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Engineered magnetic core shell nanoprobes: Synthesis and applications to cancer imaging and therapeutics

Samir Mandal, Keya Chaudhuri

Samir Mandal, Keya Chaudhuri, Molecular and Human Genetics Division, CSIR-Indian Institute of Chemical Biology, Kolkata 700032, India

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Correspondence to: Keya Chaudhuri, Emeritus Scientist, Molecular and Human Genetics Division, CSIR-Indian Institute of Chemical Biology, 4, Raja S.C Mullick Road, Kolkata 700032, India. keya.chaudhuri@gmail.com
Telephone: +91-332-4995762
Fax: +91-332-4735197

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Abstract

Magnetic core shell nanoparticles are composed of a highly magnetic core material surrounded by a thin shell of desired drug, polymer or metal oxide. These magnetic core shell nanoparticles have a wide range of applications in biomedical research, more specifically in tissue imaging, drug delivery and therapeutics. The present review discusses the up-to-date knowledge on the various procedures for synthesis of magnetic core shell nanoparticles along with their applications in cancer imaging, drug delivery and hyperthermia or cancer therapeutics. Literature in this area shows that magnetic core shell nanoparticle-based imaging, drug targeting and therapy through hyperthermia can potentially be a powerful tool for the advanced diagnosis and treatment of various cancers.

Key words: Magnetic core shell nanoparticles; Magnetic resonance imaging; Cancer therapeutics; Drug delivery; Hyperthermia

Core tip: Magnetic core shell nanoparticles have recently gained a lot of interest due to its excellent design and applicability to various fields of research including biomedical sciences. The core shell particle contains a highly magnetic core surrounded by a thin shell of desired material, the choice being dependent on the application. The applicability of core shell nanoparticles in the area of *in vivo* imaging, drug delivery and therapeutics in the form of hyperthermia have been discussed along with the various procedures for synthesis of these useful nanoprobes.

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INTRODUCTION

Nanoparticles are emerging as a prospective biomedical tool with applications in diagnostics, specific drug

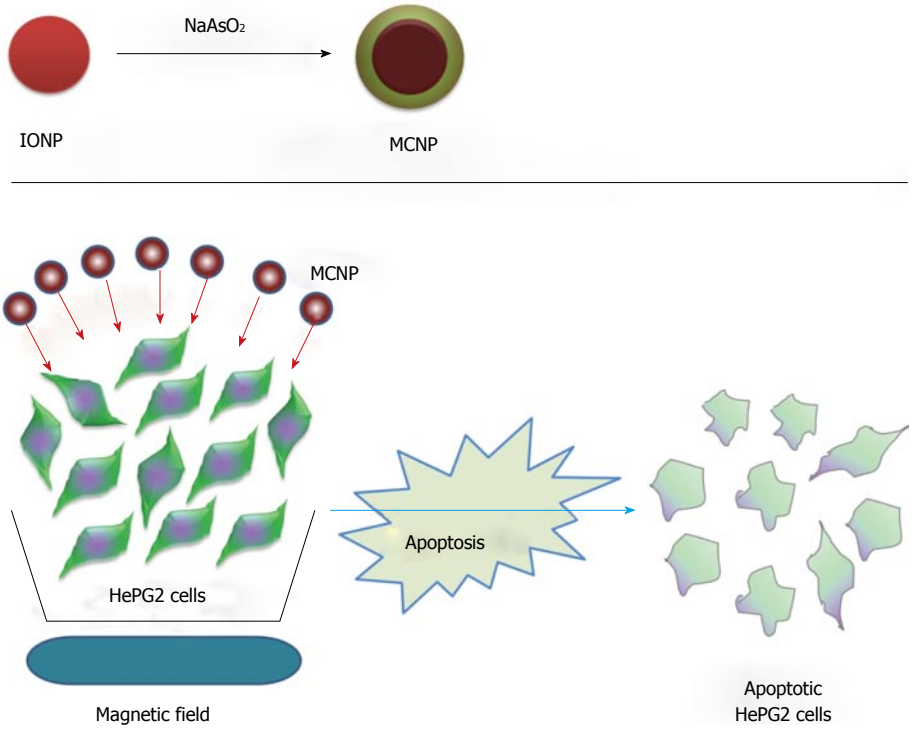

Figure 1 Schematic showing synthesis of magnetic core shell nanoparticle and their application towards targeting the cancer cells. Upper panel shows generation of MCNPs and lower panel represents magnetically facilitated arsenite delivery using MCNPs to kill cancerous cells through apoptosis. MCNP: Magnetic core shell nanoparticle; IONP: Iron oxide nanoparticle.

