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Nanosystems: the use of nanoalloys, metallic, bimetallic, and magnetic nanoparticles in biomedical applications

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There is a growing interest in the use of nanosystems such as nanoalloys, bimetallic nanoparticles, metallic nanoparticles and magnetic nanoparticles in biomedical applications. These applications can be as diverse as hyperthermic treatments; targeted drug delivery; bio-imaging; cell labelling and gene delivery. The use of nanoalloys in these applications has received only limited attention due to the fact that there were many unanswered questions and concerns regarding nanoparticles and nanoalloys such as their stability over time, tendency to agglomerate, chemical activity, ease of oxidation, biocompatibility and cytotoxicity. In this chapter we survey current applications and advances in magnetic nanoparticles used in these biomedical applications so as to understand the materials properties that can pave the way for the use of nanoalloys as a potential alternative or improve solutions that are offered by current materials.

1. Introduction

A nanoalloy can be defined as an alloy containing dispersed nanoparticles of two or more metals. In literature nanoalloys are commonly referred to as alloy nanoparticles and alloy nanoclusters.[1] Since our previous survey on biomedical applications of nanoalloys the field of medicinal application of nanoscale materials such as nanoalloys, bimetallic nanoparticles, metallic nanoparticles and magnetic nanoparticles has increased.[2] The survey has found that investigations reported in literature for biomedical applications are generally restricted to a handful of nanomaterials systems *e.g.* superparamagnetic iron oxide and gadolinium oxide. In fact there is currently a plethora of literature now where these nanomaterials are functionalised and modified to suite diverse applications that fall within the broad categories of hyperthermic treatments; targeted drug delivery; bio-imaging; cell labelling and gene delivery. Fortunately, since that review researchers have taken interest in other chemical formulations of nanosystems.

The basic premises of the use of nanoalloys in biomedical applications lies in the advantages that accrue to high surface to volume ratio offered, in general, by nanoscale materials systems. Application related physical properties are critical parameters that primarily influence the selection of a given material system however. Biomedical applications also means that the selected materials system *a priori* will be 'safe' for the duration of use and may not lead to any acute or chronic adversity. This is essentially a broad criterion than what is generally considered to be the case and does not necessarily preclude materials systems that contains elements that are commonly or historically known as giving toxic responses. For a detailed discussion on definitional and biocompatibility aspects of nanoalloys and nanomaterials the readers are referred to our previous report on this topic.[2] The current chapter discusses physical properties, especially the figures of merits of these properties, of nanomaterials (including a few nanoalloys) that have been deemed important for biomedical applications such as the use of magnetic nanoparticles in hyperthermic treatment, targeted drug delivery and bio-imaging (Fig. 1).

Hyperthermia is a therapeutic technique that has been proposed as an alternative to chemotherapy to treat tumours by heating them to a certain temperature that destroys cancer cells but does not harm healthy cells. Heat generated in magnetic materials during magnetisation–demagnetisation cycles, typically known as magnetic hysteresis, can be utilised for such heating.[3–5] Magnetic nanoparticles such as iron oxide have been widely studied due to its combination of properties such as superparamagnetism, biocompatibility, ease of synthesis and relatively low cost. The most common form of iron oxide used for this is magnetite (Fe_3O_4) which is a mixed oxide of bi and trivalent iron and thus shows a tendency to oxidise which alters its magnetic properties. This is why iron oxide nanoparticles are generally coated with a biocompatible layer such as polymers,[6–17] silica[18–21] or gold.[22–28] Hyperthermic treatments using iron oxide nanoparticles have been applied, both *in vitro* and *in vivo*, for the treatment of breast and brain tumours, with promising results.[29–35] Iron oxide coated nanoparticles have also been investigated clinically for possible hyperthermic treatment of prostate and brain tumours.[36–39]

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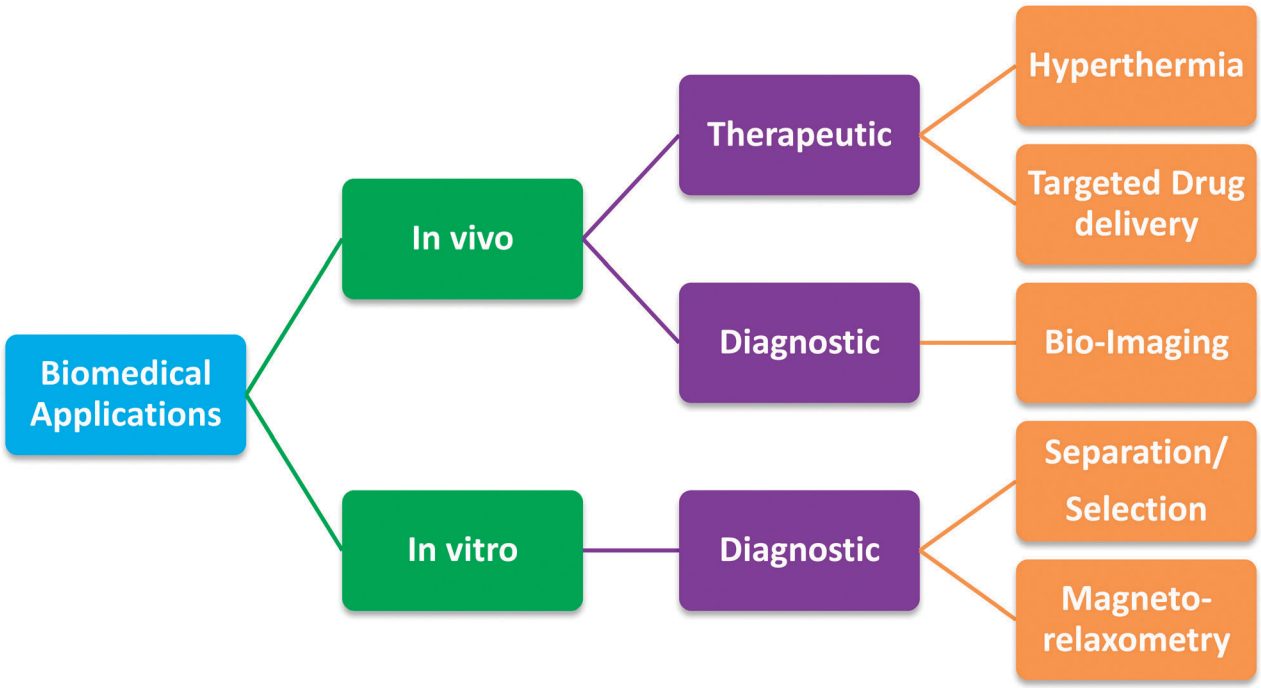

Fig. 1 Schematic showing the various biomedical applications where the use of nanoalloys and nanoparticles is being investigated.

Other nanoparticles that have been reported in the literature as potential candidates for hyperthermic treatment agents include nanoalloys such as Cu–Ni[40–45] and Fe–Co[46] and nanoparticles of ferrite based systems such as Co–Fe_2O_4,[47–49] Mn–Fe_2O_4,[50–52] Ni–Co_2O_4[53] and Fe–MgO,[54] Among these, $NiCo_2O_4$ nanoparticles have been investigated *in vitro* for possible use in hyperthermia treatment of cervical, breast and skin cancer.

Targeted delivery of drugs is another important biomedical application where magnetic nanoparticles offer an extra-corporeal control of internal release and local delivery of drugs to the specific disease/tumour site. This avoids systemic administration of drugs, increases therapeutic efficiency of drugs and allows therapy that does not affect surrounding healthy tissues. Magnetic nanoparticles, as carriers, allow drug permeation through membranes of cancerous cells. Additionally, their uptake by cancerous cells also means that these particles can be used as hyperthermic agents when exposed to an alternative magnetic field. In the so called 'active targeting' antibodies, ligands or aptamers are functionalised or conjugated onto the drug–nanoparticle complex. These antibodies, ligands or aptamers are site specific so the specific site will have the receptor for attachment of the complex. 'Passive targeting', on the other hand, can be achieved in two ways: through the enhanced permeability and retention (EPR) effect or by localised delivery.[55,56] In Section 3 we will provide highlights of the use of different chemotherapeutics such as doxorubicin,[57–60,63] paclitaxel,[61–63] tamoxifen,[64] idarubicin,[65] cisplatin[66] and rapamycin,[67] antibodies such as herceptin,[68] and peptides such as chlorotoxin[69] that have been conjugated to iron oxide nanoparticles for targeted drug delivery.

