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Advances in multifunctional magnetic nanoparticles

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ABSTRACT

Multifunctional magnetic nanoparticles have emerged as one of the important futuristic material for variety of applications starting from data storage, security/sensors to biomedical applications. The application of multifunctional magnetic nanoparticles in biological organisms has fashioned noteworthy advances in research, diagnosis and therapy of various diseases. The multifunctional magnetic nanoparticles, capable of theragnosis, drug delivery and monitoring of therapeutic response, are expected to play a significant role in the emergence of the era of personalized medicine with much of research efforts devoted toward that goal. The present review recapitulates the development of state-of-the-art multifunctional magnetic nanoparticles and the foremost applications of these multifunctional magnetic nanoparticles in magnetic targeting, drug delivery, separation, and contrast agents in magnetic resonance imaging, hyperthermia and sensors. The biocompatibility requirements and functionalization approach for multifunctional magnetic nanoparticles used in these applications are also reviewed. Copyright © 2011 VBRI press.

Keywords: Multifunctional magnetic nanoparticles; sensors; theragnostics; targeted drug delivery; nanomedicine; contrast agents; hyperthermia; magnetic separation.

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Contents

1. Introduction

Magnetism is an intrinsic facade of existence of living creatures, from iron in blood to the capability of magneto-tactic bacteria, birds, honeybees and other creatures to navigate by the Earth's magnetic field. Iron plays a crucial part in numerous aspects of human neurophysiology. Body's natural iron is usually stored within ferritin, a 12-nm hollow spherical shell that can hold up to 2,500 iron atoms in its each shell in the form of mineralized ferrihydrite. Anomalous amounts of iron possibly in nanoscale form are associated with many neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases [**1**]. The capability of magnet to act on an object at a distance makes them precious medicinal paraphernalia from long ago. The use of magnet in the removal of an iron splinter from an eye [**2**] was illustrated in 1624. Similarly other removal of safety pins, bullets and grenade splinters were demonstrated using magnets [**3, 4**]. Cattle's are fed magnets to prevent sharp metallic objects they eat from damaging the intestines. The development of stronger, tiny permanent magnets led to more delicate applications, such as temporarily fixing prosthesis in dentistry, guiding catheters through the body and navigating within the brain [**5, 6**].

Due to their size compatibility with cells (10–100 μm), viruses (20–450 nm), proteins (5–50 nm) and genes (2 nm wide by 10–100 nm long), nanoscale materials have extraordinary significance in diverse biomedical applications. Nanoparticles are sufficiently small to move inside the body without disrupting normal functions and can access spaces unapproachable by other pathological means. Cells retort to the topography of their surroundings on size scales as small as 5 nm - up to 1000 times smaller than their own size [**7**]. Changes in response to topography literally can induce growth or death. Nanostructured materials allow study of these critical processes on a single-cell level [**8**].

The development of multifunctional magnetic nanoparticles significantly impacts the advancement of both therapeutic and diagnostic agents. At the intersection between treatment and diagnosis, interest has grown in combining both paradigms into clinically effective formulations. This concept, recently coined as theranostics, is highly relevant to agents that target molecular biomarkers of disease and is expected to contribute to personalized medicine. Theranostic nanomedicine takes advantage of the high capacity of nano-platforms to ferry cargo and loads onto them both imaging and therapeutic functions. Major classes of nanoparticles include, drug conjugates and complexes, dendrimers, vesicles, micelles, core–shell particles, microbubbles, and carbon nanotubes. The preponderance of these formulations has been described as carriers of either drugs or contrast agents. To monitor these formulations and their interactions with disease, a variety of contrast agents have been used, including optically active small molecules, metals and metal oxides, ultrasonic contrast agents, and radionuclides. The prospect to swiftly evaluate and regulate treatment to the requirements of an individual tenders latent reward that will stimulate the advancement of nanoparticle based multifunctional theranostic agents. Here, we review state-of-the-art multifunctional magnetic nanoparticles from a therapeutic and a diagnostic perspective and discuss challenges in bringing these fields together. The foremost applications of such multifunctional magnetic nanoparticles in magnetic targeting, drug delivery, magnetic separation, as contrast agents in magnetic resonance imaging, hyperthermia and in sensors are recapitulated. The biocompatibility requirements and functionalization approach for multifunctional magnetic nanoparticles used in these applications are also reviewed.

2. Specific requirements for multifunctional magnetic nanoparticles

Multifunctional magnetic nanoparticles have specific requirements for their use in biomedical applications to that of materials used for other applications. *In vivo* (in the body) applications require stringent biocompatibility, while *in vitro* (outside of the body) applications have less stringent requirements. The techniques involving living cells must consider the effect of the materials on the cells. In addition to biocompatibility, materials must be capable of being functionalized with one or more molecules, must

retain their magnetic properties for a reasonable period of time in aqueous media with varying pH, must not be cleared too quickly from the bloodstream, and must form stable, non-aggregating dispersions.

2.1 . Biocompatibility

Cells can be killed by peripheral means or can be provoke to "commit suicide" via a prototype known as involuntary cell death or *"apoptosis"*. Damage from external agents includes mechanical injuries and exposure to toxic chemicals (e.g. chemotherapy). Substances toxic to cells are called *"cytotoxic"* and different types of cells can have different responses to the same material. Thus before applying/testing these multifunctional magnetic nanoparticles for biomedical applications one should check its biocompatibility.

2.2. Functionalization/coating capabilities

Coatings can improve colloidal stability, oxidation resistance, the functionalization ability, mechanical stability and biocompatibility. Unfortunately, coating with a biocompatible material does not necessarily render the nanoparticle biocompatible [**9**]. Polysaccharide coatings such as dextran, starch, and chitosan are biocompatible and offer a range of functionalization options [**10-12**]**,** however, they can be structurally weak and can be dissolved by highly acidic environments. Silicon-based coatings are used to protect particles from lysomal enzymatic digestion, and improve mechanical properties and chemical stability **[13-16]**. Silica-coating can improve chemical stability, but a porous coating may allow the contents inside to be dissolved or oxidized [**17**]. Many polymers are biocompatible and may be used as coatings for metallic or ceramic particles, or can serve as hosts by either capturing nanoparticles inside a larger polymer particle or attaching nanoparticles to their surfaces. Polyethylene Glycol (PEG) and related polymers covalently bond to surfaces or are adsorbed on magnetic nanoparticles and can prolong the circulation time in the bloodstream [**10, 11**]**.**

2.3. Clearance/retention time

Particles introduced into the bloodstream are covered rapidly by components of the circulation, such as plasma proteins, in a process called *opsonization. Opsonization* makes the particles recognizable to the body's major defense system, the reticuloendothelial system (RES). The RES comprises a diffuse system of phagocytic cells (which engulf inert material) that are primarily associated with the connective tissues in the liver, spleen, and lymph nodes. Macrophage (Kupffer) cells in the liver and macrophages of the spleen and circulation are important in removing particles identified by opsonization. A significant fraction of nanoparticles can be cleared from the circulation system in as little as 15 minutes [**18, 19**]. The clearance rate is dependent on size, charge, surface hydrophobicity and the number and nature of functional groups on the surface [**18, 20**]. These variables are interdependent, making understanding the role of each one independently challenging. Some of these variables also may affect the magnetic properties. For example, smaller particles more easily evade the RES; however, the smaller size usually results in a smaller moment. Anionic particles with negative surface charge have a high affinity for the cell membrane and are typically taken up by the endocytic process [**21**]. Cationic magnetite particles show significantly lower cell-survival rates but their toxicity depends highly on the magnitude of the surface charge. More highly cationic particles tend to be more toxic [**22**]. Hydrophilic surfaces such as dextran, polyethylene glycol, polyethylene oxide, poloxamers, polysorbates and polyoxamines provide a dynamic "cloud" of hydrophilic and neutral chains at the particle surface that repel plasma proteins and prevent rapid removal of particles from circulation [**23-25**]. Related to clearance time is the manner in which the nanoparticles attach to cells. Nanoparticles can be internalized or remain adhered to the surface. The mechanism is determined by the surface charge, adhesion properties, and chemical functionality of the cells with respect to the nanoparticle.

2.4. Fluids/suspension making capabilities

The *in-vivo* application usually requires nanoparticle suspension in water or water-based fluid. *In-vitro* applications generally also need an aqueous solution. Magnetic nanoparticles must remain suspended in fluid (or be easily re-dispersed when needed) and should not form aggregates due to van-der Waals or magnetic interactions.

Magnetic particles in a solution experience two types of relaxation: Brownian relaxation, in which the whole particle rotates, and Néel relaxation, in which the moment rotates while the particle remains immobile. The Brownian relaxation time depends on the 'hydrodynamic diameter' of the suspended particle and it characterizes how a particle moves through the fluid in which it is suspended. This hydrodynamic diameter may be different than the actual particle size due to agglomeration, coating, or interactions between the fluid and the nanoparticle surface. The Brownian relaxation time can be changed by changing the viscosity of the fluid while the Néel relaxation is independent of the fluid. The relaxation rates also get affected by immobilization of nanoparticles.