delivery and therapeutics of diseases. Among these, magnetic nanomaterials with a core shell structure has been of interest for a long time primarily owing to their vast applications for example in magnetic data recording devices, in sensors, in catalytic reactions and in various biomedical applications encompassing tissue imaging for diagnosis, drug delivery and therapeutic management of diseases[1-4]. Attachment of biomolecular markers to the surface of magnetic nanoparticles has been used to demonstrate that magnetic nanoparticles have the potential to deliver noxious drugs at a specific location in the body accurately[5], which in effect can lead to design of highly specialized bio-probes for diagnostic imaging[6,7]. These advances have encouraged the development of biocompatible magnetic nanomaterials endowed with ultra-sensitive imaging potential in order to find wide applications in targeted as well as non-invasive *in vivo* medical imaging.

One such example could be Au coated magnetic nanoparticles, a complex system that has drawn a lot of attention[8]. Au coating is responsible for more effective stabilization of the magnetic nanoparticles, particularly metallic nanoparticles with high magnetic moment under toxic biological environment. The magnetic nanoparticles can readily be functionalized by Au because of its well-developed Au-S chemistry; the gold coating provides plasmonic properties to the magnetic nanoparticles. This renders the composite core/shell nanoparticles exceedingly attractive for multidisciplinary applications comprising of magnetic, optical, and biomedical applications. Another example could be arsenicals which have been known for thousands of years to be carcinogenic or poisonous despite their therapeutic or beneficial effects which are observed at a low dose. The United States Food and Drug Administration has granted approval of arsenic trioxide (ATO) as an effective leading edge treatment for relapsed and/or refractory APL patients. Further, several reports emphasize the success of arsenic in a diverse hematological malignancies for example promonocytic leukemia, chronic myelogenous leukemia, multiple myeloma, T-cell leukemia, and a wide array of cancers derived from solid tumors such as renal cell carcinoma, neuroblastoma, glioblastoma, gastric, hepatocellular, head and neck, cervical, prostate and breast cancers[9-15]. ATO either alone or in combination with other drugs has been used for each disease. The soluble most toxic and naturally prevalent form of arsenic ($NaAsO_2$) has been shown to induce apoptosis in human malignant melanoma cells (A375) *in vitro*. Enhanced generation of reactive oxygen species, mitochondrial membrane potential damage and caspase activation are the critical mediators of apoptosis[16]. Extensive clinical application has been limited by: (1) diverse sensitivity of tumor cells to a higher dose of arsenic; and (2) less sensitive cell sensitization needing up to 10 times higher concentration of arsenic entailing the risk of arsenic-induced side effects[17-19] (illustrated in Figure 1). Cancers, especially solid tumours, at their advanced stage are therefore difficult to manage by arsenic

administration in its present form. Nanotechnology, especially the core shell magnetic nanoparticles, has been shown to have advantages over others in terms of using effective lower dose of arsenite with minimal side effect and higher efficacy[20]. In this context, the present review highlights the synthesis and applications of diverse magnetic core shell nanoparticles in diagnostics especially imaging and in therapeutics.

TYPES OF MAGNETIC CORE-SHELL NANOPARTICLES

The core shell nanoparticle is a type of nanoparticle consisting of a core or inner matter and a shell or outer coating material. Various types of core shell nanoparticles with different combinations in close interaction have been prepared with distinctive use. The combinations can be inorganic/inorganic, inorganic/organic and organic/inorganic materials. Generally magnetic core-shell nanoparticles can be classified into two following types.

Magnetic oxide core shell

The maghemite or magnetite magnetic nanoparticle has a relatively inert surface composition which generally does not permit strong covalent bond formation with functional molecules. The use of shell of silica onto the surface of magnetic nanoparticles has been shown to enhance the reactivity of magnetic nanoparticles[21]. The silica shell can be readily customized through the formation of covalent bonds with a variety of surface functional groups[22]. These silica-functionalized magnetic nanoparticles can be used to conjugate with some fluorescent dye molecules through the formation of covalent bond[23].

Ferrite nanoparticle clusters, comprising of about 80 maghemite super paramagnetic oxide nanoparticles per bead with silica shell, have a number of benefits over metallic nanoparticles. These can be summed up as: (1) greater chemical and thermodynamic stability; (2) precise size distribution; (3) greater colloidal stability; (4) adjustability of the magnetic moment with the nanoparticle cluster size; (5) retention of super paramagnetic properties irrespective of the cluster size of nanoparticles; and (6) straightforward covalent functionalization by the silica surface.