Bio-imaging contrast generation is another application of magnetic nanoparticles. A spin off from such applications is their use in image-guided therapy. There are many varieties of bio-imaging *e.g.* magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), ultrasound and optical imaging. Magnetic resonance is one of the most powerful bio-imaging tools. Currently gadolinium chelates are used as contrast agents for MRI but these chelates have a tendency to accumulate in the liver and have a short imaging time. The use of magnetic and core–shell nanoparticles as contrast agents has been proposed. In this chapter we will survey the use of these nanoparticles to be used as contrast agents for T_1 and T_2 MRI imaging modes. Among these nanoparticles iron oxide nanoparticles coated with a biocompatible outer layer is relatively more known as T_2 contrast agents. Other nanoparticles that have been surveyed here include oxides Gd_2O_3,[70,71] fluorides such as GdF_3,[72] phosphates such as $GdPO_4$[73] nanoalloys such as Fe–Co,[74,75] Fe–Ni,[76] Fe–Pt,[77–79] ferrites such as $MnFe_2O_4$[80,81] and $CoFe_2O_4$.[82]

In these discussions, we will try to make comparisons between the materials systems investigated for the figures of merit (FoM) of their desirable physical properties. This will be conducted on the basis of available data from the literature and benchmarked against more studied systems. With this the chapter aims to provide a preliminary aid as for selecting materials system for the targeted biomedical applications and implement appropriate modifications in the materials system to improve performance.

2. Hyperthermia

Principles

The concept of using heat to treat cancer has been around as early as the 1800's.[3,83,84] Hyperthermia is a method of applying

heat to an area in the body that is affected by cancerous cells and tissue. The recent advances in medicine particularly nano-medicine has brought hyperthermia treatment to the forefront again. Hyperthermia treatment is achieved by raising the temperature of the infected area to 41–46 °C to kill the cancerous cells. The advantage of this treatment is that it is restricted to the tumour area so damage to the healthy cells is minimised. Hyperthermia treatment is generally used in conjunction with other cancer treatments such as radiotherapy and chemotherapy.[3–5]

Raising the temperature for hyperthermia treatment can be achieved by many different ways like radio frequency, microwave, laser wavelengths and using magnetic nanoparticles such as iron oxide.[84,85] The use of magnetic nanoparticles offers many advantages such as being non-invasive, the magnetic nanoparticles can also be visualised using MRI and another advantage is that these magnetic nanoparticles can be functionalised and carry chemotherapy drugs to the tumour site also.[85] Magnetic hyperthermia treatments or thermotherapy have been applied to many different types of cancer such as breast, brain, prostates and also to melanomas, *in vitro*, and some clinical trials have also been reported.[3]

Heating cells to a temperature of 42 °C or above can cause cell death to occur in some tissues. Cancerous cells have a higher sensitivity to temperature than healthy cells.[86,87] There are two kinds of heating treatments, hyperthermic effect this where heating between 41–46 °C causes cell apoptosis to occur and thermoablation is where heating above 46–48 °C causes cell necrosis to occur. Cell apoptosis is sometimes called controlled cell death. In apoptosis the death of the cell occurs in a certain order. When apoptosis is occurring proteins called caspases breakdown the components in the cell that are needed for living. This protein then causes the production of certain enzymes called DNases which in turn destroys the DNA in the cell nucleus. The cell then shrinks and is removed by macrophages, which digests the cellular debris. However cell necrosis occurs when the cells are heated to high enough temperatures that the protein in cell starts to denature and the lipid bilayers melt which causes the cells to fall apart. Cell necrosis is a much quicker stage of cell death.[3,4,84,85,88–90]

Hyperthermia relies on the principle of converting electromagnetic energy into heat. When metallic objects are placed in an alternating magnetic field an induced current flows within them. The amount of current is dependent on the size of the metallic object as well as the strength of the magnetic field. As the current flows within the metal, the metal starts to resist and heat is generated. If the metal object is magnetic this enhances the process. The heat generation can be due to two mechanisms either Brownian rotation (rotation of the particles) or Neél relaxation (rotation of magnetic moment in the particle). These mechanisms are size dependent.[84,91,92]

In vitro and *in vivo* applications of magnetic iron oxide nanoparticles

The use of iron oxides in magnetic hyperthermia was first proposed by Gilchrist *et al.* in 1957.[92,93] Although superparamagnetic iron oxide nanoparticles (SPIONS) are not the most efficient nanoparticles for heating in hyperthermia treatment when compared to other magnetic nanoparticles but they do offer many advantages such as their magnetic ability, biocompatibility and ability to be functionalised. This has led to SPIONS being the most commercially available cores for hyperthermia treatment.[94–97]

As mentioned earlier magnetic hyperthermia treatments have been carried out, *in vivo* and *in vitro*, on different types of cancer. Here some of the *in vivo* investigations are discussed. DeNardo *et al.* (2005) were looking into treating breast cancer by magnetic hyperthermia. Athymic mice bearing human breast cancer HBT 3477 xenografts were used in this study. A bio-probe was created, this links antibodies with the magnetic nanoparticles, and an alternating magnetic field was then used to inductively heat the bio-probe, therapeutic and toxic responses were then determined. It was found that these bio-probes could be used to provide thermoablative cancer therapy.[29] Kawai *et al.* (2005) investigated using hyperthermia treatments to treat prostate cancer. F33 rats were used for this experiment PLS 10, rat prostate cancer cells, were injected into the flank. Magnetic cationic liposomes (MCLs) were used as the magnetic materials and were composed of a magnetite core coated with lipid membranes. The MCLs were injected into the tumour once it had grown to a diameter of 5–6 mm and then exposed to the AMF. It was found that while the body stayed at 38 °C the temperature of the tumour increased to 45 °C. It was also found that tumour regression also occurred. The results suggest that hyperthermia using MCLs is an effective therapy for prostate cancer. The overall conclusions from the *in vivo* investigations show positive results in that the hyperthermia treatment seems to shrink or kill the cancerous cells.[30] Jordan *et al.* (2006) investigated ways to treat brain tumours using hyperthermia treatment. 120 male rats were injected with RG-2 cells to induce glioblastoma multiforme tumours. Two different types of magnetic fluids were injected into the tumours, dextran coated iron oxide nanoparticles and aminosilane coated iron oxide nanoparticles. The hyperthermia treatment was carried out on days 4 and 6 after tumour induction. It was found that the aminosilane coated nanoparticles prolonged survival 4.5 times longer than the controls. Dextran coated nanoparticles did not offer any advantage. It was found that hyperthermia treatment with magnetic nanoparticles has an antitumoral effect on malignant brain tumours.[31] Kikumori *et al.* (2009) also looked into treating breast cancer by hyperthermia treatment using tumour bearing mice.[32] An anti-HER2 immunoliposomes which contained magnetite (Fe_3O_4) nanoparticles (HML) was created. This will generate heat once in an alternating magnetic field (AMF). The HML was injected into the tumour site and exposed to an alternating magnetic field for 30 minutes twice in 24 hour intervals. The growth rates of the tumour as well as the accumulation of magnetite were then investigated. It was found that the tumour temperature increased to 42 °C while the rest of the body stayed at 38 °C. Tumour regression was also observed. The overall conclusion from this experiment was that hyperthermia treatment with HML was an effective and specific therapy and may provide an alternative method to treat recurring cancer.[32]