3. Promising multifunctional magnetic nanoparticles

Diverse applications in data storage, security/sensors to biomedical applications led to noteworthy advances in development of variety of multifunctional magnetic nanoparticles. The development of biocompatible nanoparticles for molecular imaging and targeted therapy is an area of considerable current interest [**26-34**]. The basic rationale is that nanometer-sized particles have functional and structural properties that are not available from either discrete molecules or bulk materials [**26-28**]. When conjugated with biomolecular affinity ligands, such as antibodies, peptides or small molecules, these nanoparticles can be used to target malignant tumors with high specificity [**35-38**]. Structurally, nanoparticles also have large surface areas for the attachment of multiple diagnostic (e.g., optical, radioisotopic, or magnetic) and therapeutic (e.g., anticancer) agents. Recent advances have led to the

development of biodegradable nanostructures for drug delivery [**39-43**], iron oxide nanocrystals for magnetic resonance imaging (MRI) [**44, 45**], luminescent quantum dots (QDs) for multiplexed molecular diagnosis and in vivo imaging [**46-50**], as well as nanoscale carriers for siRNA delivery [**51, 52**]. Due to their novel optical and electronic properties, semiconductor QDs are being intensely studied as a new class of nanoparticle probe for molecular, cellular, and in vivo imaging [**35-49**]. Over the past decade, researchers have generated highly monodispersed QDs encapsulated in stable polymers with versatile surface chemistries. These nanocrystals are brightly fluorescent, enabling their use as imaging probes both in vitro and in vivo.

3.1. Iron oxide nanoparticles (IONPs)

Iron oxide nanoparticles (IONPs) are nanocrystals made from magnetite or hematite. Despite spin surface disorders and spin canting effect [**53**], IONPs typically possess substantial saturation magnetization (Ms) values at room temperature, especially for those made from pyrolysis protocols with good crystallinity. Unlike the bulk materials, IONPs less than 20 nm are superparamagnetic - a state where particles show zero magnetism in the absence of an external magnetic field, but can become magnetized when there is one. The underlying mechanism is that at such small scale, the thermal energy is sufficient to overcome the anisotropy energy of each small magnet (nanoparticle), and this leads to random fluctuation of the magnetizations that, macroscopically, result in zero net coercivity and magnetic moment [**54, 55**]. The superior magnetic properties of IONPs, along with their inherent biocompatibility and inexpensiveness, have made IONPs a material of choice in many bio-applications, such as contrast probes for magnetic resonance imaging (MRI) [**56-61**]. The high magnetic moments of IONPs make them effective in reducing T2 relaxation time, leading to signal attenuation on a T2 or T2*-weighted map. When the particles are engineered with targeting specificity, such signal alterations can be harnessed to report abnormal biological activity.

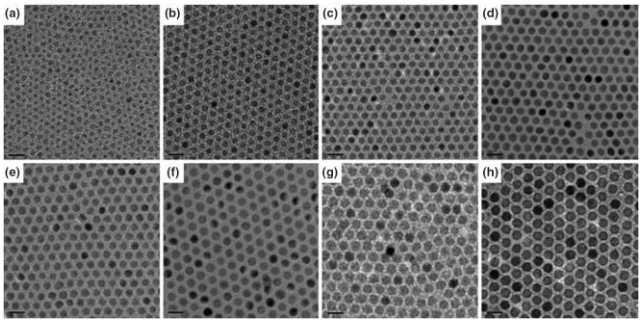

Fig. 1. TEM micrographs of iron oxide NPs with diameters of (a) 6 nm, (b) 7 nm, (c) 8 nm, (d) 9 nm, (e) 10 nm, (f) 11 nm, (g) 12 nm, (h) 13 nm. The organic phase high-temperature synthetic route enables precise control of NP size. Figure adapted from "Park J, Lee E, Hwang NM, Kang MS, Kim SC, et al. One-nanometer-scale size-controlled synthesis of monodisperse magnetic iron oxide nanoparticles, Angew Chem Int Ed 2005, 44, 2872–2877".

The synthesis of IONPs has been well documented. **Fig. 1** shows the TEM micrographs of iron oxide NPs with diameters of (a) 6 nm, (b) 7 nm, (c) 8 nm, (d) 9 nm, (e) 10 nm, (f) 11 nm, (g) 12 nm, (h) 13 nm [**62**]. The organic phase high-temperature synthetic route enables precise control of NP size. Traditionally, IONPs are made in aqueous solution by co-precipitating Fe (II) and Fe (III) precursors [**58, 63, 64**]. In order to confer colloidal suspendability to the particles, additives, typically hydrophilic polymers are added during the particle formation process, which passivate the nanocrystal surface and protect against particle aggregation. A number of ligands including polyvinylpyrrolidone (PVP), dendrimer, polyaniline and dextran have been utilized for such purposes [**58, 65, 66**], with dextran and its derivatives being the most studied. As a matter of fact, several dextran–IONP formulas have entered or already passed clinical trials as MRI contrast agents.

3.2. Transition metal (TM) ions doped inorganic QDs

Many workers have shown that inorganic quantum dots (QDs) of like ZnO, ZnS, CdS, CdSe, TiO_2 etc could efficiently work as multifunctional nanoparticles when doped with different transition metals (TM) [**67-72**]. The TM incorporation in these systems led to origin of strong magnetism, which could be utilized for diverse applications. For an example, Dutta, Sharma and Pandey [**72**] have developed the "*Luminomagnetic Nanocarriers*" (luminescent and magnetic, simultaneously) of ZnO:Fe nanocrystals by a simple protocol and modified the surface of this "*Luminomagnetic Nanocarriers*" by the ligand folate. This functionalized "*Luminomagnetic Nanocarriers*" system is a bioconjugation approach which combines the specificity of folate receptors on cancer cells with the excellent optical and magnetic properties of the nanoparticles so as to develop biocompatible molecular imaging agents, drug delivery systems and hyperthermia agents.

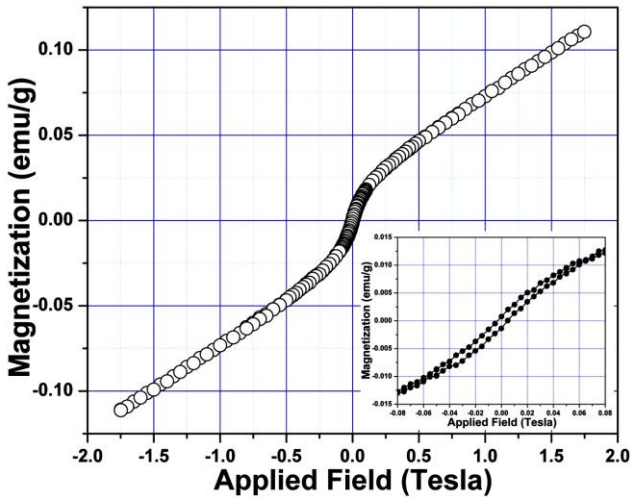

Fig. 2. Room temperature M-H loop of synthesized ZnO:Fe nanoparticles. Figure adapted from "Ranu K. Dutta, Prashant K. Sharma and Avinash C. Pandey, Design and surface modification of potential luminomagnetic nanocarriers for biomedical applications, J. Nanopart. Res., 2010, 12, 1211-1219".

The vibrating sample magnetometer (VSM) studies, **Fig. 2**, showed clear hysteresis loops having coercivity 5.1 mT with corresponding magnetization of remanence 7.6 × 10^{-3} emu/g, indicating strong magnetic character of the

samples. The photoluminescence spectrum of these nanoparticles is shown in **Fig. 3**. X-ray diffraction (XRD) and transmission electron microscopy (TEM) measurements show that these nanoparticles are spherical with 6-9 nm size and hence are quite appropriate for *in vivo* applications as well. The immobilization of folic acid was confirmed by fourier transform infrared (FTIR) analysis.

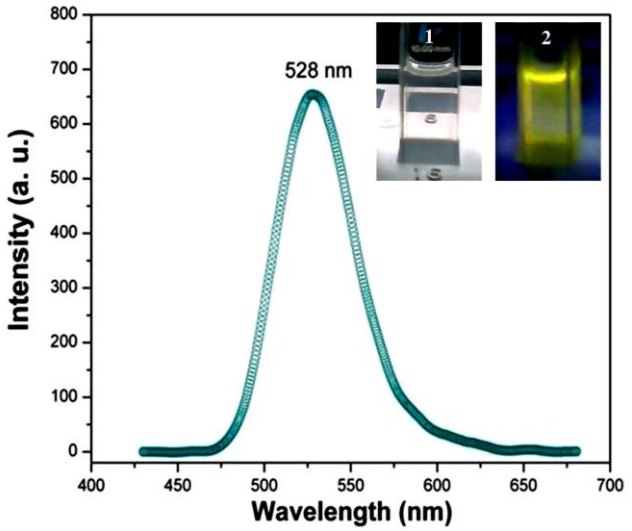

Fig. 3. Photoluminescence spectra of ZnO:Fe nanoparticles. Inset shows the liquid samples in white light (1) and UV lamp (2). Figure adapted from "Ranu K. Dutta, Prashant K. Sharma and Avinash C. Pandey, Design and surface modification of potential luminomagnetic nanocarriers for biomedical applications, J. Nanopart. Res., 2010, 12, 1211-1219".

The enhanced magnetic moment and magnetic anisotropy render them utilizable for several biological applications. These, along with their capability of being manipulated under an external magnetic field, provide controllable means for magnetically tagging of all biomolecules, leading to highly efficient bio-separation/bio-delivery, highly sensitive bio-labeling and magnetic resonance imaging (MRI) with enhanced contrast. They can be used as a delivery vector of external genetic material and enhance efficiency of transfection or transformation making them the most feasible candidates for targeted drug delivery systems and seizes great potential in bio-medical applications, making these "*Luminomagnetic Nanocarriers*" one of the most feasible candidates for folate receptor mediated biomedical applications.

