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REVIEW ARTICLE

IRON OXIDE NANOPARTICLES AS DELIVERY SYSTEM AGAINST DISEASES

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ABSTRACT

Infectious diseases caused by protozoa, viruses, bacteria and other agents may be transmitted to people world-wide which relates over 17 million death annually. The treatment of the diseases is hampered mainly by blood brain barrier, multi-drug resistance, drug- toxicity, insolubility and poor bioavailability. To overcome these barriers, currently iron oxide nanoparticles (IONPs) have gained attraction owing to their unique characteristics such as nanosized high surface to volume ratio, low cost easy synthesis methodology, microbicidal and anti-carcinogenic activities, surface modification capability, components-vectoring ability, photothermal and superparamagnetism features for generating reactive oxygen species, non-oxidative induction and metal ion release to disrupt cells. This review demonstrates the current advances regarding their synthesis, functionalization, mechanism of action, biodistribution and elimination for the application in targeted delivery and therapy against various diseases.

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INTRODUCTION

Cancer as well as infectious diseases, developed as emerging and / or re-emerging ways, is responsible for the demise of people globally. The diseases become dreadful especially when different barriers and multi-drug resistance gain prominent. Although the host immune system has the capability to protect the body from any exposed agents or microbes through endogenous antioxidant defence system and / or innate and acquired immune response (Sana *et al*., 2017; Mandal, 2017a), some infections are transmitted to host cells which are contagious and virulent to host body resulting multiplication and spread of microorganisms causing tissue damage intra and / or extra-cellularly (National Institutes of Health (US), 2007). The development of efficient treatments for such diseases has been a main criterion for the human being over 2000 years which has led to the improvement of both natural and synthetic medications to combat against cancer and infectious diseases. Cancer is characterized by uncontrolled cell cycle as well as dysregulated cellular growth, multiplication and progression resulting from cellular growth signals promoting unlimited replicative potential, evading apoptosis, inducing angiogenesis and stimulating invasion and metastasis (Lammers *et al*., 2012). In this aspect, microbial infections have the potency to generate muck for facilitating to adhere and form biofilms on any implantable devices, artificial surfaces or alimentary gut for making them resistant to drugs-treatment.

In other concern, multi-drug resistance due to abrupt and repeated usages of drug, blood brain barrier owing to the non-existence of fenestrations, diminished pinocytic activity and large tight junctions of the brain capillary endothelial layer and the over expressions of P-glycoprotein and multi-drug resistant proteins used as drug efflux pumps are the serious major issues for the treatment of diseases. Therefore, the invention of potent new antibiotics and other active molecules to inhibit the cell-wall synthesis, DNA replication and translational machinery of the cell and their targeting to a specific site of interest minimizing side effects are getting priority nowadays. The effectiveness of conventional chemotherapy has been declined by the fast clearance of many anti-cancer components and the nonspecific distribution, drug resistance at the cellular and tumor sites, significant toxicity and the low efficiency of the existing lead- molecules when exposed at higher dosage. Consequently, major efforts have been dedicated to understand the cellular and molecular mechanisms of the diseases as well as to the drugs- design for their use that have guided to the exploration of new nanomedicines as vehicle system to overcome the main drawbacks of the conventional disease treatments by exploiting disease-specific characteristics and mechanisms. Many kinds of drug vectors have been designed in nanobiotechnology for biomedical applications to date such as polymeric nanoparticles, liposomes, carbon-based systems and metallic nanoparticles.

The magnetic nanomaterial iron oxide (Fe_3O_4, Fe_2O_3) nanoparticles, being nontoxic, inexpensive, biodegradable and biocompatible, are utilized as drug delivery system and medicine owing to their unique superparamagnetism, photothermal, antimicrobial and anticarcinogenic properties (Kluchova *et al*., 2009; Zhang and Zhang, 2005). These NPs anchored with the biologically active molecules (BAMs) such as genes, drugs, nucleotides, enzymes, other proteins and components coated with ligands and / or vesicles when administered into the body, can 1) avoid non specific interactions with host cells along with avoiding capture by the reticulo-endothelial cells, 2) facilitate the transport of the BAM to the specific site of interest keeping the BAM safe during transport, 3) guard the BAM from detrimental activities like hydrolysis or enzymatic degradation during transport in the body, 4) liberate maximum quantities of attached BAM to the target site for achieving their desired concentration in a controlled manner, 5) eliminate all the components of the delivery system from the organism-body after their activities as carrier become over (Ulbrich *et al*., 2016; Sana *et al*., 2017). Surface engineered superparamagnetic IONPs may be highly applicable to treat against several diseases as their particle shape, size and surface charge may be tuned in accordance with the necessity while their sizes > 200 nm become expelled from the body by the activities of reticuloendothelial system, liver and spleen, and those of < 5 nm become eliminated by the function of kidneys (Gupta and Gupta, 2005).