Jadhav *et al.* (2013) studied the use of oleic acid functionalized Fe_3O_4 magnetic nanoparticles for use in hyperthermia treatment. A wet chemical method was used to cap the iron oxide nanoparticles, characterisation studies, induction heating and *in vitro* studies were then carried out. Mouse skin fibrosarcoma cell lines (Wehi 164) were used for the *in vitro* study. The results showed that oleic acid capped iron oxide nanoparticles were efficient in the killing of tumor cells in combination with induction heating. These results suggest their suitability for applications in hyperthermia treatment however this needs further validation in *in vivo* tumor models.[33] Yan *et al.* (2014) investigated the use of Fe_2O_3 nanoparticles for magnetic fluid hyperthermia (MFH) treatment of liver cancer. Hepatocarcinoma cells were cultured *in vitro* and treated with a ferrofluid containing Fe_2O_3 nanoparticles and irradiated with an alternating radio frequency magnetic field. The results showed that this ferrofluid could cause cellular necrosis, induce cellular apoptosis, and inhibit cellular growth. These results were dependent on the concentration of the Fe_2O_3 nanoparticles in the fluid.[34] Sadhasivam *et al.* (2015) researched the use of carbon encapsulated iron oxide nanoparticles with polyethylene glycol–folic acid (PEG–FA) to induce selective hyperthermia in folate over expressed cancer cells. The carbon encapsulated iron oxide nanoparticles were prepared by carbon arc method, chemically oxidized and surface modified with PEG–FA. The size, morphology, heating efficiency, biocompatibility and *in vitro* cell uptake of the nanoparticle complex were characterized. Human fibroblast and HaLa cells were used for the *in vitro* and biocompatibility studies. The results showed that nanoparticle complex exhibited superparamagnetic behaviour with the saturation magnetisation of 25.0 emu g^{-1}. The *in vitro* hyperthermia assay confirmed the rapid heating efficiency of nanoparticles under AMF to the hyperthermia range. The intracellular uptake studies demonstrated the specific targeting of cancer cells (Table 1).[35]

Clinical investigations of hyperthermia using magnetic iron oxide

Some clinical studies have been carried out to investigate if hyperthermia treatment is both suitable and as effective in humans. Johannsen *et al.* (2005) carried out the first clinical trial on one patient to treat prostate cancer *via* magnetic hyperthermia treatment. Nanoparticle suspensions were injected into the prostate with the help of ultrasound and fluoroscopy. The treatments were carried out using the first magnetic field applicator for use in humans. It was found that hyperthermia treatment was feasible.[36] Johannsen *et al.* (2007) carried out further studies on the use of hyperthermia for treatment of prostate cancer. 10 patients took part in this phase I trial. The patients were injected into the prostate with ferric nanoparticles coated with aminosilane. The patients then received six thermal therapies for one hour in weekly intervals using an alternating magnetic field applicator. The heating technique was found to be feasible with hyperthermic to thermoablative temperatures being achieved.[37] Maier-Hauff *et al.* (2007) also investigated the use of magnetic nanoparticles in hyperthermia treatment for patients suffering from brain tumours. 14 patients were receiving treatment through a combination of radiotherapy and thermotherapy. The aminosilane coated iron oxide nanoparticles were injected into multiple sites throughout the tumour and exposed to an alternating magnetic field. This study showed that hyperthermia treatment could be applied to brain tumours and hyperthermic temperatures could be achieved. This therapy proves to be promising.[38] Maier-Hauff *et al.* (2011) continued the study of using magnetic hyperthermia as a treatment for recurring giloblastoma. 66 patients received the treatment a liquid dispersion of iron oxide nanoparticles coated with aminosilane was injected into the tumours and the patients were then exposed to an alternating magnetic field. This treatment was combined with radiotherapy. The results showed that hyperthermia therapy in combination with radiotherapy is safe and effective and leads to longer survival when compared to other therapies in the treatment of recurrent glioblastoma. More studies need to be carried out regarding the use of hyperthermia therapy for the treatment of cancer however the current results look promising.[39]

Other magnetic nanoparticles for hyperthermia treatment

Other magnetic nanoparticles such as, Cu–Ni, Fe–Co, Co–Fe_2O_4, Mn–Fe_2O_4, Ni–Co_2O_4 and Fe–MgO have also been investigated for use in hyperthermia treatments. Bettge *et al.* (2004) investigated the development of nickel–copper nanoparticles for eventual use in hyperthermia treatments. The Ni–Cu alloy was produced by a physical process, ball milling. The Curie temperature of

Table 1 Summary of some *in vivo* and *in vitro* studies carried out investigating the effects of targeted hyperthermia on cancer cells

Core material	Coating/complex	Cell line	Cancer	Curie temperature (°C)	Saturation magnetisation M_s (emu g^{-1})	Ref.
Fe_3O_4	MCLs	PLS 10	Prostate	45	—	30
Fe_3O_4	Dextran Aminosilane	RG-2	Brain	43–47	—	31
Fe_3O_4	Herceptin–liposome	anti-HER2	Breast	45	—	32
Fe_3O_4	Uncapped	Fibroblasts	Skin	60	57.3	33
	(OA[a])-0.25			55.6	43.1	
	OA-0.5			51.2	26.8	
	OA-1			46.4	24.1	
Fe_3O_4	—	SMMC-7721	Liver	39–54	—	34
Fe_3O_4	Carbon with PEG–FA[a]	Fibroblasts HeLa	Cervical	43–45	25	35

[a] MCLS – magnetic cationic liposomes, OA – oleic acid, PEG–FA – polyethylene glycol–folic acid.

these alloys must be carefully monitored this was done by using the phase diagram of Ni–Cu. It was found that it was possible to develop magnetic Ni–Cu nanoparticles with a desired Curie temperature for hyperthermia treatment.[40] Chatterjee *et al.* (2005) also investigated the use of Cu–Ni nanoparticles with the aim of using them in hyperthermia treatments. The Cu–Ni nanoparticles were produced by both chemical and physical processes. In order to ensure biocompatibility the bimetallic alloy was encapsulated in a polyethylene glycol (PEG) coating. The nanoparticles were found to have a Curie temperature of 43–46 °C and would be ideal for hyperthermia therapy.[41] Ban *et al.* (2011) investigated the production of bimetallic Cu–Ni nanoparticles for potential use in magnetic hyperthermia treatments. The nanoparticles were ball milled with different compositions until the ideal Curie temperature of 45 °C was obtained. The results showed that Cu–Ni nanoalloys maybe good candidates for self-regulating magnetic hyperthermia applications. These particles would need to be coated with an ideal material to improve biocompatibility and decrease agglomeration.[42]

Stergar *et al.* (2013) investigated the development of nickel–copper nanoparticles for eventual use in hyperthermia treatments. A micro-emulsion method was used to synthesise the Cu–Ni alloy nanoparticles and the Curie temperature and saturation magnetisation were investigated. Results showed a Curie temperature of 43 °C and saturation magnetisation of 2.5 emu g^{-1} which is suitable for self-regulating hyperthermia.[43] Amrollahi *et al.* (2015) investigated the use of Cu–Ni alloy nanoparticles for use in hyperthermia treatments. Cu–Ni nanoparticles were synthesised by a mechano-thermal method.[44] Both the Curie temperature and cytotoxicity of these nanoparticles was investigated. Curie temperature was found to be 44 °C and the nanoparticles were found to be biocompatible in low concentrations. This may improve if a biocompatible coating is used.[44] Ferk *et al.* (2014) investigated the magnetic properties of Ni–Cu alloy nanoparticles for the potential use in hyperthermia treatments. Ni–Cu alloy nanoparticles were synthesised *via* a sol–gel process. Both the Curie temperature and saturation magnetisation of these nanoparticles was investigated. The results showed a Curie temperature of 65 °C and saturation magnetisation of 8 emu g^{-1} with a composition of $Ni_{67.5}Cu_{32.5}$. These parameters can be adjusted by selecting different compositions.[45]

Shokuhfar and Afghahi (2014) investigated the use of Fe–Co alloy nanoparticles for possible use in magnetic hyperthermia treatments. These nanoparticles were prepared *via* a micro-emulsion method. It was found that by increasing the water-to-surfactant molar ratio, the nanoparticles increase in size. The magnetic properties of the nanoparticles were investigated to see if there was a size effect. It was found that the increasing size affected the magnetic properties but these particles would be effective for hyperthermia treatment.[46]