3.3. Rare-earth ion doped inorganic QDs

Stable colloids of magnetic nanoparticles (MNPs) in physiological medium, also known as biocompatible magnetic fluids (BMFs), have been used as potential candidate for variety of applications starting from data storage, security/sensors to diagnosis and therapy in clinical, biomedical, and biotechnological applications. The main emphases of these works were on cancer therapy and early detection [**73-75**]. Small changes in the band structure of a solid, originating from nanoscale size, are expected to have dramatic effects on the luminescent and magnetic properties, simultaneously. These small nanoparticles, also known as quantum dots (QDs), represent a new form of highly fluorescent agents that can expand the range of possible fluorescent studies [**76, 77**]**.** Rare-earth (RE) ions doped inorganic QDs are one of the most promising materials for a variety of applications such as in solid-state lasers, security, sensors, lighting, displays and biolabels [**78**]. QDs allow multiplexed detection, are resistant to photo-bleaching, and can be tracked over extended periods of time [**79**]. QDs can also be engineered to attach the biological molecules and have great potential for detecting and characterizing certain diseases, such as cancer, at the single cell or tissue level [**80, 81**].

3.4. Rare-earth oxides Gd_2O_3 and hydroxides $Gd_2(OH)_3$

Recently, nanoparticles made of RE oxides have been investigated as emerging materials for fluorescent labeling [**82-84**] due to their large stokes shift, sharp emission spectra, long lifetime and flexibility of excitation wavelengths. As RE oxides are used as commercial phosphors, it can be predicted that biological labels based on these materials will have better photo-stability than the commercially available polystyrene nanoparticles doped with lanthanide chelates. On the other hand, the magnetic properties of rare earths QDs are very sensitive to the structure and filling of the conduction bands because these originate almost entirely from their incomplete 4*f* shells. In the same pursuit several nanoparticles viz Gd_2O_3, $GdPO_4$, GdF_3 etc are extensively synthesized and studied by various research groups. Among these nanoparticles, because of its high relaxivities at nanometric scale, particularly Gd_2O_3 nanoparticles have been synthesized by numerous approaches and studied thoroughly. *R. K. Dutta*, *P. K. Sharma* and *A. C. Pandey* [**85**], have engineering the superparamagnetic $Gd_2O_3:Eu^{3+}$, **Fig. 4**, nanoparticles and called them *"Eurogadofluoroprobes (EGFP)"* and evaluated their biocompatibilty through blood platelet aggregation studies.

Gd_2O_3 nanoparticles are reported as potential contrast agents for MRI because they accelerate the *T*1 and *T*2 relaxation processes of water protons within their surroundings and have proven to show positive contrast effect *T*1-weighted imaging [**86**]. Furthermore, since Gd^{3+} is a known contrast agent for magnetic resonance imaging (MRI), $Gd_2O_3:Eu^{3+}$ nanoparticles may function as both fluorescence and MRI labels [**87**]. Because of a large number of unpaired electrons in the gadolinium ion, complex species of Gd^{3+} ion have been commonly used as an MRI contrast agent for positive intensity images. They displayed the potential applications combining with fluorescence to achieve multi-imaging *in vivo* [**88**].

On the other hand the initial precursor/intermittent product of Gd_2O_3, $Gd(OH)_3$ of various shapes (nanotubes, nanorods, nanowires and nanobundles) is synthesized [**89, 90**]. In one such synthesis *Parashar* and *Pandey et al* have developed the $Gd(OH)_3$ nanosheets [**91**] as shown in **Fig. 5**.

3.5. Rare-earth sesquisulphides and monosulphides

From the past three decades, rare-earth sesquisulphides, Ln_2S_3 in the series of Ln = La - Dy have emerged as an attractive class of magnetic materials. Among these material systems, GdS, a model example of a Heisenberg system is antiferromagnetic (Neel temperature about 50 K)

with the NaCl structure, an increase of sulfur leads to ferromagnetic ordering and transition to the Th_3P_4 structure for Gd_3S_4 and Gd_2S_3. Whereas excess Gd leads to an antiferromagnet–ferromagnet transition adjunct with a semiconductor–metal transition. The magnetic properties of α–Gd_2S_3 have captured the interest of several research groups in past [**92-96**].

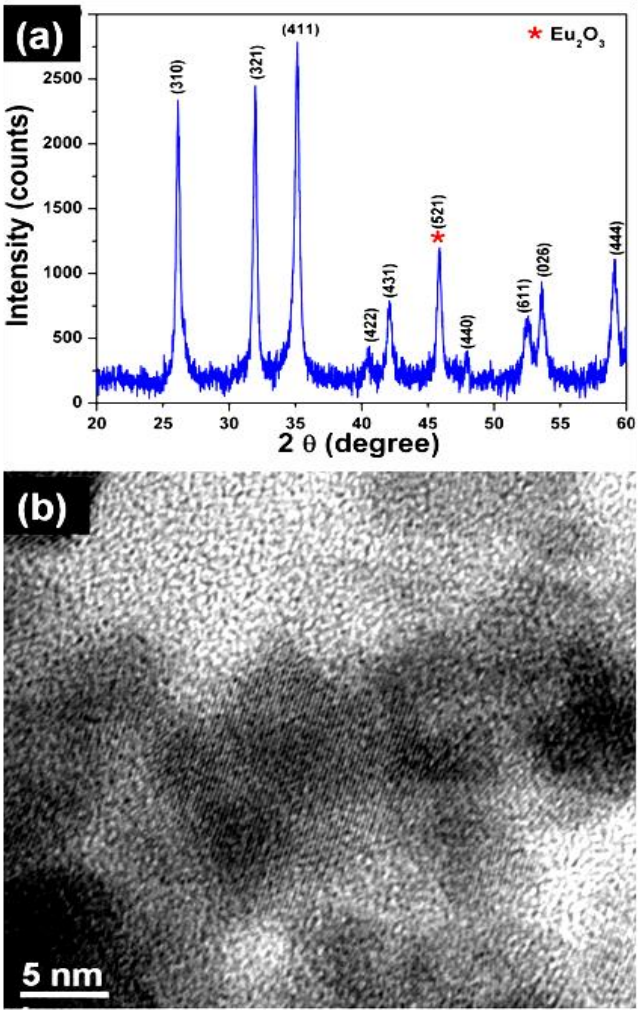

Fig. 4. (a) X-ray diffraction spectra and (b) TEM image of Gd_2O_3:Eu^{3+} nanoparticles. The XRD spectra showed crystalline nature having cubic structure of Gd_2O_3 having space group $12_13(199)$. Figure adapted from "R. K. Dutta, P. K. Sharma and A. C. Pandey, Engineering of superparamagnetic eurogadofluoroprobes (EGFP) and their biocompatibilty evaluation through platelet aggregation studies, article to be published, 2011".

This compound has an orthorhombic structure (Pnma) wherein two types of cation polyhedra which are linked to form a three dimensional (3D) structure [**97-99**]. There are five structure types for Ln_2S_3 (Ln ¼ lanthanides), two of which are known for Gd_2S_3: α–Gd_2S_3 and γ– Gd_2S_3. The latter has a Th_3P_4-type structure ($I4_3d$) where 1/9th of the sites of the metal sub lattice are vacant [**100, 101**]. Until recently, interest in the magnetic and electrical properties at low temperatures has focused on the γ-type structure. In a very recent work, published in *Appl. Phys. Letts*. [**102**], *Dutta*, *Sharma* and *Pandey* have reported the first ever room temperature synthesis of ultra small multifunctional magnetic nanoparticle of Gd_2S_3. These nanoparticles show orthorhombic (P_{nma}) crystal symmetry with excellent magnetic and luminescent characters, simultaneously. **Fig. 6** shows the X-ray diffraction (XRD) spectra of Gd_2S_3:Eu^{3+} nanoparticles. Inset shows the high resolution transmission electron microscopic (HRTEM) image.

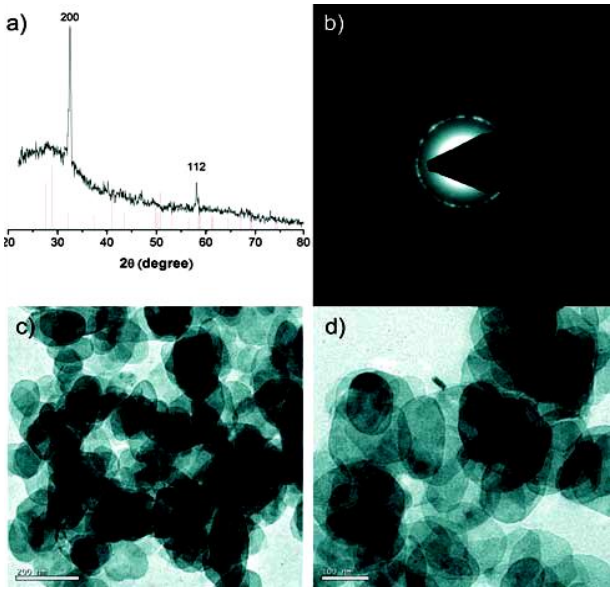

Fig. 5. (a) XRD patterns of the $Gd(OH)_3$ nanosheets. The standard data for $Gd(OH)_3$ (JCPDS No. 83-2037) is also presented in the figure (red) for comparison. b) Selected area electron diffraction (SAED) pattern of $Gd(OH)_3$ nanosheets. Low (c) and high (d) magnification of TEM images of $Gd(OH)_3$ nanosheets. Figure adapted from "V. Parashar and A. C. Pandey, Synchronized detection and removal of thiols using a $Gd(OH)_3$ nanosheet-sodium pentacyanonitrosylferrate (II) complex, Anal. Methods, 2010, 2, 1227–1229".