Metallic magnet core shell

The core material of magnetic naoparticles may be deactivated by mild oxidation, use of surfactants and/or polymers[24]. In an oxidative surroundings, antiferromagnetic CoO layer was formed onto the surface of the Co nanoparticle. Lately, the exchange bias synthetic protocol has been used to generate Co core CoO shell nanoparticles having gold outer shell[25]. Also, much interest has been generated in nanoparticles with a magnetic core consisting either of elementary iron or cobalt with a nonreactive shell made of grapheme, which have been synthesized recently[26]. The advantages compared to ferrite or elemental nanoparticles are: (1) higher magnetization; and (2) higher stability in acidic and basic solutions as well as organic solvents.

Synthesis of magnetic core shell nanoparticles

Magnetic core shell nanoparticle synthesis involves mainly two steps: First is the synthesis of magnetic nanomaterials and after that coating of the magnetic nanomaterials with desired organic or inorganic materials according to the requirement. The synthesis can be affected by a variety of combinations including inorganic/organic, organic/inorganic and inorganic/inorganic materials in close interaction. The selection of shell materials in core-shell nanoparticles is largely decided by the end application and utility. Generally silica, different types of metal and nonmetallic oxides, polymer and drug molecules are employed as coating materials. Thus here the main important task is the synthesis of magnetic nanomaterials (core). These core nanomaterials can be synthesized by the following four methodologies.

CO-PRECIPITATION TECHNIQUE

Iron oxide (Fe_3O_4 or γ-Fe_2O_3) nanoparticles could be prepared by the slow addition of a base into a mixture of aqueous Fe^{2+}/Fe^{3+} salt solutions under an inert atmosphere at elevated temperature or room temperature depending upon requirement. This method is termed as co-precipitation technique. The composition and morphology of the magnetic nanoparticles prepared by co-precipitation method is highly dependent on the precursor salt and reaction conditions such as temperature, pH and ionic strength of reaction system. The quality of the magnetite nanoparticles is fully reproducible if the synthetic conditions are fixed. The experiment showed that the magnetic saturation values of magnetite nanoparticles are lower than bulk value (90 emu/g). Under ambient conditions, magnetite nanoparticles are not very stable. These nanoparticles are readily oxidized to a more stable maghemite form or dissolved in an acidic pH. Being a ferrimagnet, oxidation process is less problematic. The conversation of magnetite to maghemite is accomplished by forming acidic dispersion, followed by iron (Ⅲ) nitrate addition. Now this maghemite particle shows chemical stability through a wide range of pH.

Although the magnetite particles are transformed into maghemite nanoparticles at the initial stage, the experimental challenge in the formation of Fe_3O_4 involving co-precipitation technique lies in controlling narrow particle size distribution. As particle size and morphology largely depend on blocking temperature, a broad range of particle size distribution would be due to the fluctuation of blocking temperature, which results in irregular magnetic activity. Nanoparticles obtained by co-precipitation technique are polydisperse in nature.

Recently, considerable approaches in synthesizing

monodisperse magnetite nanoparticles having diverse sizes and morphology have been finished by the exploitation of various organic stabilizers and reducing agents. For instance, the stabilization of magnetite nanoparticles having dimensions of 3-11 nm was done by applying an aqueous solution of 1 wt% polyvinlyalcohol (PVA).

On the other hand chainlike clusters precipitate of magnetite nanoparticles could be formed by the application of PVA having 0.1 mol% carboxyl groups as stabilizing agent[27]. The above fact shows that the appropriate surfactant choice is a key matter to stabilize the particle. Formation of magnetite by the use of trisodium citrate in an alkaline pH, followed by successive oxidation at 90 ℃ for 30 min with iron (Ⅲ) nitrate produces size-tunable maghemite nanoparticles. The adjustment of the molar ratio of metal ions (Fe^{2+}/Fe^{3+}) and citrate ions is the main key to vary the particle size from 3 to 8 nm[28]. The special effect of carboxylate and hydroxy carboxylate ions on the preparation of iron oxides or oxyhydroxides has been investigated elaborately[29]. Deprotonated carboxy and deprotonated α-hydroxy groups are essentials for the formation of surface complexes[30]. The advanced investigations have revealed that the best stabilization of magnetic Fe_3O_4 nanoparticles was done by oleic acid[31,32].