Kim *et al.* (2008) also studied the use of $CoFe_2O_4$ nanoparticles for potential applications in hyperthermia treatments. The nanoparticles were synthesised by a reduction technique and were then investigated as heating agents before *in vitro* or *in vivo* studies were carried out. The heat generation from $CoFe_2O_4$ nanoparticles under the influence of an AC magnetic field was monitored. It was found that the heat generation from the nanoparticles was dependent on the strength and intensity of the AC magnetic field. By adjusting the AC field and frequency $CoFe_2O_4$ nanoparticles have the desired heating for magnetic hyperthermia.[47] Surendra *et al.* (2014) researched the potential use of $CoFe_2O_4$ nanoparticles in hyperthermia treatments. These mangentic nanoparticles were synthesised *via* a co-precipitation method. Polyacrylic acid (PAA) was used as a coating for biocompatibility. The nanoparticles size varied from 6–14 nm, their magnetic properties as well as their cytotoxicity were investigated. The results showed that saturation magnetisation was found to vary from 33 to 44 emu g^{-1} with increase in the particle size, nanoparticles were non-toxic and could be used in biomedical applications such as hyperthermia treatment.[48] Sabale *et al.* (2015) examined $CoFe_2O_4$ nanoparticles for use in hyperthermia treatments. These nanoparticles were synthesised by a polyol method. Induction heating and cytotoxicity tests were carried out on these nanoparticles to establish if they were suitable for use in hyperthermia treatment. The results showed that the nanoparticles have an average particle size of less than 10 nm. It was found that $CoFe_2O_4$ nanoparticles are able to produce threshold hyperthermia temperature and the cell viability of these nanoparticles is also acceptable for *in vivo* application studies.[49]

Kim *et al.* (2009) studied spinel $MnFe_2O_4$ (Jacobsite) nanoparticles for the potential use in magnetic hyperthermia therapy. These nanoparticles have high magnetic moments and are also biocompatible. The nanoparticles were synthesised *via* thermal decomposition and the ideal size of the nanoparticles for hyperthermia treatment was found.[50] Kim *et al.* (2010) researched $MnFe_2O_4$ nanoparticles for the potential use in magnetic hyperthermia therapy and drug delivery. $MnFe_2O_4$ nanoparticles were synthesized using the seed mediated growth method and coated with the polymer chitosan. Chitosan was coated on the surface of $MnFe_2O_4$ nanoparticles using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) as a linking agent. Heating studies were carried out on the non-coated and chitosan coated nanoparticles. The results showed that these nanoparticles display significant heating for hyperthermia applications.[51] Shah *et al.* (2013) examined the PEG-coated folic acid-modified superparamagnetic $MnFe_2O_4$ nanoparticles for use in hyperthermia and drug delivery. The $MnFe_2O_4$ magnetic nanoparticles were prepared by co-precipitation method. The nanoparticles were then coated with a polyethylene glycol (PEG) layer. In order to conjugate the folic acid to the PEG layer is must be activated using DCC (dicyclohexyl carbodiimide). The drug doxorubicin was then loaded onto the complex. Magnetic heating was studied by exposing the magnetic fluid to high frequency magnetic field. Temperature of the fluid rose to 45 °C from 25 °C in about 22 min, which is an effective and appropriate temperature for the localized hyperthermia treatment of cancer.[52]

Kale *et al.* (2012) investigated the use of $NiCo_2O_4$ (NCO) nanoparticles for their potential use in magnetic hyperthermia treatments. The NCO nanoparticles were synthesised *via* a combustion method and were functionalised by coating with mercaptopropionic acid (MPA) to improve biocompatibility. The biocompatibility of these nanoparticles was then tested

Table 2 Summary of the key FoMs associated with the use of nanoparticles in hyperthermic applications. Nanosystems marked with ^ can be pursued as candidate materials for possible use in hyperthermia treatment. More experiments are needed to find the correct composition for the Cu–Ni nanoalloys but they offer good saturation magnetisation and Curie temperatures for possible use in hyperthermia treatments. The possible cytotoxic effect can be curtailed by coating these nanosystems with suitable biocompatible layers such as polymers

Core material	Composition	Coating	Synthesis	Particle size (nm)	Curie temperature (°C)	Saturation magnetisation M_s (emu g^{-1})	Ref.
Cu–Ni^	29 : 71	—	Ball milling	436	46–47	—	40
	30 : 70	—	Ball milling	300–400	76	6–8	41
	30 : 70	—	Polyol red	50–80	76	45	
	30 : 70	PEG[a]	—	200–500	46–56	—	
	40 : 60	—	Ball milling	10	—	4.4	42
	30 : 70			11	24	17.5	
	27.5 : 72.5			12	45	20.7	
	27 : 73			11	53	13.2	
	25 : 75			11	137	48.5	
	20 : 80			10	174	32.9	
	27.5 : 72.5	—	Reduction	7	46	2.5	43
	0.5 : 0.5	—	Mechano-thermal	20	44	18	44
	67.5 : 32.5	—	Sol–gel	16–20	65	8	45
Co–Fe_2O_4^	—	—	Reduction	5		49.2	47
	—	PAA[a]	Co-precipitation	6	48	33	48
	—			10	58	42	
	—			14	68	44	
	—	—	Polyol	4	46–50	48	
Mn–Fe_2O_4^	—	PEG–FA[a]	Co-precipitation	16	45	44	52
Ni–Co_2O_4	—	MPA[a]	Combustion	8	48	—	53
Fe–MgO	—	—	Vapour condensation	75	—	210	54
Fe–Ni	75 : 25			—	78–82	66	98

[a] PEG – polyethylene glycol, PAA – polyacrylic acid, PEG–FA – polyethylene glycol–folic acid, MPA – mercaptopropionic acid.

on human cervical cancer, human breast cancer and mouse skin cancer cell lines. The results showed 100% cell viability on all cell lines and leaching of Ni or Co was not detected. The nanoparticles were then subjected to RF absorption which showed heating up to 43 °C after 1 minute. This study suggests that $NiCo_2O_4$ nanoparticles are promising agents for hyperthermic treatment of cancer.[53]

Chalkidou *et al.* (2011) investigated the use of Fe–MgO nanoparticles as potential hyperthermia agents. The heating efficiency and biocompatibility of these core–shell nanoparticles was investigated *in vitro* using different human breast cancer cells. The experiment showed good cytotoxicity, high absorption and fast thermal response indicating potential use for hyperthermia treatment but more experiments are need (Table 2).[54]

3. Targeted drug delivery

Principles

The idea for targeted drug delivery originated in and around the late 1970s.[92,99–101] Targeted drug delivery is being developed as one alternative to chemotherapy. In chemotherapy the treatment relies on the circulatory system to deliver the anti-cancer drugs to the tumour. There are drawbacks to this treatment including heavy dilution rate, reduced efficacy, non-specificity and the toxicity of the drug. This causes sides effects such as the targeting of healthy cells and organs as well as cancerous cells. This is where targeted drug delivery is useful. In targeted drug delivery the treatment is directed to the specific area where the tumour is. One such treatment that has been researched is the use of nanoparticles, specifically magnetic nanoparticles. The advantages of using nanoparticles are their high surface to volume ratio, unique optical, electronic and magnetic properties. The use of nanoparticles in drug delivery systems has many advantages such being able to target specific locations, the reduction in the amount of drug needed to obtain a certain concentration and this also helps reduce the concentration of drugs at non-target sites therefore reducing the side effects.[102,103] The success of the therapy can be dependent on a number of factors such as the strength of magnetic field and magnetic properties of the nanoparticles being used. As this therapy is injected intravenously other parameters such as the flow rate of the blood, infusion route, circulation time and concentration of the nanoparticles also play an important role in delivery of the treatment.[91,92,104–106]

The main idea behind targeted drug delivery is that the magnetic nanoparticle is coated with a suitable coating in order to functionalise the nanoparticles and allow the drug to be attached or encapsulated. Once the drug–nanoparticle complex is administered into the circulatory system and once in the bloodstream the external magnetic field is used to guide the drug–nanoparticle complex to the target site. The drug is then released by either enzyme activity or by changes in pH, temperature or osmolality.[92,107]