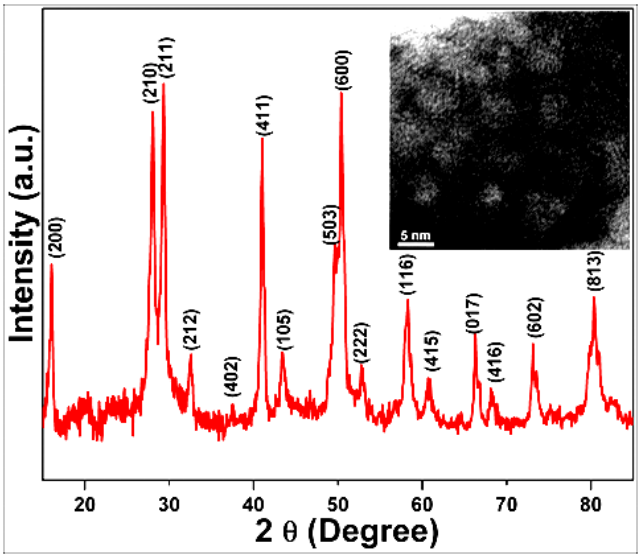

Fig. 6. X-ray diffraction (XRD) spectra of Gd_2S_3:Eu^{3+} nanoparticles. Inset shows the high resolution transmission electron microscopic (HRTEM) image. Figure adapted from "Ranu K Dutta, Prashant K Sharma and Avinash C Pandey, DNA base (cytosine) modified/capped ultrasmall Gd_2S_3:Eu^{3+} gadofluoroprobes for platelet isolation, App. Phys. Lett. 2010, 97, 253702."

Recently *Pandey and coworkers* [**103**] had described a method for the synthesis of cubic GdS nanoparticles at low temperature. The nanoparticles were made in solution using the ionic starting materials $GdCl_3$ and Na_2S in the presence

of dextrose. In this method reaction is carried out in ethanol which acts as a mild fuel which stimulates the reaction with sufficient activation energy at lower temperature. **Fig. 7** (a) TEM images showing crystalline GdS NPs obtained with dextrose, (b) histogram of nanoparticle size distribution, (c) selected area electron diffraction (SAED) pattern of cubic GdS NPs, (d) XRD pattern of as-prepared GdS nanoparticles.

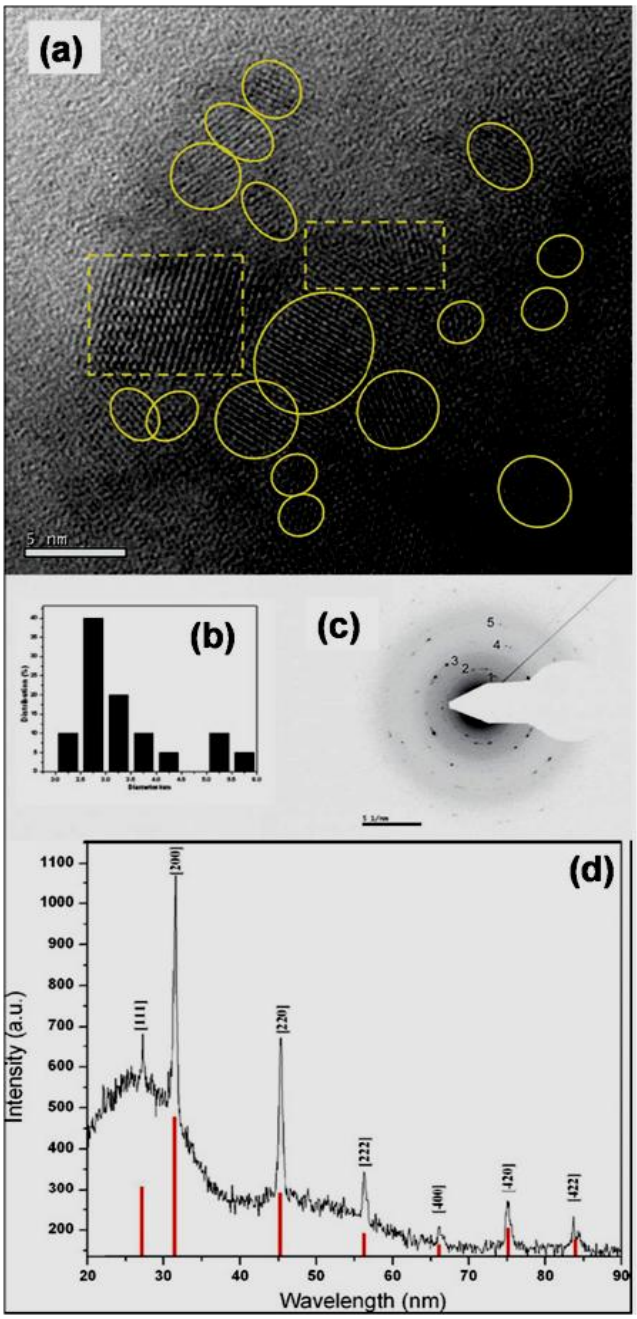

Fig. 7. (a) TEM images showing crystalline GdS NPs obtained with dextrose, (b) histogram of nanoparticle size distribution, (c) selected area electron diffraction (SAED) pattern of cubic GdS NPs, (d) XRD pattern of as-prepared GdS nanoparticles. Peaks in red represent GdS (cubic, JCPDS Card 26-1423). Figure adapted from "V. Parashar, S. K. Pandey and A. C. Pandey, Low-temperature synthesis of quantum size gadolinium monosulfide (GdS) nanoparticles and their pathogen capture efficiency, Chem. Commun., 2010, 46, 3143–3145".

4. Functionalization of multifunctional magnetic nanoparticles

The primary shortcoming of most chemotherapeutic agents is their relative non-specificity and thus potential side effects to healthy tissues. To overcome this problem, Magnetic nanoparticles functionalized with the drug can serve as potential drug carriers in a new drug delivery strategy, based on the application of external magnetic fields. Current drawbacks associated with anticancer drugs are accumulation, non specificity, limited stability *in vivo* and rapid clearance from the body due to short half lives. Targeted delivery of therapeutics possesses the potential to localize therapeutic agents to specific tissue as a mechanism to enhance treatment efficacy and mitigate side effects. Therefore, ligand specific targeting using molecules like folate [**104-106**], thiamine [**107**], transferin [**108**], antibodies [**109**], peptides [**110**], oligonucleotides [**111**] are being investigated. Nanoparticles have also been capped with various biocompatible polymers such as PVA, dextran, silica [**112**] and inorganic capping agents like biotin [**76**], citric acid [**113**], avidin, carbodiimide, SiO_2 [**114**], chitosan- PEG [**115**]**.** These molecules then act as attachment points for the coupling of cytotoxic drugs or target antibodies.

By tagging folic acid with these luinomagnets, tumors and other lesions can be detected at the cellular and molecular level [**116, 117**]. Folate receptors are up-regulated on a variety of human cancers, including cancers of the breast, ovaries, endometrium, renal cell carcinoma, lungs, kidneys, colon, brain metastases, colorectal and neuroendocrine carcinoma [**118-121**] due to their enhanced mitosis rates. This over-expression of folate receptors (FR) on cancer tissues have been identified as tumor markers and can be exploited to target folate-linked imaging and therapeutic agents specifically to FR-expressing tumors, thereby avoiding uptake by most healthy tissues that express few, if any, FR. The expression of FR increases with the advancement in the stage of cancer [**122**]. Folic acid is a short chain, non immunogenic and high affinity ligand. The FR is a glycosyl phosphotidylinositol linked membrane glycoprotein with an apparent mol wt of 38-40 KDa. Folate is an essential precursor for the synthesis of nucleic acid and some amino acids. It is not produced endogenously by mammalian cells and requires internalization by cells via receptor mediated endocytosis or carrier based uptake mechanism. Conjugation of folate to anticancer drugs, liposomes and micelles facilitated their cellular uptake [**123**]. Besides this, FR is expressed on the basolateral surface (blood side) of transformed cells as compared to the apical surface expression in normal cells [**124**]. This property complements the cancer cell specificity of folic acid as a targeting agent when delivered through the blood. These along with their capability of being manipulated by an external magnetic field leads to highly sensitive agents for biolabelling and magnetic resonance imaging with enhanced contrast. Besides, these can be designed to be used as delivery vector of external genetic material and enhance efficiency of transfection and transformation.

One such example for the functionalization of nanoparticles with folic acid is depicted in **Fig. 8**.

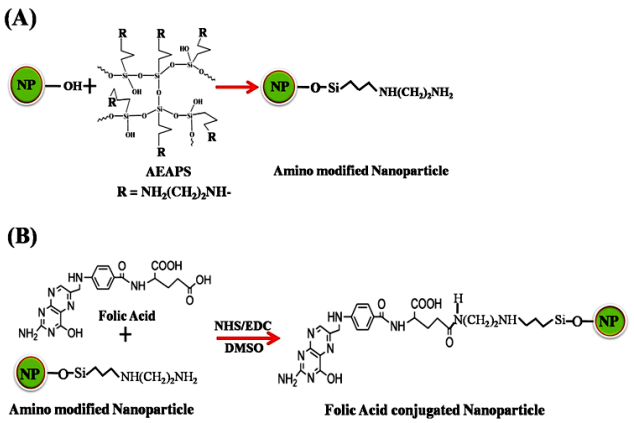

Fig. 8. Reaction mechanism for functionalization of nanoparticles with folic acid. Figure adapted from "Ranu K. Dutta, Prashant K. Sharma and Avinash C. Pandey, Design and surface modification of potential luminomagnetic nanocarriers for biomedical applications, J. Nanopart. Res., 2010, 12, 1211-1219".

