and further mobilized with curcumin showed a 27% decrease in tumour volume when treated using PDT and PTT together.[121] In another study, SPOIN loaded with the photosensitizer curcumin were used for PDT that was free of any organic reagents.[122] Mn- and Cr-based photosensitizers were used for PDT and delivery of the drug curcumin, where it was found that the Mn-based nanocomposite loaded with curcumin was more suitable than the Cr-based nanocomposite nanocarrier as a drug-delivery system, as seen *via* its ability to reduce the cell viability to 4.6%.[123]

4.5 Magnetofection

Nanoparticle-mediated magnetofection is a transfection method used for delivering nucleic acid under the influence of an external magnetic field.[124] The particles containing vectors are attached to MNPs *via* non-covalent bonds. Magnetofection is a novel and powerful technique, which increase the efficiency of delivering genetic material into cells.[125–128] Using this approach, DNA/RNA/plasmids can be transfected to the targeted cells.[129,130]

In the cell culture medium, the external magnetic field moves nucleic acid-bound MNPs from the medium to the cell

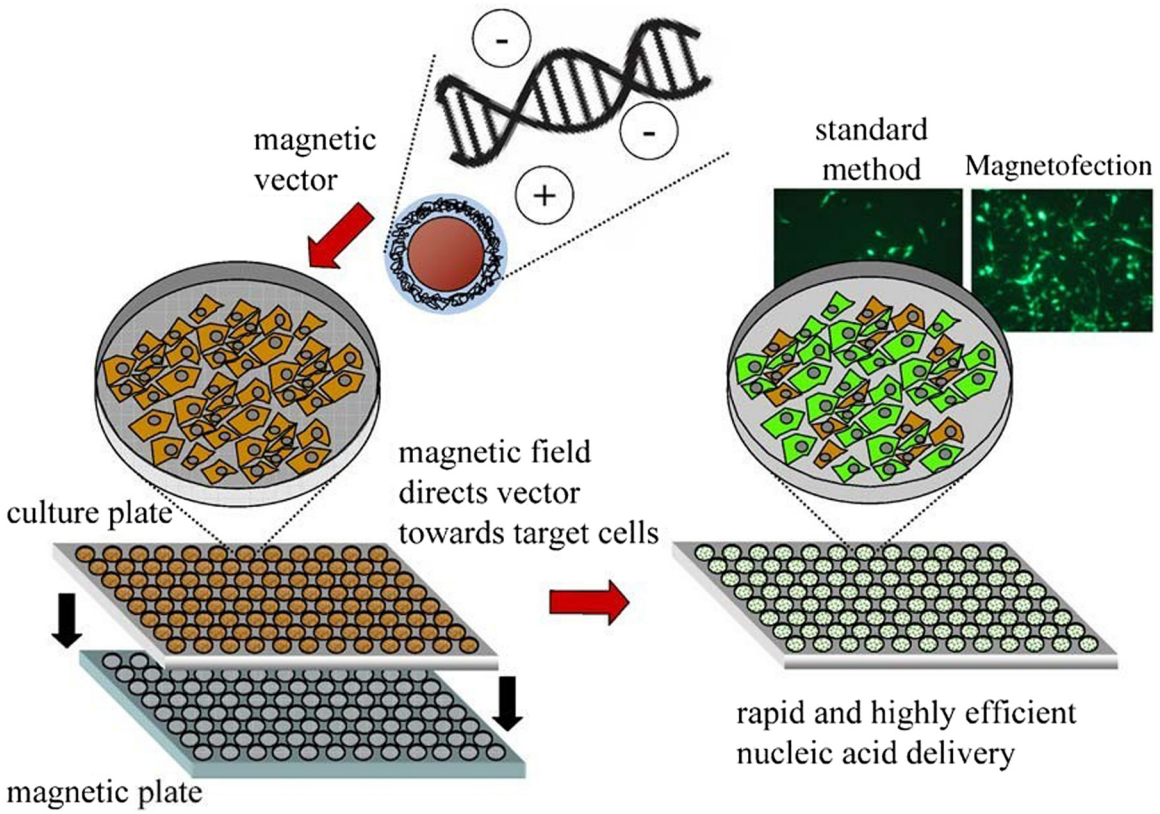

Fig. 15 Various steps of magnetofection in cell culture.[133] Copyright 2005, Elsevier.

surface. Rapid sedimentation to the targeted area results in lowering the time and dosage of the vector with low cell cytotoxicity, thereby increasing the efficiency of transfection.[131]

Genes bound to MNPs are injected intravenously, and guided to the targeted cells/tissues using high-gradient magnets. At the target site, the functional genes are freed *via* enzymatic cleavage or polymer degradation, as shown in Fig. 15.[132,133] Chemical reagents like peptides, polymers and liposomes have a low transfection efficacy and are non-toxic, whereas the *in vitro* and *in vivo* transfection of nucleic acids, such as plasmids, siRNA, shRNA and antisense oligonucleotides, has a high efficiency of transfection.[130]