Targeted drug delivery can be classified into two types either active targeting or passive targeting (Fig. 2). In active targeting

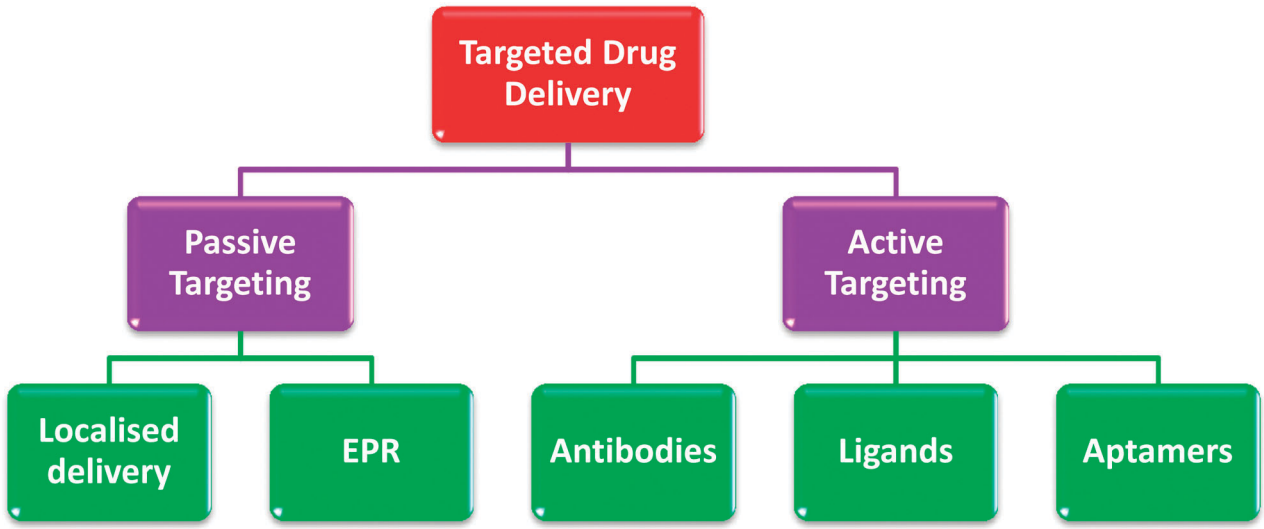

Fig. 2 Schematic showing the different possible routes for targeted drug delivery.

antibodies, ligands or aptamers are functionalised or conjugated to the drug–nanoparticle complex. These antibodies, ligands or aptamers are site specific so the specific site will have the receptor for attachment of the complex. Passive targeting can be achieved in two ways, the enhanced permeability and retention (EPR) effect or by localised delivery. Passive targeting takes advantage of the differences between healthy cells or tissues and diseased cells or tissues (tumours). Some diseased tissues or tumours are disorganised and highly porous and through the enhanced permeability and retention (EPR) effect nanoparticles can accumulate in these tumour tissues. Localised delivery relies on injecting the anticancer–nanoparticles complex directly into the tumour site.[55,56]

Magnetic nanoparticles for targeted drug delivery

There are certain requirements that must be met before magnetic nanoparticles can be considered for targeted drug delivery. Magnetic nanoparticles must have monodispersity, which means that the particles must be the same shape and size. This is important as the properties of the nanoparticles/nanoalloys depend on the dimensions of the nanoparticles.[95] These nanoparticles must also be superparamagnetic. Stability is another requirement; the nanoparticles must be stable which can be achieved through a core–shell structure. Core–shell structures consist of a metallic core with an inorganic or polymeric coating. The nanoparticles must also be biocompatible, they must not cause any harm in the body. The coating on the nanoparticle generally offers this biocompatibility as well as the ability to provide functionalization. These nanoparticles must also be less than 1–100 nm in order to be absorbed. For targeted drug delivery the drug will be encapsulated or attached to the surface coating of the core–shell nanoparticle by physical adsorption or by covalent conjugation.[3,108,109]

In order to fight and kill cancer cells chemotherapeutic agents such as doxorubicin (DOX), paclitaxel (PTX), danorubicin, tamoxifen, mitoxantrone, fludarabine, amethopterin and rapamycin are attached to or encapsulated in the functionalised magnetic nanoparticles. The use of some of these chemotherapeutics in MNP targeted drug delivery will be discussed in this section.[3] Nobuto *et al.* (2004) carried out *in vivo* experiments on hamsters with osteosarcoma to investigate the effectiveness of systemic chemotherapy. Magnetite liposomes containing doxorubicin were prepared by a reverse phase evaporation method and the efficiency of this method of chemotherapy was evaluated using external magnetic field. The results showed that this method of systemic chemotherapy reduced tumour growth and prevented metastases.[57] Arruebo *et al.* (2006) investigated the release of doxorubicin from magnetic nanoparticles as a potential alternative to traditional chemotherapy. Zeolite–magnetite nanoparticles were prepared by mechanical activation and were found to have a thin aluminosilicate coating. These nanoparticles were then dispersed in a doxorubicin hydrochloride solution and the doxorubicin was allowed to absorb onto the nanoparticles until no difference in concentration was observed. *In vitro* tests showed that the nanoparticles were able to store and release sufficient amounts of doxorubicin.[58] Sahu *et al.* (2015) investigated the use of PEG coated FePt–Fe_3O_4 composite nano-assemblies for targeted drug delivery. A hydrothermal method was used to prepare the composite material which was then coated with PEG. The composite material was then loaded with the anticancer drug doxorubicin and its effectiveness was investigated *in vitro* on L929 mice fibroblast and cervical cancer cells. Doxorubicin loaded composite nano-assemblies shows pH responsive drug release in a cell-mimicking environment. The results show that this release is enhanced by the application of an AC magnetic field. CNAs show non-appreciable cytotoxicity in L929 mice fibroblast cells but show toxic effects in cervical cancer (HeLa) cells.[59] Zou *et al.* (2015) researched the use of chitosan coated mesoporous magnetic nanoparticles loaded with doxorubicin for targeted drug delivery in breast cancer cells. A solvothermal method was used to prepare the mesoporous magnetic nanoparticles and these were then coated with chitosan. *In vitro* studies were carried out on MCF-7 breast cancer cell line.

The cytotoxicity of the drug free and the drug-loaded magnetic nanoparticles was tested. The results showed that both formulations exhibited a concentration-dependent cytotoxic effect. However the drug loaded nanoparticles exhibited a greater cytotoxic effect when compared to the drug free nanoparticles. This study showed that magnetic nanoparticles can be targeted to tumor cells under the presence of oscillating magnetic field.[60]