The logic behind the selection of IONPs as a vector to load BAM to a specific site, is that iron, the principal constituent of haemoglobin, is utilized in erythropoiesis i.e. a huge amount of iron is used for the synthesis of haemoglobin to develop red blood cells in the bone marrow by forming a complex with the transferrin protein present in the plasma and transported to bone marrow cells through binding to transferrin receptors located on their surfaces, and thus some amount of iron materials, used before for the treatment of diseases, become utilized in erythropoiesis. However, the lifetime NPs- blood circulation may be increased and modified by diversifying the nature of coated ligand substances around the particles-core. Different functionalities such as plasmids, drugs, antibiotics, small organic molecules and other components may be attached on to the NPs-surface by the adjustment of surface charge dependent on the existence of surplus cations or anions in their vicinity.

In another aspect, the behaviour of the iron-oxide nanomaterial by the application of a magnetic field may be tuned to super paramagnetism with the particle size as low as 10 nm while magnetic domains integrate into a single domain possessing one cumulative magnetization orientation in the applied field i.e. zero coercivity with no hysteresis (Chomoucka *et al*., 2010; Cullity, 1972). Therefore, in the delivery field, IONPs may be recognized as small, thermally agitated magnetic vehicle due to their applicabilities both on magnetic and attaching properties along with effective targeting efficiencies (Mahmoudi *et al*., 2011). Their superparamagnetismic features effectively function as the activation mechanism owing to the disappearance of the magnetization on the dismissal of the external magnetic field for avoiding agglomeration and embolization of the capillary vessels (Mahmoudi *et al*., 2008). This review demonstrates the biological efficiency of IONPs for consideration as potent therapeutical delivery system for the treatment of cancer and infectious diseases.

Synthesis of iron oxide nanoparticles composites: The chemical-based synthesis of IONPs is mainly performed by co-precipitation method utilizing ferrous chloride tetrahydrate ($FeCl_2.4H_2O$) and ferric chloride hexahydrate, ($FeCl_3.6H_2O$) with some modifications (Bellova *et al*., 2010). The needed amounts of 0.1 M $FeCl_2.4H_2O$ and 0.2 M $FeCl_3.6H_2O$ are added to 100 mL of deionised water and stirred by operating a magnetic stirrer until a homogeneous solution is formed. Then the solution is sealed and heated at 60^{o}C for 15-20 min in a water bath following the inclusion of 14 mL 25% sodium hydroxide. Upon completion of the reaction, a black precipitate is formed, which is spun at 7000 rpm for 15 min, cleansed 3 times with deionised water and proceeded to dry at 60^{o}C for getting powder IONPs.

To protect IONPs from agglomeration as well as oxidation, they are usually coated with organic or inorganic molecules. IONPs may be coated during the nucleation and the magnetic core growth. Organic surfactants are utilized to stabilize and coat magnetic NPs while fatty acids stabilize the aqueous fluids to form a surface bilayer having a primary chemisorbed fatty acid layer and a secondary interpenetrating layer while the latter gets physisorbed onto the 1st layer possessing the hydrophilic head-groups pointed outwards (Shen *et al*., 2000). Grafting components, adsorbed physically by hydrogen binding or electrostatic interactions, exhibit limited stability compared to chemically adsorbed components dependent upon the quantity of the chemical interactions between molecule / macromolecule and NPs-surface. For covalent conjugation, an ordered molecular assembly of the system is performed by the adsorption of active molecules such as thiolates, carboxylates, siloxane and phosphate on the solid surface of IONPs with various terminal groups such as -COOH, -NH and –OH (Love *et al*., 2005; Chen *et al*., 2001). These coatings can allow terminal groups for further functionalization by chemical reactions assimilated in different polymers for attachment of the species on the surface while the stability relies on the affection of the active molecule for the solid surface, ionic strength and pH of the surroundings.

Hence, for surface modification, one method is followed (Mahammadi *et al*., 2013). Briefly, 20 mg chitosan is dissolved in 100 mL deionised water mixed with 1M acetic acid, and vortexed for 5 min. Then 70 mg synthesized IONPs are dissolved in already prepared chitosan solution and retained overnight for about 18 h on a magnetic stirrer at 25^{o}C. During this encapsulation proceeding, chitosan molecules are absorbed over the IONPs-surface resulting into changing from black to brown color. After this color change, the suspension is spun at 7000 rpm for 30 min. The pellet is then cleansed 2 times with deionised water to detach free chitosan molecules and residues of acetic acid followed by drying to powder at 70^{o}C to get coated IONPs. Another method for surface modification with drug entrapping, IONPs capped with ethylene diamine tetraacetate (EDTA) are also synthesized by the co-precipitation method. In this case, an aqueous 400 mL 0.32 M hydrochloric acid (HCl) is added drop-wise to the mixture of a 50 mL aqueous solution of $FeCl_2.2H_2O$ (0.121 mmol) and $FeCl_3.6H_2O$ (0.24 mmol), and stirred abruptly under the nitrogen flow. 25 mL aqueous EDTA (0.24 mmol) solution together with 25 mL 1M NaOH solution are poured to this solution and the reaction mixture temperature is gradually increased to 70^{o}C and further stirred for 1h under nitrogen atmosphere to get a homogenous mixture. Then, the reaction mixture is spun at 8000 rpm for 5 min and the deposits are