Thermal decomposition

Synthesis of magnetic particles with desired shape and size generated from the idea of quality semiconductor nanocrystals and oxide-nanoparticles synthesis involving thermal decomposition technique using non-aqueous media[33-35]. Organometallic compounds on thermal decomposition in high-boiling organic solvents with stabilizing surfactants produce monodisperse magnetic nanocrystals with smaller size[36,37]. In this process, the frequently used surfactants are fatty acids, oleic acid[38], and hexadecylamine[39]. Metal acetylacetonates [M(acac)n] (M = Fe, Mn, Co, Ni, Cr; *n* = 2 or 3, acac = acetylacetonate), metal cupferronates (MxCupx) [M = metal ion; Cup = N-nitrosophenylhydroxylamine, $C_6H_5N(NO)O$-] or carbonyls[40] can be used as organometallic precursors. The size and shape of magnetic nanocomposite can be regulated by varying the ratio of the starting reagents including organometallic compounds, surfactant, and solvent. The reaction temperature, time and aging period are also vital for the precise control of size and shape of magnetic nanoparticles. In case of the metal in zero valent state, for example in carbonyls, thermal decomposition primarily tends to the creation of the metal, however a two-step procedure is often used to make oxide nanoparticles. For example, at 100 ℃, iron pentacarbonyl is capable of decomposing into a mixture of oleic acid and octyl ether, followed by the addition of a mild oxidant like trimethylamine oxide $(CH3)_3NO$ at a higher temperature, produces monodisperse γ-Fe_2O_3 nanocrystals of approximately 12 nm in size[41]. A precursor with cationic metal centers on decomposition produces oxide nano. For example, Fe_3O_4 is formed on decomposition of $Fe(acac)_3$ in the presence of oleoylamine, 1,2-hexadecanediol and oleic acid in phenol ether[37,42]. The pyrolysis of metal fatty acid salts (such as salts of decanoic acid, lauric acid, myristic acid, palmitic acid, oleic acid, stearic acid) in a non-aqueous solution (octadecene, n-eicosane, tetracosane, or a mixture of octadecene and tetracosane) generated size and shape controlled magnetic oxide nanocrystal[43]. This method provides nearly monodisperse Fe_3O_4 nanocrystals having a wide range of size adjustable capacity (4-50 nm) with controlled shapes, including dots and cubes. This method has successfully employed for the synthesis of Cr_2O_3, MnO, Co_3O_4, and NiO magnetic nanocrystals. Variation of the reactivity and concentration of the precursors is the key factor to control the size and shape of the nanocrystals. Variation of concentration and chain length of the fatty acids determine the reactivity of the materials. Generally faster reaction rate associates with the shorter chain length. Alcohols or primary amines are often employed to speed up the reaction rate and decrease the reaction temperature.

Hyeon *et al*[41] employed a similar thermal decomposition procedure for the synthesis of monodisperse iron oxide nanoparticles[27]. They have generated an iron oleate complex *in situ* by using iron (Ⅲ) chloride and sodium oleate which were then decomposed between 240 ℃ and 320 ℃ in different solvent systems like 1-hexadecene, 1-octadecene, 1-eicosene, octyl ether or trioctylamine. In this process particle size is determined by the temperature of decomposition and period of aging. Here aging was an important and necessary step for the generation of iron oxide nanoparticles. The nanoparticles prepared by this root can be dispersed in a variety of organic solvents alongside hexane and toluene. Iron pentacarbonyl and the iron oleate complex on decomposition at different temperatures produce monodisperse iron nanoparticles (6-15 nm) which can again be oxidized to magnetite[44]. This process is comparable with seed-mediated growth and explained by the classical LaMer mechanism. Hyeon synthesis involves thermal decomposition of iron pentacarbonyl at a moderately low temperature and the decomposition of the iron oleate complex at a higher temperature leading to the formation of iron oxide nanoparticles which disperse easily in organic solvents.

In biotechnology application, magnetic nanoparticles which are water soluble are more advantageous. This requirement led to the preparation of water soluble Fe_3O_4 nanocrystals with $FeCl_3 \cdot 6H_2O$ as an iron source and 2-pyrrolidone as a coordinating solvent under refluxing condition (245 ℃)[45]. In this method, the mean particle size is controlled at 4, 12, and 60 nm, respectively, when the reflux times are 1, 10, and 24 h. With increasing reflux time, change of shapes of the particles from spherical to cubic morphologies was observed. Recently, water-soluble magnetite nanoparticles have been synthesized using one-pot synthesis under analogous reaction states with the addition of a surface capping agent like α,ω-dicarboxyl-terminated poly (ethylene

glycol)[46]. These nanoparticles are exploited as magnetic resonance imaging (MRI) contrast agents for the diagnosis of cancer.