Zhang *et al.* (2005) investigated the use of lyophilized paclitaxel magnetoliposomes as a potential drug delivery treatment for breast cancer. Paclitaxel magnetoliposomes were prepared by the reverse evaporation method with magnetite (Fe_3O_4) as the magnetic core. *In vivo* studies were carried out on mice which were injected with the EMT-6 breast cancer cell line. The paclitaxel magnetoliposomes were delivered to the solid tumours by parenteral administration. The paclitaxel magnetoliposomes complex was shown to be selectively taken up by the tumour. This study showed that paclitaxel magnetoliposomes had an antic-cancer effect on the tumour. Magnetic targeting was also used in this study and proved to be promising.[61] Hua *et al.* (2010) investigated the use of magnetic nanoparticles coated with biocompatible polymers with anticancer drug paclitaxel (PTX) bound to the polymer for treatment of prostate cancer. Polyaniline (PNa) was chosen as the biocompatible polymer, this was modified to poly[aniline-cosodium *N*-(1-one-butyric acid) aniline] (SPAnNa). The Fe_3O_4 magnetic nanoparticles were then coated with this modified polymer and PTX was immobilised covalently on the surface. An external magnetic field was used to guide the SPAnNa–MNP-bound-PTX complex to the target site. Human prostate carcinoma cells (PC3 and CWR22R) were used investigate the use of PTX for treatment of prostate cancer. The results found that bound-PTX was more cytotoxic to human prostate carcinoma cells than free PTX. Cellular growth was further inhibited when magnetic targeting was applied to the bound-PTX. It was concluded that this is an effective treatment for prostate cancer.[62] Cui *et al.* (2013) studied the effect of using transferrin-conjugated magnetic silica PLGA nanoparticles loaded with doxorubicin and paclitaxel as a treatment for malignant brain glioma. Transferrin is a plasma protein that transports iron through the blood. Transferrin receptors are widely produced in glioma cells. The core consisted of superparmagnetic iron oxide coated with mesoporous silica nanoparticles, this is where is doxorubicin was loaded. The core was then coated with PLGA as a shell which was where the paclitaxel was loaded. Transferrin was conjugated on the surface to enhance the transport across the blood brain barrier and target the brain glioma cells. *In vitro* and *in vivo* tests were then carried out on the complex. For *in vitro* testing U-87 MG-luc2 cells were used to investigate the cytotoxicity and cellular uptake of the complex. The cellular uptake was enhanced by the presence of a magnetic field. For *in vivo* testing, mice were injected with U-87 MG-luc2 glioblastoma cells. The results showed that the complex had inhibited the growth of the tumour. This complex was also found to be biocompatible and would be a suitable treatment for malignant brain glioma.[63]

Hu *et al.* (2006) studied the use of poly(L-lactic acid) (PLLA) coated Fe_3O_4 nanoparticles loaded with the anticancer drug tamoxifen for targeted drug delivery. A solvent evaporation/extraction technique was used to prepare these nanoparticles. MCF-7 breast cancer cells line was used to investigate the *in vitro* anti-cancer activity. The results from the cytotoxicity assay shows that while the PLLA coated Fe_3O_4 nanoparticles exhibit no significant cytotoxicity. However PLLA coated Fe_3O_4 nanoparticles loaded with tamoxifen showed that 80% of the MCF-7 breast cancer cells were killed after incubation for 4 days. These results indicate that the PLLA coated Fe_3O_4 nanoparticles loaded with tamoxifen have good potential as a carrier for the targeted drug delivery.[64] Gunduz *et al.* (2014) researched the use of PEG coated magnetic nanoparticles conjugated with folic acid loaded with idarubicin for targeted drug delivery for breast cancer. The results showed that idarubicin-loaded magnetic nanoparticles showed higher toxicity when compared to drug free magnetic nanoparticles. The results are promising for improvement in cancer chemotherapy.[65] Unterweger *et al.* (2014) investigated the development of superparamagnetic iron oxide nanoparticles with a dextran and cisplatin-bearing hyaluronic acid coating. *In vitro* tests were carried out on the nanoparticle complexes to evaluate the effectiveness of the cisplatin. The biological activity was investigated using nonadherent Jurkat cells in flow cytometry and for adherent PC-3 cells in xCELLigence experiments. Both tests showed that the nanoparticles without the drug were biocompatible and no cytotoxic effects were observed. However the nanoparticles incorporated with cisplatin induced apoptosis in a dose-dependent manner, with secondary necrosis after prolonged incubation. It was found that combination of dextran-coated SPIONs with HA and cisplatin shows a promising approach for use in magnetic drug targeting for cancer therapy.[66] Li *et al.* (2015) examined magnetic Fe_3O_4 coated carboxymethylchitosan (CMCS) nanoparticles loaded with anticancer drug rapamycin for targeted drug delivery. Drug release kinetics, cytotoxicity, cellular uptake and apoptosis studies were characterised *in vitro*. Cell culture experiments were carried out using human hepatocarcinoma cell lines (HepG2) and liver cell lines (LO2). The results showed that the Fe_3O_4–CMCS nanoparticles loaded with rapamycin showed lower cytotoxicity to liver cell line (LO2) and higher cytotoxicity to human hepatocarcinoma cell line (HepG2) than native Rapa. Fe_3O_4–CMCS nanoparticles loaded with rapamycin could enhance cellular uptake and reduced the damage to normal cells improving the effectiveness of the drug to tumor cells.[67]

Antibodies and peptides have also been combined with magnetic nanoparticles as therapeutic agents to try to combat cancer. Wuang *et al.* (2008) investigated the use of the antibody herceptin functionalised to polypyrrole coated Fe_3O_4 magnetic nanoparticles in the treatment of breast cancer. The polypyrrole coated Fe_3O_4 nanoparticles were synthesised by an emulsion polymerisation method. Hyaluronic acid was used as a surfactant as it offers both biocompatibility and functionalisation to herceptin. Herceptin interferes with the HER-2 gene which is associated with breast cancer. *In vitro* studies were carried out on human breast cancer cells (SK-Br-3) to examine the cellular uptake of polypyrrole–Fe_3O_4 herceptin nanoparticles. The results found that the functionalised magnetic nanoparticles were absorbed

Table 3 Summary of some *in vitro* studies carried out investigating the effects of targeted drug delivery on cancer cells. Iron oxide nanoparticle/coating systems marked with ^ are expected to find possible use in targeted drug delivery. More research is needed on the possible use of different nanosystems such as nanoalloys as possible magnetic carriers for targeted drug delivery. The results such as % cell death are dependent on a number of factors such as the drug, antibody or peptide and type of cells lines used

Core material	Coating	Drug/antibody	Cell line	Cancer	% efficiency (cell death)	Assay	Ref.
FePt–Fe_3O_4 ^	PEG[a]	Doxorubicin	HeLa	Cervical	70	SRB	59
Fe_3O_4 ^	Chitosan	Doxorubicin	MCF-7	Breast	65	MTT	60
Fe_3O_4 ^	SPAnNa[a]	Paclitaxel	PC3 CWR22R	Prostate	70–80 85–95	XTT	62
Fe_3O_4 ^	MSN–PLGA–Tf[a]	Doxorubicin paclitaxel	U-87	Brain	80	MTT	63
Fe_3O_4 ^	PLLA[a]	Tamoxifen	MCF-7	Breast	80	MTT	64
Fe_3O_4 ^	PEG–folic acid	Idarubicin	MCF-7	Breast	80–90	XTT	65
Fe_3O_4	CMCS[a]	Rapamycin	LO2 HepG2	Liver	40–10 50–70	CCK-8	67
Fe_3O_4	Polypyrrole	Herceptin	HER-2 SK-Br-3	Breast	41	MTT	68
Fe_3O_4	PEG[a]	Chlorotoxin	C6	Brain	80	Alamar-blue reagent	69

[a] PEG – polyethylene glycol, SPAnNa – poly[aniline-*co*-sodium *N*-(1-one-butyric acid) aniline], MSN–PGLA–Tf – mesoporous silica–poly(D,L-lactic-*co*-glycolic acid)–transferrin, PLLA – poly(L-lactic acid), CMCS – coated carboxymethylchitosan.

by the cancer cells with a cytotoxic effect on the cancer cells. This method can be potentially exploited for cancer treatment.[68] Veiseh *et al.* (2009) investigated the use of PEG coated iron oxide nanoparticles functionalised with chlorotoxin (CTX) for treatment of brain tumours. Chlorotoxin is a peptide that binds preferentially to glioma cells and inhibits MMP-2 enzymatic activity which is needed for glioma cells to grow. *In vitro* studies were carried out on C6 rat glioma cells to study the cellular uptake of nanoparticle–PEG–CTX (NPC). The results showed increased cellular uptake as well as a high invasion inhibition rate. This nanoparticle system could potentially be used for treatment of brain cancer (Table 3).[69]

4. Bio-imaging: MRI contrast agents

Magnetic resonance imaging (MRI) principles

With the recent advances in bio-medicine, the use of nanoparticles and magnetic nanoparticles in biomedical applications has increased. One such biomedical application that has benefited from this is bio-imaging. Bio-imaging used different techniques such as magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), ultrasound and optical imaging to look at internal organs and detect diseases. Some of these techniques will be discussed in this section.