In this particular scheme, nanoparticles were conjugated with folic acid by a chemical method. First, the nanoparticles were surface modified with AEAPS (3 amino ethyl trimethoxy silane) to form particles with $-NH_2$ groups, which were subsequently conjugated with folic acid through amidation between NH_2 groups on nanoparticle surface and γ-carboxylic acid group (-COOH) of γ - {*N*-{2-[2-(2-aminoethoxy) ethoxy] ethyl} folic acid. 0.2 g of nanoparticle was taken and dissolved in 50 ml toluene and sonicated for 30 minutes. To this solution, 10 ml of AEAPS was added. The suspension was stirred for 2 hours and the particles were recovered and washed with millipore water. 0.1 g of folic acid was taken and dissolved in 10 ml aqueous solution of *N*-hydroxysuccinimide (NHS) (358 mmol, 41 mg) and 18 mg of 1-ethyl-3-[3-(dimethylamino)-propyl] carbodiimide (EDC) and kept in the dark for 2 hours. The particles were then immersed in this mixture and left overnight for proper reaction to occur.

Shivang R. Dave and Xiaohu Gao [**125**] have shown a general functionalization scheme of multifunctional magnetic nanoparticles by inorganic, organic and ligands, **Fig. 9**.

5. Applications of multifunctional magnetic nanoparticles

Chemotherapy, a common treatment of cancer, is non-selective and causes significant negative side effects. Chemotherapy dosages are calculated primarily by the individual tolerance levels of a particular patient, which means that physically weaker patients are not able to receive adequate doses for successful treatment. Targeting the drugs and preventing release until they reach the tumor decreases the damage to normal cells and increases the dosage at the tumor. The first evidence for the utility of nanospheres in cancer treatment was demonstrated in the early 1980s. Since then the research of nanoparticle based chemotherapy has exploded. Till few years back, the majority of magnetic nanoparticles used for drug delivery are based on iron-oxide or its derivative compounds. Although recently, a phase II/III liver-cancer trial was suspended in U.S., still lots of other studies are going on at rapid speed suggesting a very bright future for the nanoparticle based chemotherapic treatment of cancer.

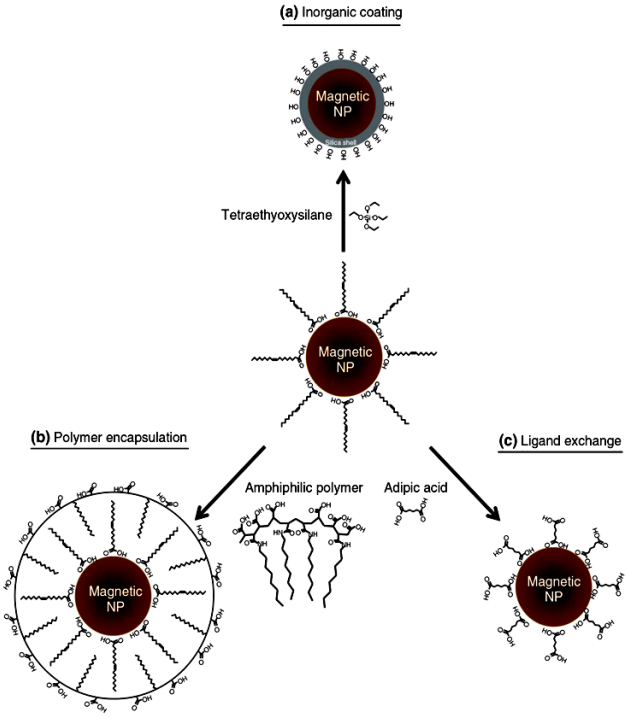

Fig. 9. General surface modification schemes for magnetic NPs. (a) Inorganic surface coating with tetraethoxysilane produces an amorphous silica shell. Polymer coating encapsulates the magnetic NP and native surface ligands (b), whereas the ligand exchange is to replace native surface ligands (c). These routes present polar or charged functional groups onto the outer surface of the NP for water solubility. Shivang R. Dave and Xiaohu Gao, Monodisperse magnetic nanoparticles for biodetection, imaging, and drug delivery: a versatile and evolving technology, WIREs Nanomedicine and Nanobiotechnology, John Wiley & Sons, Inc. Volume 1, November/December 2009, page 583.

5.1. Targeted drug and gene delivery

Some materials are taken up easily by all types of cells, while others are preferentially taken up by specific types of cells. Multifunctional magnetic nanoparticles can be localized by physical, chemical, and/or magnetic targeting. *Physical or passive targeting* uses surface features of nanoparticles, such as hydrophobicity, charge or pH, to induce reactions that cause the nanoparticles to stick to or enter the cells. This mechanism is highly non-specific. *Chemical targeting* uses functionalization of particles to increase the specificity of binding. Functionalization is the physical or chemical association of ligands-targeting agents, therapeutics, surfactants, etc., with a magnetic nanoparticle. Functional groups may be incorporated using covalent or non-covalent bonding, and/or physical adsorption. Binding to a receptor of interest is called specific binding, while binding to that and other sites is called non-specific binding. Antibodies, for example, specifically bind to their antigen, providing an effective means of tagging. Molecules used for targeting include proteins, oligonucleotides, antibodies and their fragments, lectins, hormones, charged molecules, nucleic acids, peptides, and receptor ligands. *Magnetic targeting* is used when a therapy has limited ability to be chemically targeted

to specific types of cells or tissues due to high non specific binding.

Magnetic nanoparticles functionalized with the drug can serve as potential drug carriers in a new drug delivery strategy, based on the application of external magnetic fields. Schematic of one such multifunctional nanoparticle for drug delivery is shown in **Fig. 10**.

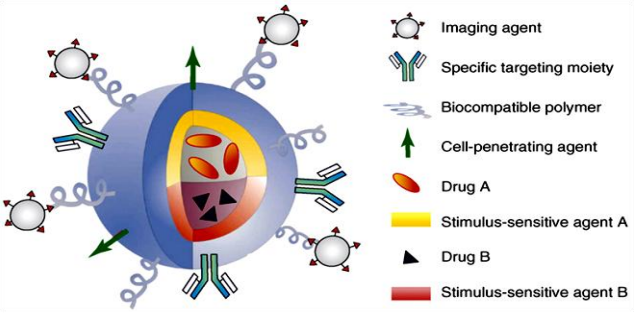

Fig. 10. Multifunctional nanoparticles for drug delivery. Multifunctional nanocarriers can combine a specific targeting agent (usually an antibody or peptide) with nanoparticles for imaging (such as quantum dots or magnetic nanoparticles), a cell-penetrating agent (e.g. the polyArg peptide TAT), a stimulus-sensitive element for drug release, a stabilising polymer to ensure biocompatibility (polyethylene glycol most frequently) and the therapeutic compound. Development of novel strategies for controlled released of drugs will provide nanoparticles with the capability to deliver two or more therapeutic agents.

The principle of drug delivery by nanomagnets is based on the use of both constant and high-frequency oscillating magnetic fields. Since these particles are magnetic in nature, they can be targeted to specific areas (for e.g. cancer tissues) by a constant external magnetic field. Releasing mechanism is accomplished by thermal excitations of these conjugated magnetic nanoparticles induced by an external high-oscillating magnetic field. Magnetic-field-induced excitations produce heat that increases the temperature of nanomagnets. Such specific heating represents an eliciting mechanism for the controlled release of conjugated drug from the nanomagnets when they are heated to adequately high temperatures (around 40° C). This specific heating can be achieved by calculating hysteresis loss (heat loss) from the magnetic loop.

The functionalized magnetic nanoparticle experiences a force which is produced by the magnetic field gradient and can be expressed as:

$$F_m = V\chi\nabla\frac{B^2}{2\mu_0} = V\chi\nabla(\frac{1}{2}\overline{B}.\overline{H}) \quad \text{---------- (1)}$$

For this reason, high-gradient, magnetic fields are commonly used for both magnetic nanoparticle-based drug delivery as well as for magnetofection applications. This equation also indicates that the variable parameters that can be used to increase the force (and, *in vivo*, the likelihood of capture) on the magnetic particle carrying the therapeutic drug or a gene of interest, are the particle volume, magnetic field strength, magnetic field gradient and the magnetic susceptibility of the particles. Earlier theoretical work done by researchers like Voltairas [**126**] indicated that for the most of the magnetic carriers, the magnetic flux density (field strength) at the target site must be of the order of 200 – 700 millitesla (mT) in order to efficiently attract particles flowing in the blood vessels. In addition to this, for targeted drug delivery the nanoparticles must have dimensions around 3-10 nm.

The ligand molecules along with the magnetic field help to drag the drug conjugated multifunctional magnetic nanoparticles to the target site when a high gradient magnetic field is applied outside the body near the tumor. A magnet is focused outside the body so that its magnetic field gradient attracts the magnetic nanoparticles to the target site. Once the complex reaches the desired location, the drug can be released by the way of self specific heating of magnetic nanoparticles as discussed earlier. The enlarged schematic diagram of the mechanism of the receptor mediated endocytosis of folic acid and drug conjugated multifunctional magnetic nanoparticles in cancer cell is depicted in **Fig. 11**.

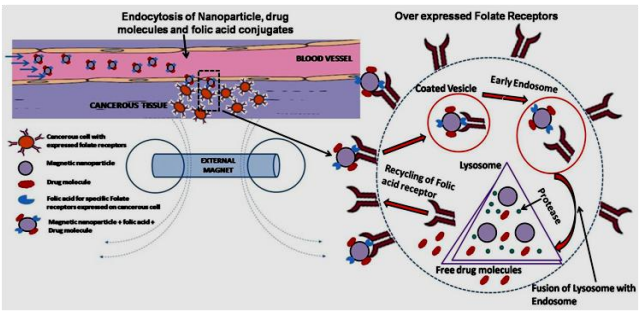

Fig. 11. Schematic representation of folate conjugated luminomagnetic nanocarriers mediated targeted drug delivery along with receptor mediated endocytosis of folic acid and drug conjugated luminomagnetic nanocarriers in cancer cells. Figure adapted from "Ranu K. Dutta, Prashant K. Sharma and Avinash C. Pandey, Design and surface modification of potential luminomagnetic nanocarriers for biomedical applications, J. Nanopart. Res., 2010, 12, 1211-1219".