Metallic nanoparticles can also be prepared by thermal-decomposition method. The metallic nanoparticles have a large number of advantages over other metal oxide nanoparticles owing to their larger magnetization. Thermal breakdown of [$Fe(CO)_5$] in the presence of polyisobutene in decalin in a nitrogen atmosphere at 170 ℃ produces metallic iron nanoparticles[47]. Depending on the $Fe(CO)_5$/polyisobutene ratio, the size of the particle can be adjusted from 3 to 10 nm, with a polydispersity of approximately 10%. Susceptibility measurements revealed that the iron nanoparticles prepared by this way can be easily oxidized by exposure to air. This oxidation can generate a marginal increase of particle sizes approximately by a factor of 1.3. Iron nanocubes can be synthesized by the breakdown of $Fe[N(Si(CH_3)_3)_2]_2$ with H_2 in the presence of hexadecylammonium chloride or hexadecylamine and oleic acid at 150 ℃[48]. The edge-length of the nanocubes varied from 7 nm to 8.3 nm along with the varying relative concentrations of amine and acid ligand. These nanocubes can accumulate into expanded crystalline superlattices by way of their crystallographic axes aligned.

Cobalt nanoparticles can also be prepared by the thermal-decomposition method. Their shape and morphology both can be controlled by this method[49]. Cobalt nanodisks can also be prepared by thermal-decomposition of a cobalt carbonyl precursor[50,51]. The high-temperature reduction of noncarbonyl organometallic complexes produces cobalt nanorods[52,53] and nickel nanorods[54]. For example, decomposition of [$Co(H_3\text{-}C_8H_{13})(h_4\text{-}C_8H_{12})$] with H_2 in anisole at 150 ℃ in the presence of a combination of hexadecylamine and a fatty acid (lauric, octanoic, or stearic acid) produces monodisperse ferromagnetic cobalt nanorods. The variation of diameter and length of the cobalt nanorods largly depends upon different acids used[53].

For easy handling and application under oxidizing conditions, air-stable magnetic nanoparticles are very important. The thermolysis of $Co_2(CO)_8$ in the presence of alkyl-aluminum compounds produces monodisperse colloidal cobalt nanoparticles[54]. The Co particles can be regulated in the size-range of 3-11 nm, by changing the alkyl chain length of these organo aluminum complexes. Air-stable particles can be synthesized by mild surface oxidation of the cobalt nanoparticles with synthetic air. The oxidation step is necessary as saturation magnetization of the CoO particles decays rapidly while exposed to air subsequent to the peptization with the surfactant KorantinSH.

Magnetic alloy nanoparticles have many benefits over other magnetic nanoparticles owing to their high magnetic anisotropy, enhanced magnetic susceptibility and large coercivities[55]. Currently metal phosphides have generated a lot of scientific interest in nanotechnology and chemistry beside $CoPt_3$ and FePt[56-59]. For ferromagnetism, magnetoresistance, and magnetocaloric effects, hexagonal iron phosphide and allied materials have been rigorously studied[60,61]. Recently FeP and MnP nanoparticles have been synthesized from the reaction of iron(Ⅲ) acetylacetonate and manganese carbonyl, respectively, with tris(trim ethylsilyl)phosphane at elevated temperatures[62,63]. Antiferromagnetic FeP nanorods were prepared by the thermal decomposition of a precursor/surfactant mixture solution[64]. Thermal decomposition of permanently supplied iron pentacarbonyl in trioctylphosphane using a syringe pump produces discrete iron phosphide (Fe_2P) nanorods.

Microemulsion techniques

Thermodynamically stable isotropic liquid mixture, where the micro-domain of either or both liquids is stabilized by an interfacial surfactant film, is called microemulsion[64]. In case of water-in-oil microemulsions, the aqueous phase is dispersed as micro size droplets bounded by a monolayer of surfactant molecules in the continuous hydrocarbon phase. The molar ratio of water to surfactant determined the size of the reverse micelle[65]. Mixing of two identical water-in-oil microemulsions including the preferred reactants results in continuous collision, and break again, finally forming a precipitate in the micelles[66]. Addition of solvent like acetone or ethanol to the microemulsions produces a precipitate, which can be collected by filtration or centrifugation. In this concept, a microemulsion served as a nanoreactor for the generation of nanoparticles.