Magnetic resonance imaging (MRI) is a non-invasive imaging technique used to produce high resolution images of internal organs. It is based on the principle of nuclear magnetic resonance and radio frequency pulses. The body is composed of water molecules, and these water molecules contain two hydrogen protons. When the body is placed in a static magnetic field the protons align with the direction of the field. Depending on the strength of the magnetic field the molecules resonate at the resonate frequency. A radiofrequency pulse is then applied, which causes net magnetisation to occur. When the field is off the molecules then return to their original state by emitting energy in the form of photons. This is called the relaxation process. The relaxation process occurs in two ways called longitudinal relaxation (T_1) or transverse relaxation (T_2). The magnetic resonance image can be produced by monitoring either process. Contrast agents are generally used in order to identify the healthy tissue from diseased tissue. They are also used to shorten the relaxation time of the protons. T_1 imaging can differentiate fat from water with water being darker contrast and fat being lighter contrast. T_2 imaging is the opposite with water being lighter contrast and fat being darker contrast. The most common contrast agents in use are gadolinium(III) based compounds such as Gd–DTPA (diethyltriaminepentaacetic acid). Generally compounds in the lanthanide and transition metals series are ideal MRI contrasting agents as they are paramagnetic.[91,102] However these gadolinium chelates have a tendency to accumulate in the liver and have a low imaging time. Recently studies have turned to finding contrast agents that have enhanced relaxation properties and biocompatibility.[110–112]

Nanoparticles for T_1 based contrast agents

In order to improve the T_1 relaxation time and increase the biocompatibility of contrasting agents for MRI, different compounds have been investigated to find a suitable alternative to the gadolinium chelates. Core–shell nanoparticles have been investigated as possible contrasting agents as they offer an increased biocompatibility and if they are magnetic the relaxation time can be improved. Core–shell nanoparticles gadolinium oxide (Gd_2O_3), gadolinium fluoride (GdF_3), sodium gadolinium fluoride ($NaGdF_3$) and gadolinium phosphate ($GdPO_4$) have been investigated as contrasting agents for MRI some of which will be discussed here. Park *et al.* (2009) investigated the use of gadolinium oxide nanoparticles as MRI contrast agents. Several methods, reduction, decomposition, dehydration and combustion were used to synthesise gadolinium oxide nanoparticles which varied in diameter. In order to analyse the T_1 relaxation and reduce the toxicity from gadolinium these nanoparticles were coated with D-glucuronic acid as a biocompatible layer. The results found that there was a contrast enhancement.[70] Zhou *et al.* (2012) also investigated the use of gadolinium oxide nanoparticles doped with lanthanide as contrasting agents for MRI. The Gd_2O_3 nanoparticles were synthesised by a hydrothermal method followed

Table 4 Summary of the key FoMs associated with the use of nanoparticles as T_1 contrast agents

Material	Coating	Particle size (nm)	Saturation magnetisation M_s (emu g^{-1})	Relaxation time r_1 (mM^{-1} S^{-1})	Ref.
Gd_2O_3	—	10	—	3.4892	71
	—	50	—	0.3149	
	—	270	—	0.1451	
	PEG	3	—	9.4	113
	DEG	3	—	1.6	
$GdPO_4$	—	23.2	—	13.9	73

by calcination these were then doped with lanthanide. A silica coating was applied to provide biocompatibility and functionalisation if needed. Cytotoxicity and *in vitro* tests were carried out on the lanthanum doped Gd_2O_3 to assess the toxicity, optical imaging and magnetic resonance of the nanoparticles. The results showed that lanthanide-doped Gd_2O_3 nanoparticles were biocompatible and had with novel multicolour up-conversion luminescence and good magnetic resonance imaging capabilities.[71] Evanics *et al.* (2006) studied the use of gadolinium fluoride (GdF_3) and a mixture of gadolinium fluoride and lanthanum fluoride (GdF_3/LaF_3) as contrast agents for magnetic resonance imaging. The GdF_3 and GdF_3–LaF_3 nanoparticles were coated with citrates to obtain high solubility. The study found that the GdF_3 and GdF_3–LaF_3 nanoparticles had high solubility in different solvents, high relaxivity, minimal binding to macromolecule of interest, no leaching occurred and the nanoparticles were easily removed. T_1 and T_2 relaxivity measurements show the potential for the use of these nanoparticles as contrast agents.[72] Table 4 summarises key FoMs associated with the use of these nanoparticles as T_1 contrast agents.

Nanoparticles for T_2 based contrast agents

Core–shell nanoparticles have been investigated as possible contrasting agents for T_2 relaxations. Iron oxides especially superparamagnetic irons oxides nanoparticles (SPION) and ultra-small superparamagnetic iron oxide nanoparticles (USPION) have been investigated as possible contrast agents for magnetic resonance imaging. This is due to a number of properties such as high saturation magnetisation, high magnetic susceptibility, non-toxicity, chemical stability, biodegradability, biocompatibility, ease of synthesis and the ability to functionalise.[104,114–116] Superparamagnetic irons oxides nanoparticles (SPION) have a size greater than 50 nm and ultra-small superparamagnetic iron oxide nanoparticles (USPION) have a diameter that is smaller than 50 nm.[91,117] Iron oxide nanoparticles have a tendency to oxidise so coating with a biocompatible shell is common place. Some examples of coatings include polymers such as dextran,[6–8] poly(ethylene glycol) (PEG)[9–12] and chitosan[13–17] or coatings such as silica[18–21] or metallic coatings such as gold.[22–25] At the moment five superparamagnetic iron oxide nanoparticles are clinically approved they are ferumoxytol, ferumoxides, ferucarbotran, ferristene and ferumoxsil with 2 more in clinical trials.[118–120]

Other nanoparticles and nanoalloys such as, Fe–Co, Fe–Ni, Fe–Pt, $MnFe_2O_4$ and $CoFe_2O_4$ have also been investigated as possible T_2 contrast agents. The development of these nanoparticles is to improve the relaxivity and therefore the contrast, one way of achieving this is by improving the saturation magnetisation of the core nanoparticle. The magnetic properties of iron oxide nanoparticles are improved by doping with magnetically susceptible elements such as Mn, Co and Ni. The use of metal alloys such as Fe–Co, Fe–Ni and Fe–Pt can also improve the contrast as the magnetic moments of the alloys is higher than iron oxide and the doped iron oxide nanoparticles which results in a longer relaxation time and improved contrast.[74–82,121–125] Some of these systems will be discussed here.

Seo *et al.* (2006) investigated Fe–Co nanocrystals for possible use in magnetic resonance imaging. A chemical vapour deposition method was used to synthesise two different size Fe–Co nanocrystals with a graphite shell. These nanocrystals were functionalised using PL-PEG. It was found that the nanocrystals had high saturation magnetisations and relaxations. *In vitro* experiments were also carried out showing no obvious cytotoxicity and high negative-contrast enhancement in magnetic-resonance imaging. *In vivo* experiments showed long-lasting positive-contrast enhancement.[74] An *et al.* (2014) studied the use of dextran coated Fe–Co nanoalloys as possible magnetic resonance imaging contrast agents. A wet chemical approach was used to synthesise the dextran coated Fe–Co nanoalloy. *In vitro* cytotoxicity testing, *in vitro* and *in vivo* MR imaging of the nanoalloy was carried out in order to assesses the use of the nanoalloy as a MRI contrast agent. The cytotoxicity results showed that the nanoalloy was biocompatible up to a certain concentration. The *in vitro* MR imaging test showed that the nanoalloy could be up-taken by the human cervical carcinoma cell line (HeLa cells). *In vivo* testing was carried out using mice. The dextran coated Fe–Co nanoalloy was injected into the mice through the tail vein. The results showed that dextran coated Fe–Co nanoalloys could be used as T_2 negative contrast agents.[75]

Yang *et al.* (2011) investigated the use of Fe–Ni nanoparticles as potential contrast agents for magnetic resonance imaging. Fe–Ni nanoparticles were synthesised by a high temperature pyrolysis method. These nanoparticles were made water soluble by a ligand exchange method. *In vitro* cytotoxicity tests were carried out on the nanoparticles as well as saturation magnetisation and relaxivity measurements. The results showed that the Fe–Ni nanoparticles had high saturation magnetisation, relaxivity and low cytotoxicity meaning potential use as MRI contrast agents.[76]