Although seemingly straightforward, there are many variables that complicate the execution of this technique. Parameters such as the physicochemical properties of the drug-loaded magnetic nanoparticles, field strength and geometry, depth of the target tissue, rate of blood flow, and vascular supply, all play a role in determining the effectiveness of this method of drug delivery.

5.2. Magnetic detection and separation

The detection of specific molecules is critical from the security, sensing, diagnosis, treatment, and prevention of disease point of view. The development of fast, handheld analysis units capable of detecting multiple species is made more urgent by fears of biological and chemical terrorism. Magnetic separation has been applied to everything from detecting and separating different hazardous elements like sulphor, ammonia, different nitrates from chemicals and different warfare agents, tin from stainless steel at recycling centers to separating pure natural diamonds from diamonds with inclusions of other (magnetic) minerals.

Some cells are naturally magnetic, such cells could be separated utilizing their own intrinsic magnetism. In some other cases, the cells were attached to a multifunctional

magnetic nanoparticle for separation. Magnetic cell separation allows separation of target cells directly from blood, bone marrow and other fluids in short times due to the fast reaction kinetics. Magnetic cell sorting first was proposed using surface markers for cell receptors. The limiting factor for magnetic separation is identifying a linking molecule with high specificity for the desired cell. Applications include purging malignant cells from autologous stem cell products, water purification, minimizing and recycling nuclear waste and recovering heavy metals. Blood purification using magnetic carriers has been used to treat autoimmune and inflammatory diseases, including myasthenia gravis, lupus and Guillain-Barré syndrome. T4 and T8 cells in HIV-infected patients have been isolated using magnetic separation.

5.2.1. Simultaneous magnetic detection and separation of thiols and disulfides from sulphor containing compounds

A novel procedure for visible detection and separation of thiols and disulfides was described by *Parashar and Pandey*. The method uses a $Gd(OH)_3$ nanosheets-sodium pentacyanonitrosylferrate (II) paramagnetic complex which produce an intermediate chromophore when coupled with a sulfur containing analyte, which is detectable with the naked eye and simultaneously can be removed by applying an external magnetic field (**Fig. 12**). **Fig. 12b** shows the color appearance with the [$Gd(OH)_3$/SPII] nanosheets complex on amicrotiter plate with various thiols at a concentration of 200 mM. Water was used as a negative control. Interestingly, with this system different sulfur analytes develop different colors. The developed color is stable for more than 24 h at room temperature, and the concentration dependent color intensity is reproducible over a wide range of concentrations.

5.2.2. Magnetic cell separation

Magnetic separation consists of three parts: tagging or labeling the desired cells with a magnetic marker as described earlier, separating magnetically labeled cells from unlabeled cells, and measuring the magnetic properties to quantify the number of cells present. Separation may be done in batch or flow configurations, depending on the specific application. In batch processing, the magnetic beads and the analyte material are mixed. The reaction kinetics determines the amount of time necessary to wait for a sufficient amount of binding to occur. A magnet is used to separate the magnetically targeted cells from the non-targeted cells, as shown in **Fig. 13**. The most commonly used (and commercially available) materials for cell separations are micron-sized polymer beads into which a magnetic material, usually maghemite, has been embedded.

Fluid-flow techniques allow continuous processing and are advancing rapidly due to micro-fabrication capabilities. A permanent magnet can be used to either deflect or collect magnetically labeled particles. In a similar intresting demonstration *Dutta, Sharma* and *Pandey* have proposed the easy separation and simultaneous visualization of blood platelets from the mice-blood platelet rich plasma (PRP), **Fig. 14**, [**109**]. Such technique offers advantages of simplicity of operation, low cost, specificity, and sensitivity afforded by the use of immunospecific reagents. The magnetic microbeads coupled with the specific antibodies can effectively separate cells such as leukemic cells from urine.

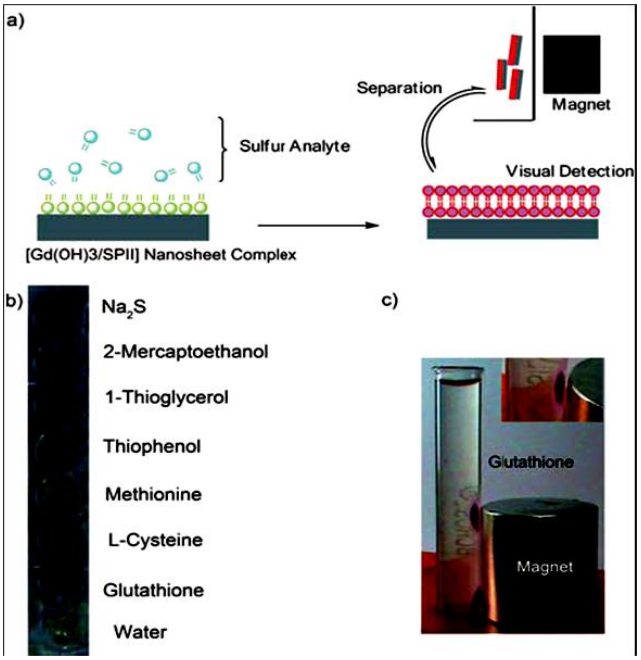

Fig. 12. (a) Synchronized detection and removal of sulfur analyte using the [$Gd(OH)_3$/SPII] nanosheets complex. b) Visual detection of various sulfur analytes (1 mM) with the [$Gd(OH)_3$/SPII] nanosheets complex. c) Glutathione (1 mM) was detected by the nanosheets complex and simultaneously attracted towards the magnetic poles when a permanent magnet was applied externally. Figure adapted from "V. Parashar and A. C. Pandey, Synchronized detection and removal of thiols using a $Gd(OH)_3$ nanosheet-sodium pentacyanonitrosylferrate (II) complex, Anal. Methods, 2010, 2, 1227–1229".

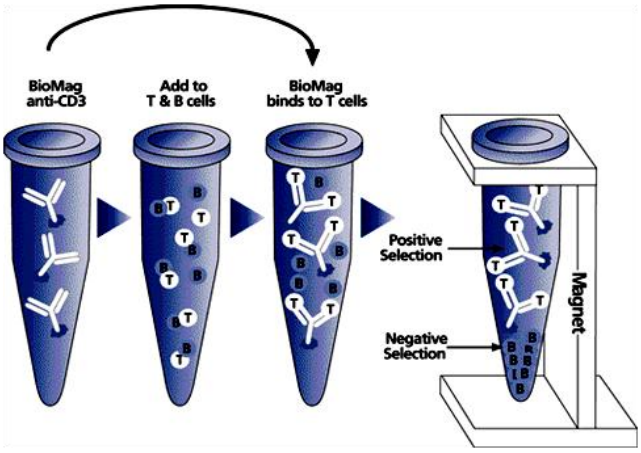

Fig. 13. A schematic illustration of the magnetic cell separation process.

5.3. Hyperthermia

The therapeutic power of heat has been used to alleviate a variety of diseases. This heat treatment is recognized as new and promising form of cancer rehabilitation out-of-the-way from surgery, chemo therapy, and irradiation. It is well established that cancer growth stops at temperatures higher than about 42°C [Wilfried et al., 1998], while normal cells

can tolerate even higher temperatures. Hyperthermia is heating of certain organs or tissues to temperatures between 41°C and 48°C as a treatment of cancer. Hyperthermia induces almost reversible damage to cells and tissues, however, it can enhance radiation and chemotherapy injury of tumor cells.

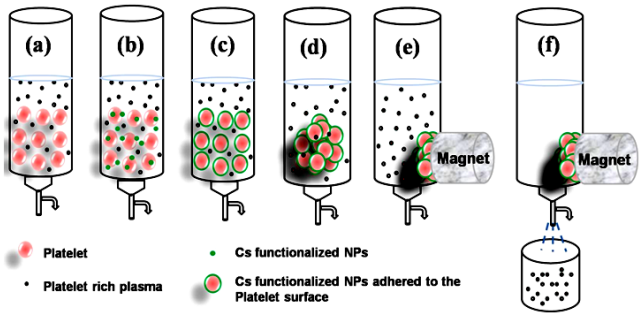

Fig. 14. Schematic representation of (a) platelets in PRP, (b) added cytosine capped nanoparticles, (c) cytosine capped nanoparticles adhered on the surface of platelets, (d) aggregation of platelets mediated by cytosine capped nanoparticles, (e) cytosine capped nanoparticles being attracted to the wall by using an external magnet, and (f) isolation of aggregated platelets using magnet. Figure adapted from "Ranu K Dutta, Prashant K Sharma and Avinash C Pandey, DNA base (cytosine) modified/capped ultrasmall $Gd_2S_3:Eu^{3+}$ gadofluoroprobes for platelet isolation, App. Phys. Lett. 2010, 97, 253702."

Hyperthermia and thermal ablation have been accomplished using capacitive or inductive coupling of radio frequency (RF) fields (10–100 MHz), microwaves (> 300 MHz), ultrasound, lasers or external heat. The absorbed power per mass is called the specific absorption rate (SAR). SAR determines the heating ability of magnetic materials in the presence of an AC magnetic field and can be defined as the amount of heat generated per unit gram of magnetic material per unit time. The SAR (W g^{-1}) value was calculated by using the formula:

$$\mathbf{SAR} = \mathbf{C}\frac{dT}{dt}\frac{m_s}{m_m} \qquad \text{---------- (2)}$$

where, C = specific heat capacity of suspension = 4.186 Jg^{-1} $°C^{-1}$ (specific heat of water, in this case), (dT/dt) = slope of temperature versus time graph, ms = mass of the suspension, and mm = mass of the magnetic material in the suspension.