Metallic Co, Co/Pt alloy, and gold-coated Co/Pt nanostructures have been prepared using this microemulsion technique in reverse micelles of cetyltrimethlyammonium bromide, with 1-butanol as co-surfactant in octane oil phase[66]. Using microemulsion technique, spinel ferrites can be synthesized. Water-in-toluene inverse micelles and sodium dodecylbenzenesulfonate (NaDBS) as surfactant were employed to prepare $MnFe_2O_4$ nanoparticles of sizes 4-15 nm[67]. A clear aqueous solution of $Mn(NO_3)_2$ and $Fe(NO_3)_3$ has been employed for this synthesis. An NaDBS aqueous solution is administered to the metal salt solution, followed by addition of a huge volume of toluene when reverse micelles are formed. The size of the resulting $MnFe_2O_4$ nanoparticles was determined by the volume ratio of water and toluene. A sol-gel reaction was employed to prepare iron oxide nanorods through reverse micelle formation from oleic acid and benzyl ether, using $FeCl_3 \cdot 6H_2O$ as iron precursor and propylene oxide as a proton scavenger[68]. The shape of nanorods was controlled by the fluctuation of reaction temperature, environmental conditions, and hydration state of the gels during reflux or heating in tetralin.

The reaction of methylamine and *in situ* formation of cobalt and iron dodecyl sulfate (formed by combination of aqueous sodium dodecyl sulfate with iron chloride or cobalt acetate solution) produces cobalt ferrite fluid[69]. An increase of sodium dodecyl sulfate concentration and

a decrease of total reactant concentration decrease the size of the cobalt ferrite particles.

Although the microemulsion procedure has been used to prepare magnetic nanoparticles in a controlled fashion, the size and shape of the products vary over a wide range. Furthermore, compared to other methods the yield of nanoparticles is low in microemulsion technique. For the synthesis of material, large amounts of solvent are necessary. Moreover, the efficiency of the process is low and it is rather difficult to scale up.

Hydrothermal synthesis

A wide range of nanostructures can be synthesized by applying hydrothermal conditions. A liquid-solid-solution reaction has been employed for the synthesis of a diverse array of nanocrystals. The system employed for the synthesis consists of a solid- liquid-solution matrix containing metal linoleate (solid), an ethanol linoleic acid (liquid) and a water-ethanol solution at different reaction temperatures under hydrothermal conditions[70]. This approach is based on phase transfer and separation mechanism occurring at the liquid-solid-solution interfaces present during the synthesis. Using hydrothermal reduction, monodisperse, hydrophilic, single crystalline ferrite microspheres were synthesized. According to this process, a mixture of $FeCl_3$, sodium acetate, ethylene glycol, and PEG was stirred vigorously till a clear solution is formed, followed by sealing in a Teflon-coated stainless-steel autoclave, and heated to 200 ℃ for 8-72 h.

The above four synthetic methods have some advantages and disadvantages. Among the four roots co-precipitation is the preferred route in terms of simplicity of the synthesis. Thermal decomposition method can be considered the best in terms of control of size and morphology of the nanoparticles. As a substitute, microemulsions can also be employed to synthesize monodispersed nanoparticles having various morphologies. However, a large amount of solvent is needed in this method. Hydrothermal synthesis, although generates superior quality nanoparticles, is a comparatively little investigated method for the synthesis of magnetic nanoparticles. To date, magnetic nanoparticles are synthesized on a large scale by use of co-precipitation and thermal decomposition procedures.

MRI AND CANCER THERAPY

MRI, magnetic resonance tomography or nuclear MRI (NMRI) is an important non-invasive imaging technique to visualize internal structures of the body in detail by using the magnetic property of the various interacting magnetic nuclei present inside the body. When a person is kept under a powerful static magnetic field, the average magnetic moment of the magnetic nuclei present inside the body becomes aligned with the direction of that magnetic field. These magnetic nuclei upon excitation with another external electromagnetic field having the correct frequency (known as the resonance frequency) can flip the spin to the reverse direction by absorbing this radiation. This resonance frequency is generated by turning on the radio frequency current for a very short period. As soon as the electromagnetic field is turned off, the nuclei return to the original thermodynamic equilibrium position and the bulk magnetization re-aligns along the static magnetic field. During this relaxation phase, an electromagnetic radiation in the radio frequency range is emitted which is measured with receiver coils.