Though appropriate surface modification, MNPs can act as efficient transfection agents. In addition, the drug/gene can be magnetically guided to the targeted site. In cancer gene therapy, MNPs@siRNA (silencing RNA) in a tumour-bearing mouse model does not show any adverse side-effects when delivered magnetically.[134] In addition, this approach helped to cross the blood–brain barrier in brain gene delivery while other methods show inflammatory reactions with a low transfection rate.[130] However, a key disadvantage associated with magnetofection is the agglomeration of MNPs, which can result following the removal of the external magnetic field.[135]

5. Challenges and future outlook

MNPs show significant potential in various therapeutic applications, particularly in magnetic field hyperthermia and drug targeting. Research in the biomedical field has improved the design and safety of MNPs. However, there are still some challenges, like agglomeration and low magnetization, that need to be addressed by researchers. For *in vivo* clinical applications, the biocompatibility and safety of nanoparticles is the most important aspect. Toxicity caused by MNPs depends on various factors such as the dosage, size, biodegradability, solubility, *etc.* Thus, the toxicity of MNPs needs accurate assessment.

Controlling the chemical composition, size, and shape of MNPs, which strongly affects their properties, is a big challenge for biomedical applications. The nature of the components that respond to a magnetic field, such as iron, cobalt, nickel, *etc*., and the size of NPs with their core and coating are responsible for the safety and biocompatibility of MNPs. Owing to their excellent biocompatibility, both magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) show a wide range of biomedical applications, such as drug delivery, cancer treatment through magnetic hyperthermia, contrast enhancement in MRI, immunoassay, *etc.* By contrast, magnetic nanomaterials made up of cobalt, nickel, *etc.*, despite being highly magnetic, have a poor safety profile and are highly susceptible to oxidation; hence, they have limited potential in biomedical applications.

The choice of synthesis protocol and particle functionalization is also important as it strongly influences the particle characteristics. Another important challenge associated with MNPs in therapy applications is site-specific delivery. Researchers used a permanent magnet to control the direction of the drug, which was not ideal as it has a very low tissue penetration. Initially, a small magnetic carrier was used to attract the MNPs. MHT is a promising application but cannot be used in the early stages of cancer as the tumour needs to be localized. In addition, MHT does not allow deep tissue penetration as the magnetic gradient is inversely proportional to the distance. Thus, MHT needs further advances.

The biggest reward of magnetic nanoparticles lies in combined therapy and diagnostics applications using a single nanoformulation. The see–treat–see action in the near future will be appealing as it will enable the real-time monitoring of theranostic agents that will be beneficial for the patient. The synthesis of multi-functional nanoparticles will be of great interest, as it will enable multi-modal therapy with lower or minimal side effects. In addition, using low-toxicity elements for the development of new-generation nanocarriers that have unique imaging and therapy applications will be attractive for researchers in the future. We can say that MNPs are likely to be the future in cancer theranostics, *i.e.*, diagnosis with precise drug delivery. Moreover, the issues of toxicity will be resolved in the future to increase their efficacy. Therefore, more research is needed in this field to fully exploit the unique properties of MNPs in biomedical applications.

6. Conclusion

This Review aims to present a wide view of recent advances in the use of magnetic nanoparticles for therapy applications. We have provided accounts of various synthesis approaches to prepare magnetic nanoparticles. Advancements in the synthesis and formulation of monodisperse nanoparticles with controlled size, shape and magnetic properties help scientists to address and overcome difficulties associated with the use of magnetic nanoparticles for clinical applications. Magnetic hyperthermia gives the medical community an incredible tool to fight diseases such as cancer *via* apoptosis and necrosis. The properties of MNPs, like the high surface-to-volume ratio and magnetic saturation, make them an excellent candidate for targeted drug delivery. The challenges of low blood-circulation times, low targeting efficacies and premature drug release can be overcome using magnetic nanocomposites (magnetic hydrogels, mesoporous silica nanoparticles, magnetic liposomes, *etc.*), thus making them excellent choices for drug delivery. Light-activated photothermal and photodynamic therapies have low side effects and high cure rates, and thus they serve as an alternative to conventional cancer treatments like chemotherapy and radiotherapy. The synergistic effect of either magnetic hyperthermia with drug delivery or magnetic hyperthermia with photodynamic therapy has presented promising results in treating cancer. Providing two therapies in one carrier will significantly reduce the dosage and toxicity of NPs. Indeed, nanomaterials for biomedical research encompasses a broad and comprehensive interdisciplinary research field that offers numerous opportunities to treat disease in a timely, effective, and risk-free manner.

Abbreviations

MNPs	Magnetic nanoparticles
MRI	Magnetic resonance imaging
PTT	Photothermal therapy
PDT	Photodynamic therapy
IONPs	Iron oxide nanoparticles
FDA	US Food and drug administration
SPIONs	Superparamagnetic iron oxide nanoparticles
PEG	Polyethylene glycol
PVP	Polyvinyl pyrrolidine
SAR	Specific absorption rate
ROS	Reactive oxygen species
PS	Photosensitizer
FA	Folic acid
RES	Reticuloendothelial system

Author contributions

Both authors contributed to the conceptualization, writing, and editing of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors acknowledge funding support from the BRICS STI Framework Programme (Sanction order DST/IMRCD/BRICS/PilotCall2/TherNC/2018 (G)).

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