The coupling of an external RF magnetic field to magnetic particles in the body results transfer of energy to the tissue by:

i. Eddy current heating,
ii. Hysteretic heating: heat generated when a magnetic material is forced around part or all of the hysteresis loop,
iii. Viscous heating: heat generated by the kinetic motion of a particle within a viscous fluid, and
iv. Magnetic resonance. The loss power of the magnetic particles should be as high as possible so as to allow the lowest possible dose.

Modeling magnetic hyperthermia is difficult due to the complex magnetization reversal mechanisms found in nanoparticles. Optimization of nanoparticle properties is important to limit the amount of material that must be introduced. The SAR achievable for a given combination of field, frequency, and type of particle usually must be determined experimentally. SAR values range from a few W/g to a few hundred W/g. The SAR depends on many factors, including the effect of coating on surface spin dynamics, the effect of surface properties on Brownian relaxation, size, and crystallinity among other factors.

Magnetic nanoparticle hyperthermia has a potential advantage over radio- and chemo- therapies because there is no systemic buildup in organs, so larger doses are possible. The nanoparticles can be introduced into the body once, and then used for multiple treatments. Nanoparticles can be magnetically targeted, injected directly into the tumor in some cases, or injected into the vasculature supplying the tumor. The use of iron oxides for hyperthermia of tumors was first proposed by Gilchrist *et al.* [**127**]. The first clinical human trials using magnetic hyperthermia were reported by Lubbe, *et al.* [**128-131**] who used 100-nm starch-coated iron-oxide particles bound with epirubicin for treatment of advanced solid cancers.

Larger bones, such as the pelvis and skull shield tissues and produce inhomogeneous heating. Non-uniformity of tumors poses a complication, as large tumors heat at a greater rate than small tumors due to the poorer tissue cooling and differences in heat conduction in the necrotic regions of large tumors [**132-134**]. One approach to controlling temperature is to use materials with a Curie temperature between 42 and 50 °C, as these materials automatically "turn off" when the temperature becomes too high. Substituted ferrites such as $(Co_{1-x}Zn_x)Fe_2O_4$, manganates such as $La_{1-x}Me_xMnO_3$ [Me=Sr, Ba, Pb, Ag, Na] and substituted yttrium-iron garnet $Y_3Fe_{5-x}Al_xO_{12}$ are ideal candidates due to their stability against oxidation (relative to metals) and the ability to tune the Curie temperature by composition [**135, 136**].

5.4. Magnetic switches

Magnetic fields can be used to trigger the release of a drug vaguely. For instance, an applied ac field causes the magnetic particles to heat, which in turn opens the lipid layer, encapsulating magnetic nanoparticles and drugs, and releases the drug [**137, 138**]. Similarly, the thermoresponsive gels, which are chemically cross-linked polymer network characterized by pores, elasticity, and the ability to change volume when stimulated by temperature, can be used. Entrapping magnetic nanoparticles in the gel allows control of the pore size via the external ac magnetic field. Drug entrapped in the pores is released when the gel swells and the pores expand. Similarly, magnetically induced stress has been used to control drug release. Polymer spheres filled with magnetic nanoparticles and drug subjected to an oscillating magnetic field produced small stress-induced cracks in the polymer. The cracks allowed liquid to enter the spheres and carry out drug. Using magnetism as a "release-on-demand" mechanism could be useful for insulin-dependent diabetics [**139, 140**]. Innovent, Inc. has developed a magnetic capsule made of two or more parts that are held together magnetically. Demagnetizing the magnetic capsule by applying alternate pulses of opposite magnetic polarity allows the capsule to open. The resulting capsule parts are small enough for the

patient to eliminate. This capsule is small enough to be used for delivery of drugs to the gastrointestinal tract **[141]**.

5.5. Magnetic sensors

Integrated structures utilizing nanolithography can perform sorting and quantitative analysis in a single device. Magnetic transducers have low interference, low background signal, do not require sample pre-treatment, and can be small enough to be portable.

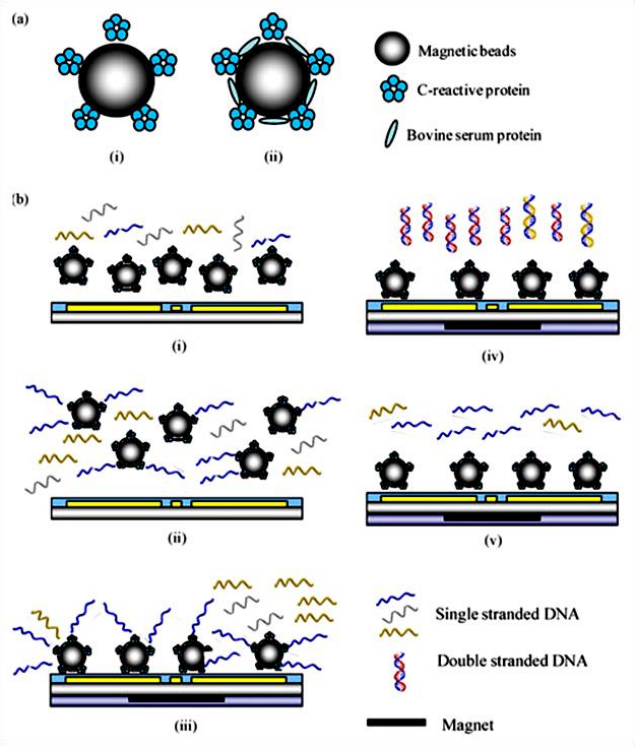

Fig. 15. Schematic illustration of the extraction and the amplification processes in the magnetic bead-based microfluidic system. Figure adapted from "Huanga, C.J., H.I. Linb, S.C. Shieshb, G.B. Leea. Integrated microfluidic system for rapid screening of CRP aptamers utilizing systematic evolution of ligands by exponential enrichment (SELEX). Biosensors and Bioelectronics 2010, 25, 1761–1766".

Magnetoresistive techniques have an advantage over techniques that use, for example, MFM or AFM tips to manipulate magnetic beads attached to molecules, in that they are much faster and have the potential to detect more than one molecule at a time. Spin-valve and other magnetoresistive devices detect the stray field from a magnetic micro- or nanobead, as illustrated by **Fig. 15**.
Similarly, a novel saccharides detection assay based on covalent immobilization of amino phenyl boronic acid (APBA) in thin films of carboxyl functionalized chitosan (HOOC-chitosan) containing <5 nm Gd_2O_3:Eu^{3+} nanoparticles at a platinum disc electrode was developed by Tiwari *et al.* [**142**].

Lithographically fabricated microcircuits may be used to manipulate the magnetic particles. Detection limits in the 102 nM can be achieved, and detection of single particles is theoretically possible. Detection of multiple species on a single chip is possible by fixing a probe molecule (often DNA) to a polymer layer covering the sensor. The analyte DNA is a single strand complementary to the probe DNA and is labeled (often with biotin). Magnetic microspheres functionalized with streptavidin (which attaches to biotin) are then introduced; the microspheres bind to the biotin, which is present only on the successfully trapped DNA. The signal measured by sensor can be used to quantify the amount of analyte present. The response to the sensor is determined by the in-plane component of the stray fields induced by the magnetized microspheres.

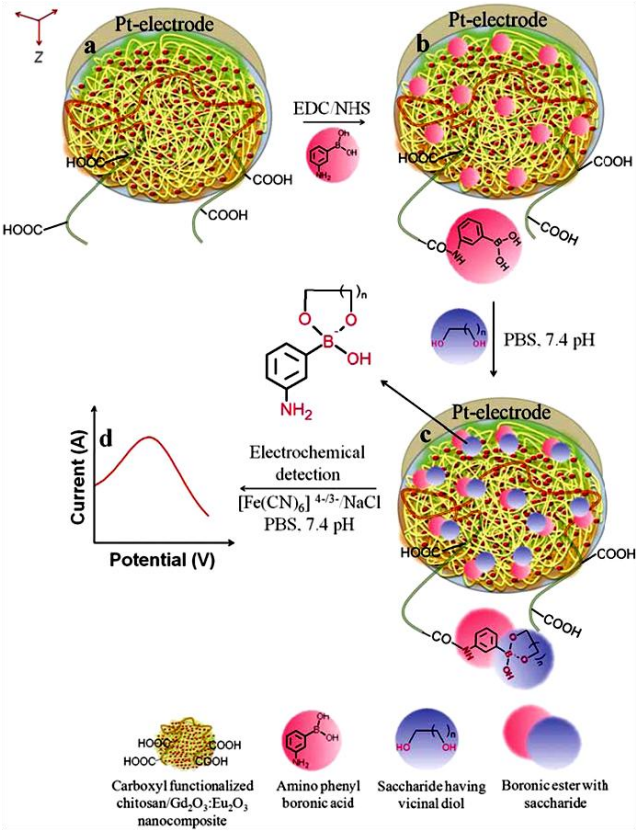

Fig. 16. Schematic illustration of electrodes fabrication and electrochemical saccharide(s) detection process. Figure adapted from "Ashutosh Tiwari et al., an ultra sensitive saccharides detection assay using carboxyl functionalized chitosan containing Gd_2O_3:Eu^{3+} nanoparticles probe, Anal. Methods, 2011, 3, 217-226".