MRI signal strengths are influenced by the factors T1 (spin-lattice/longitudinal relaxation time), T2 (transverse relaxation time) and r (spin energy). To enhance the tissue contrast, several exogenous contrast agents like complexes of gadolinium(Ⅲ) and magnetic nanoparticles are injected intravenously. However, Gd(Ⅲ) complex system has some serious drawbacks regarding Gd(Ⅲ) ion exchange using endogenous metals like Zn, Cu and uptake of complexes in extravascular space. This problem can be overcome by employing monodisperse, cross-linked iron oxide (CLIO) nanoparticles as an MRI contrasting agent[71,72]. Owing to highly stable, non-toxic and high cellular uptake, CLIO has been widely used as an exogenous contrast agent[71,73,74].

Advancement of MRI contrast agents which can be frequently applied for biomedical imaging is a demanding assignment. This is primarily due to the prospect of a suitable MRI agent with: (1) ability to be synthesized in huge amount; (2) long shelf life; (3) proper biocompatibility; (4) hindrance to its aggregation in biological fluids; and (5) large relaxivity, which will bring about better contrast in biological imaging. FePt@Fe_2O_3 core-shell magnetic nanoparticles, for example, act as a T2 MRI contrast agent and at the same time as a carrier of drug and can therefore be employed in cancer management applications[75]. For the latter application FePt@Fe_2O_3 core-shell nanoparticles are at first synthesized followed by functionalization using polyethylene glycol (PEG). Further, efficient targeting of folate receptor positive tumor cells is mediated by using folic acid conjugated FePt@Fe_2O_3-PEG nanoparticles. The chemotherapy drug, doxorubicin (DOX), is finally attached to these nanoparticles through hydrophobic adsorption, to deliver the drug in a selective manner for killing of cancer cells. Use of these FePt@Fe_2O_3-PEG nanoparticles has been done for *in vivo* MRI, to generate tumor MR contrasts, which can be accumulated in a passive tumor or can be utilized for active tumor targeting. Moreover, FePt@Fe_2O_3-PEG did not reveal any noticeable toxicity in both *in vitro* and *in vivo* experiments. Therefore, PEGylated FePt@Fe_2O_3 core-shell nanoparticles can be exploited as a potential multimodal integrated therapeutic and diagnostic nanoplatform.

Recently DOX and magnetic nanoparticles were incorporated into antibody-conjugated poly-(D,L-lactide-co-glycolide) (PLGA) nanoparticles where DOX serves as an anticarcinogenic drug and Fe_2O_3 nanoparticles utilized

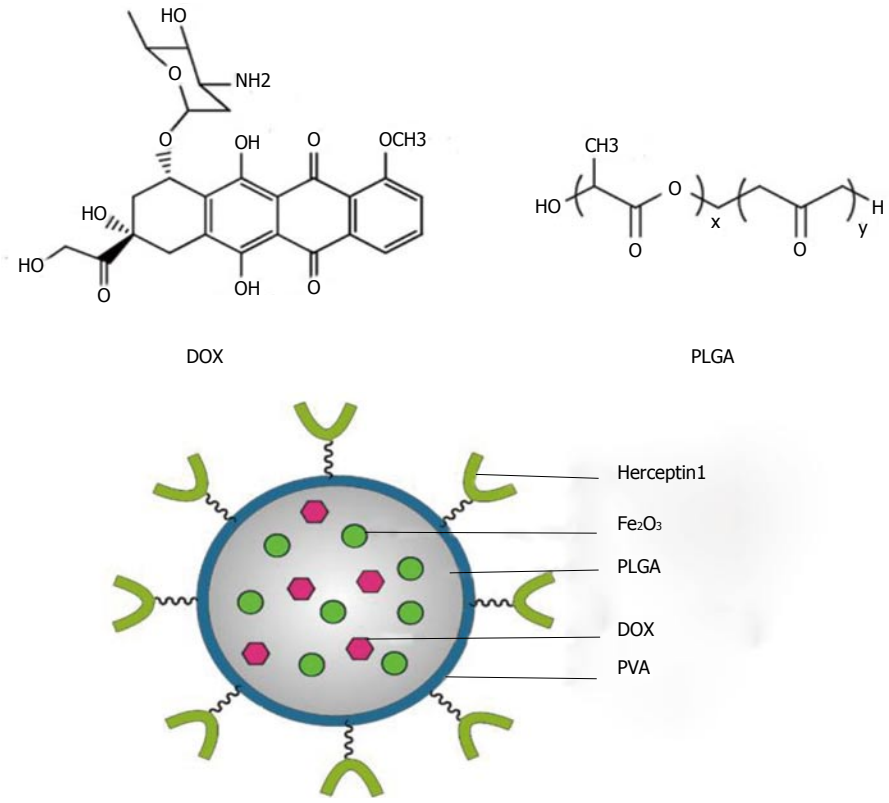

Figure 2 Use of magnetic nanoparticles embedded into poly-(D,L-lactide-co-glycolide) nanoparticles for diagnosis and treatment of cancer. DOX: Doxorubicin; PLGA: Poly-(D,L-lactide-co-glycolide); PVA: Polyvinlyalcohol.

as an imaging agent (Figure 2). This nanocomposite has been employed for the concurrent targeted iagnosis and management of breast cancer[76].