Yang *et al.* (2010) studied the use of amphiphilic Fe–Pt nanoparticles as contrast agents in magnetic resonance imaging (MRI). These nanoparticles were synthesised *via* high temperature pyrolysis in the presence of tetraethylene glycol (TEG) and oleic acid (OA) to make the nanoparticles amphiphilic. Human nasopharyngeal epidermal carcinoma (HeLa) cell line was used to assess the amphiphilic Fe–Pt nanoparticles biocompatibility. The magnetic properties of these nanoparticles were also investigated. The as-prepared amphiphilic Fe–Pt nanoparticles showed good biocompatibility and less toxicity against cell lines. *In vitro* showed that Fe–Pt nanoparticles can potentially be used as an effective MR cell-labelling agent.[77] Lai *et al.* (2012) researched the use of bifunctional silica-coated FePt nanoparticles for

Fluorescence/MR Dual Imaging. Fe–Pt nanoparticles were synthesised *via* a reduction method and then coated with bifunctional fluorescein-isothiocyanate incorporated silica *via* a micro-emulsion method. The magnetic properties and performance were characterised by VSM. The cytotoxicity of Fe–Pt and FePt–SiO_2–FITC nanoparticles was evaluated by MTT assay using human cervical epithelioid carcinoma (HeLa) cells. The results showed that the nanoparticles that exhibited significant T_1 and T_2 MR contrast abilities and were not cytotoxic. These results suggest that silica-coated superparamagnetic Fe–Pt nanoparticles are potential nano-devices for the combination of fluorescence and MRI contrast used for cancer diagnosis.[78] Liang *et al.* (2015) looked into developing an L-cysteine coated Fe–Pt nanoparticle as a contrasting agent for MRI/CT imaging for the diagnosis of malignant gliomas. A co-reduction route was used to synthesise the Fe–Pt–Cys nanoparticles. The MRI and CT imaging ability of Fe–Pt–Cys nanoparticles were evaluated

Table 5 A list of key FoMs of nanoparticles for T_2 contrast agents. Systems marked with ^ are the most likely candidates as future contrast agents due to their higher relaxation times and M_s

Material	Coating	Particle size (nm)	M_s (emu g^{-1})	r_2 (mM^{-1} S^{-1})	H (Oe)	Ref.
Fe_3O_4, γ-Fe_2O_3	Dextran	4.96	45	120	—	126–129
Fe_3O_4	Carboxydextran	4		186	—	
Fe_3O_4	Dextran	5.85	61	65	—	
					—	
Fe_3O_4	—	30–50	65.53	—	0	130
	Chitosan	30–50	24.67	—	21.69	
$MnFe_2O_4$^		5.3	37	—	—	51
		7.1	42.1	—	—	
		10.5	48.8	—	—	
		12.1	51.8	—	—	
		7.6	53.1	227.6	—	131
		7	39	189.3	—	132
		6	68	208	—	121, 129 and 133
		9	98	265	—	
		12	110	358	—	
$CoFe_2O_4$^		8	65.3	392.5	—	131
		5.5	50	—	12	134
		12	99	172	—	121, 129 and 133
FeCo^	Graphite (PL-PEG)	7	215	644	—	74
		4	162	185	—	
	Carbon	7	230	392	—	135
	—	35	148	—	—	136
	—	45	205	—	—	137
	ZrO_2		170	—	—	
	—	8	192	—	—	138
	—	21–31	204	—	—	139
	—	20–30	221	—	—	140
$Fe_{60}Co_{40}$	—	50–90	230	—	—	141
$Fe_{20}Co_{80}$			180		380	
$Fe_{60}Co_{40}$	—	100	212	—	200	142
FePt^	TEG/OA	4	25	122.6	—	77
	—	9	—	239	—	123
FeNi	—	9	40	43.1	—	76
	—	150	150.4	—	297	143
	—	20–180	84.5	—	—	144
	Carbon	10–70	55.3	—	—	
$Fe_{25}Ni_{75}$	—	50–100	69	—	191	145
$Fe_{35}Ni_{65}$	—	50–100	89	—	103	
$Fe_{49}Ni_{51}$	—	100–480	137	—	59	146
$Fe_{46}Ni_{54}$	—	70–350	135	—	111	
$Cu_{40}Ni_{60}$	—	10	4.4	—	—	22
$Cu_{30}Ni_{70}$	—	11	17.5	—	—	
$Cu_{27.5}Ni_{72.5}$	—	12	20.7	—	—	
$Cu_{27}Ni_{73}$	—	11	13.2	—	—	
$Cu_{25}Ni_{75}$	—	11	48.5	—	—	
$Cu_{20}Ni_{80}$	—	10	32.9	—	—	

using different gliomas cells (C6, SGH44, U251). The biocompatibility of the Fe–Pt–Cys nanoparticles was evaluated using three different cell lines (ECV304, L929, and HEK293). Fe–Pt–Cys nanoparticles displayed excellent biocompatibility and good MRI/CT imaging ability, thereby indicating a potential as a MRI/CT contrast agent.[79]

Lu *et al.* (2009) studied the synthesis of manganese ferrite nanoparticles for use as MRI contrast agents in liver imaging. The $MnFe_2O_4$ nanoparticles were synthesised and encapsulated in a block copolymer mPEG-*b*-PCL. The magnetic properties were examined through a magnetisation measurement and the T_2 relaxivity was measured with a clinical MR scanner. The biocompatibility was investigated *in vitro* and *in vivo* using the human hepatocarcinoma cell strain (HepG2) and a mouse cell line. The contrast effect of MRI was evaluated on a mouse liver at 3.0 T in a Philips MRI scanner. The results showed that the nanoparticles were biocompatible, superparamagnetic at room temperature and improved the MRI contrast.[80] Sahoo *et al.* (2014) investigated the possible use of multifunctional mesoporous silica coated $MnFe_2O_4$ nanoparticles for magnetic resonance imaging (MRI) applications. The $MnFe_2O_4$ nanoparticles were synthesised by a solvothermal method and coated with silica by hydrolysis and were then functionalised with amine. The amine functionalized nanoparticles were further conjugated with folic acid (FA) for cancer-cell targeting. *In vitro* cellular MR imaging studies were carried out in HeLa cells to investigate the effectiveness of these nanoparticles as MRI contrast agents. The results showed that the folate-conjugated nanoparticles exhibited stronger T_2-weighted MRI contrast towards HeLa cells as compared to the nanoparticles without folate conjugation, justifying their potential importance in MRI based diagnosis of cancer.[81] Wu *et al.* (2011) investigated the use of $CoFe_2O_4$–multi walled carbon nanotubes for magnetic resonance imaging and targeted drug delivery. A solvothermal method was used to synthesise these magnetic hybrids. *In vitro* cytotoxicity and MRI tests were carried out on MWCNT–$CoFe_2O_4$ hybrids. The results showed that the hybrids had a low cytotoxicity and excellent MRI enhancement. There is good potential for use as MRI contrast agents.[82]

Table 5 summarises key FoMs associated with the use of these nanoparticles as T_2 contrast agents where M_s is the saturation magnetisation, r_1 is the T_1 relaxation time, r_2 is the T_2 relaxation time and H is the coercivity.

5. Conclusions

From this review it can be seen that the use of nanoalloys, metallic and bimetallic nanoparticles in biomedical applications has increased significantly. The use of magnetic nanoparticles in hyperthermia treatment is showing promising results with clinical trials already taking place. From the *in vitro* and *in vivo* results the use of magnetic nanoparticles targeted drug delivery is looking encouraging for the treatment of different types of cancer. However this application is still in its early stages and these methods need to be applied to clinical trials in order to ascertain if this method can be applied to humans. The use of magnetic nanoparticles in MRI is the most successful biomedical application as at the moment there are five iron oxide based contrasts agents that are clinically approved with two more that are in clinical trials.

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