Superconducting Interference Device (SQUID) sensors are more sensitive than GMR devices, but require low temperatures and magnetic shielding. RF SQUIDS have been used to measure magnetic markers to which monoclonal antibodies have been attached. SQUID sensors also can be used to detect changes in relaxation due to binding or changes in local environment. Recently, *R. K. Dutta, P. K. Sharma* and *A. C. Pandey* have engineered the highly susceptible paramagnetic nanostructures of Gd_2S_3:Eu^{3+} as potentially an efficient new material for room temperature gas sensing applications. Their preliminary result, **Fig. 17**, shows good sensitivity for ammonia gas at room temperature, speculating the possible application of this material in gas sensing.

5.6. Contrast agents for magnetic resonance imaging

MRI is as a powerful imaging modality due to its non-invasive nature, high spatial resolution and tomographic capabilities. The applications of MRI have steadily increased over the past decade, offering the advantage of high spatial resolution of contrast differences between tissues. MRI is a diagnostic scanning modality based on principles of NMR. It measures the signal from the hydrogen nuclei of water, which is modified by the surrounding chemical environment. NMR spectroscopy measures the characteristics of any hydrogen nuclei depending on their position in the molecule. NMR gives information about chemical shifts and coupling constants, whereas MRI gives spatial distribution of the intensity of the water proton signal in the volume of the body. This signal intensity depends essentially on three factors:

i. The density of proton spins in a given volume,
ii. The longitudinal and transverse relaxation times T1 and T2 of these spins.
iii. Using different RF pulse sequences, image intensity can be weighted with respect to T1 or T2.

It visualizes contrasts in images via monitoring the response of water protons to external magnetic field. MRI obtains real-time images of the internal anatomy and physiology of living organisms in a noninvasive manner. Furthermore, it is currently the most sensitive method to depict soft tissues. Therefore, it has been extensively used for imaging brain and central nervous systems, for assessing cardiac function, and for detecting abnormal tissues such as tumors. Now a days, MRI is one of the most powerful and central techniques in diagnostic medicine and biomedical research. The applications of MRI have steadily increased over the past decade, offering the advantage of high spatial resolution of contrast differences between tissues.

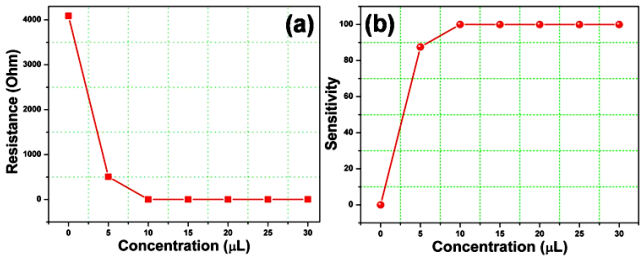

Fig. 17. Resistance (a) and sensitivity of $Gd_2S_3:Eu^{3+}$ magnetic nanoparticles as function of ammonia concentration. Figure adapted from "Ranu K. Dutta, Prashant K. Sharma and Avinash C. Pandey, Engineering of Highly Susceptible Paramagnetic Nanostructures of $Gd_2S_3:Eu^{3+}$: Potentially an Efficient Material for Room Temperature Gas Sensing Applications, Sensors & Transducers Journal, Vol. 122, Issue 11, November 2010, pp. 36-45".

MRIs make use of the unique property of atomic nuclei rotating in a strong magnetic field. These nuclei have a special "resonance" frequency that depends on the magnetic field. By absorbing radio waves of the same frequency, the nucleus' energy can be increased. Radio waves are re-emitted by the nuclei as they return to the lower energy state. The time it takes for the radio wave to do this is known as the 'relaxation time', and the different relaxation times result in varying bright and dark spots on the image.

However, since there is little difference between normal and abnormal soft tissues in terms of relaxation time and hence the resulting contrast, additional supplements have been used for more accurate detection and diagnosis. The most effective supplement is a chemical compound known as a *contrast agent* that is introduced to a living body to enhance imaging quality. Moreover, the interrelation between the contrast agent and the biological system often reveals biological and functional information. Capping the nanoparticles with nonimmunogenic, nonantigenic and protein-resistant layers of a biocompatible material such as polyethylene glycol (PEG) could help in preventing aggregation, enhancing the blood retention, facilitating nanoparticle cell uptake and providing binding sites for targeting agents. The development of MRI has also concurrently led to the development of chemical contrast-enhancement products called contrast agents (CAs). The lack of high contrast and targeted delivery has prevented precision diagnosis. In the same pursuit scientists have developed verity of contrast agents in recent times. The development of multifunctional magnetic nanoparticles further spurred the discovery of contrast agents.

In comparison with conventional gadolinium chelates, nanoparticle-based contrast agents offer enhanced cellular internalization and slower clearance from the tumour site [**143, 144**]. For MRI purposes iron oxide cores are commonly used as so-called T2 contrast agents and can be divided into either super-paramagnetic iron oxides (SPIOs), with diameters of > 50 nm, or ultra small SPIOs (USPIOs) with diameters of < 50 nm [**145**]. Currently, there are several formulations for clinical applications such as bowel (lumiren and gastromark) and liver or spleen imaging (endoderm and feridex). As with all nanoparticles, the tissue distribution is heavily influenced by size, thus the larger SPIOs tend to rely on passive targeting, such as uptake by the cells of the RES, rather than direct labelling, and the USPIOs benefit from slower opsonization and RES clearance [**146**]. The next generation of active targeting contrast agent is currently being researched, which provide exciting new opportunities for imaging, diagnosis and treatment [**147**]. Monoclonal antibodies were the first targeting agents to exploit molecular recognition to deliver mNPs [**148, 149**]. For example, Suzuki *et al* developed an MRI contrast agent, which was prepared by covalently linking polyethylene glycolcoated magnetite to an antibody specific for a human glioma cell surface antigen [**150**]. However, one drawback of using monoclonal antibodies is their large size (~12 nm), which can cause poor diffusion through typical biological barriers. Following this, mNPs have been examined intensively as MRI agents to improve detection and diagnosis of solid tumors [**151, 152**]. More recent applications utilizing antibody directed targeting tend to focus on using shorter, smaller single chain fragments, which consist of antibody heavy- and light-chain variable domains connected with a flexible peptide linker [**153**]. The resulting fragment is smaller than 20% of an intact antibody, but maintains a high binding affinity and specificity [**154**]. The signal enhancement caused by conventional iron oxides, however, is still unsatisfactory compared with that obtained with other imaging modalities

such as fluorescence and PET. A further area of research is to thus develop magnetism-engineered iron oxide (MEIO) nanoparticles, which possess exceptionally high and tunable nanomagnetism [**155**]. A recent study by Lee *et al* demonstrated such engineered particles enhanced sensitivity for cancer cell detection and also made the *in vivo* imaging of small tumours possible [**156**]. There are reasons to expect that MRI will become much more sensitive in the next few years. As its sensitivity approaches and perhaps exceeds that of fluorochromes (fluorescent substances used to stain biological specimens), the need for nanoparticles in MRI molecular imaging might seem to fade away. However, there is a separate reason why nanoparticles will be required even in more sensitive versions of MRI, and this is theranostics. The payload of the nanoparticle can consist of drug molecules and of signal generating moieties. This combination allows the nanoparticle to be located within the living subject and at the same time to release drugs into a target site, enabling molecular imaging to be combined with therapy. This 'therapy' plus 'diagnostics' or 'theranostics' holds promise in future of monitoring the effectiveness of therapy simultaneously with delivering the therapy [**157, 158**]. For example C. Sun *et al*. [**159**] recently demonstrated the specific accumulation of CTX-targeted iron oxide nanoparticles in 9L glioma flank xenografts resulting in more thorough contrast enhancement of tumors in comparison to nontargeted control nanoparticles (**Fig. 18**).

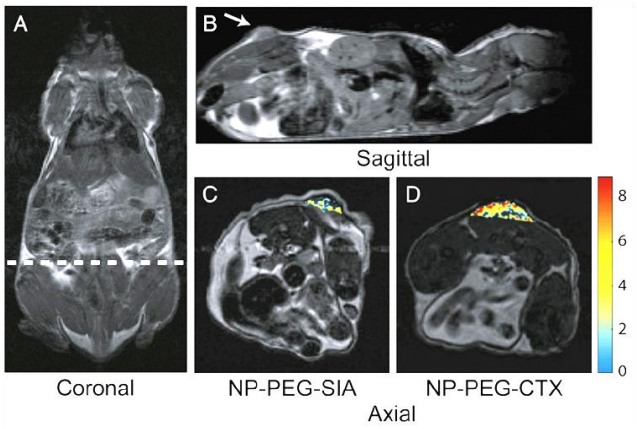

Fig. 18. MRI anatomical image of a mouse in the (A) coronal plane with the dotted line displaying the approximate location of the axial cross sections displayed in (C) and (D). Anatomical image in the (B) sagittal plane displaying the location of the 9L xenograft tumor. Change in R2 relaxation values for the tumor regions (superimposed over anatomical MR images) for mouse receiving (C) non-targeting PEG-coated iron oxide nanoparticles and (D) CTX-targeted PEG-coated iron oxide nanoparticles 3 h post nanoparticle injection. Figure adapted from Small, Volume 4, Issue 3, Pages 372 – 379.

6. Conclusion

The present review summarize the development of state-of-the-art multifunctional magnetic nanoparticles and their foremost applications in security/sensors, magnetic targeting, drug delivery, magnetic separation, as contrast agents in magnetic resonance imaging, hyperthermia etc. The basic requirements and functionalization approach for multifunctional magnetic nanoparticles used in these applications are also reviewed. The detailed applications of multifunctional magnetic nanoparticles in biological organisms have been discussed in view of fashioned noteworthy advances in research, diagnosis and therapy of various diseases.

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