Recently, multimodal nano-materials have been exploited for immediate diagnosis and therapy. In this situation, simultaneous bio-imaging and drug delivery could be done by forming homogeneous core-shell composite particles through the integration of mesoporous silica with superparamagnetic monodisperse nanocomposite. For example, distinct, monodisperse, and perfectly size regulated core-shell mesoporous silica nanoparticles having a size < 100 nm with single Fe_3O_4 nanocrystals as cores (designated as Fe_3O_4@$mSiO_2$) were employed for synchronized MR/fluorescence imaging as well as drug delivery[77]. Multimodal imaging agents like magneto-fluorescent nanoparticles have been developed by creating optical imaging and MRI property simultaneously in the nanoparticles[78-81]. For example, glycine functionalized CLIO-Cy5.5 (CLIOGly) had a great affinity for activated macrophages, while the 3,3′,4,4′-benzophenontetracarboxylic dianhydride attached CLIO-Cy5.5 (CLIO-bentri) selectively interacted with latent macrophages.

APPLICATION OF MAGNETIC CORE-SHELL NANOPARTICLES IN DRUG DELIVERY

A frontline application of magnetic nanomaterials is as drug carriers wherein magnetic field induced drug delivery popularly known as "magnetic drug delivery" is the method of choice. The idea of magnetic drug delivery involves the injection of drug-loaded magnetic nanomaterials which are guided to the specific site by the influence of magnetic field gradient. These nanomaterials are held at the targeted site until the therapy is done, after which these are removed. By this process high local concentration of desired drug could be created, thus avoiding toxicity and other undesirable side effects on normal cells in other parts of the body. Although significant success has been achieved in *in vivo* experiments, so far, definite clinical studies are still lacking. Many basic concerns over magnetic drug delivery methods are yet to be deciphered, some of which are: (1) size regulated preparation and shelf-life of magnetic nanoparticles; (2) compatibility of the covering layers (polymer or silica); (3) binding of drug molecules; and (4) the physiological considerations[66,82].

APPLICATION OF MAGNETIC CORE-SHELL NANOPARTICLES IN HYPERTHERMIA

Magnetic nanoparticles can be used in the management of hyperthermia. This method is regarded as a complementary treatment to chemotherapy, radiotherapy and surgery in cancer[6,83]. Magnetic materials when subjected to exposure to an oscillating magnetic field,

lead to heat production through magnetic hysteresis loss, Neel-relaxation and Brown-relaxation mechanisms. This principle is employed in magnetic induction hyperthermia[47]. Induced currents are generated in metallic objects during the application of alternating magnetic field, leading to the generation of heat. Due to the collective magnetic behaviour of metals, this phenomenon is greatly enhanced in case of metals. As a result, magnetic fluid containing magnetic nanoparticles, upon exposure to an alternating magnetic field, become a powerful heat sources. The heat, generated by this way, destroys cancer cells due to its higher sensitivity to temperatures in excess of 41 ℃ compared to the normal cells.

Frictional forces due to the rotation of the particles in a medium of low viscosity (Brown-relaxation) or loss processes during the reorientation of the magnetization (Neel-relaxation) are responsible for the heating of magnetic oxide substances having poor electrical conductivity. Magnetic anisotropy is used to determine the losses from the reorientation of magnetization by means of the measurements of intrinsic magnetic properties. Due to the thermal fluctuations, re-magnetization process may occur for single domain particles. As the particle dimension is less, the barrier energy would also be less. The external energy may influence magnetic moment in exceeding the energy barrier.

Another loss type may arise in the case of ferro fluids in addition to the losses caused by magnetization rotation inside the particles. This is associated with the rotational Brownian motion of the magnetic elements. For this process, rotational friction within the suspension fluid of a definite viscosity dictates the energy barrier. The structural properties of the nanoparticles are mainly responsible for the amount of heat generation. Therefore, water soluble metal oxide synthesis in water dispersion medium with regulated shape and size is the challenging task in the advanced research.

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