separated magnetically. Subsequently, the deposits are cleansed 3 times with milliQ water and ethanol for removing untreated impurities and then dried at 60°C for 2 days under vacuum. 300 mg of these NPs are dispersed in 30 mL milliQ water where 100 mg pluronic F-127 is added. Then the mixture is stirred overnight on a magnetic stirrer at room temperature and spun at 6000 rpm for 5 min for getting pluronic F-127 functionalized IO / EDTA -NPs. 2 mL drug solution (4.5 mg/mL) is then added to 10 mL milliQ water dispersed with 30 mg of these NPs and mixed by stirring abruptly for 24h at room temperature. The drug-loaded IONPs are allowed to settle down by a magnet keeping outside the flask containing drug-loaded NPs for 6h followed by decanting supernatant. After that, the drug-loaded NPs are suspended in milliQ water for washing twice and further use.

For surface functionalization, 5 mg oleate-coated IONPs (15 nm) are dispersed in 5 mL chloroform. 20 mg dopamine dissolved in 2 mL dimethyl sulfoxide (DMSO) is adjoined to the solution. Then the mixture is stirred for forming a homogeneous solution, and heated to 70°C for 1 h. After allowing the solution to cooling down at room temperature, the NPs are collected through centrifugation and drying under nitrogen atmosphere and redispersing in DMSO by sonication. Consequently, doxorubicin powder (16 mg/mL) is dissolved in DMSO. For an ideal preparation, dopamine-grafted IONPs (5 mg Fe/mL in DMSO) are mixed with doxorubicin solution at 1:1 (v/v) for 10 min. The solution is then added drop-wise to human serum albumin (HSA) solution in water (12 mg/mL, 1:7 v/v) with sonication to get a homogeneous solution. The NPs are collected by spinning, and re-dispersed in milliQ water / phosphate buffer saline (PBS) for further use.

Aqueous dispersion of the IONPs is acquired by encapsulating their surfaces with hydrophilic polymers such as dextran, chitosan or starch (Bhattarai *et al*., 2007; Chertok *et al*., 2008) suggesting their safe transport and release of drug, gene or other components to the specific site in the body associated with photodynamic therapy (Kumar *et al*., 2009; Sun *et al*., 2009; Dougherty *et al*., 1998; Bi *et al*., 2009; Aviles *et al*., 2008). IONPs may also be coated with poly-(N-isopropylacrylamide) for suitable magnetic targeting following simultaneous magnetic hyperthermia as well as drug release (Purushotham and Ramanujan, 2010). Gelatin can bind drug like doxorubicin to form drug-polymer-conjugate owing to the presence of multifunctional groups such as -COOH, $–NH_2$ in its chain and thus magnetic IONPs are coated with gelatin for biomedical applications (Gaihre *et al*., 2009). The synthesis of IONPs encapsulated with poly (2-dimethylamino) ethyl methacrylate is performed as a potent carrier for targeted drug delivery and sustained liberation (Zhou *et al*., 2009) while IONPs synthesized by alkaline precipitation are modified by α-bromoisobutyric acid for the linkage of atom transfer radical polymerization initiators to the surface. The molecular weights of the polymers such as poly lactic acid (PLA) and poly (1-lactide-co-glycolide) (PLGA) play a crucial role in the drug-loading capability on the polymer-surface showing at low molecular weight, high loading efficiencies which encapsulate monodisperse IONPs synthesized through the reaction of ferric acetylacetone, a long-chain alcohol and phenyl ether as solvent, and may be coated with ligands (Abdalla *et al*., 2010; Sun *et al*., 2004; Sun and Zeng, 2002; Granitzer *et al*., 2010). In this concern, polyethylene glycol (PEG), the biocompatible soluble stabilizer may be used for not only grafting the IONPs but also conjugating antibodies, peptides or receptors to get a specific targeted delivery (Mahmoudi *et al*., 2010; Nasongkla *et al*., 2006; Mahmoudi *et al*., 2010; Bulte *et al*., 1999; Shultz *et al*., 2007; Li *et al*., 2005; Sun *et al*., 2008; Dodd *et al*., 2001). Amyloid-β protein, involved in Alzheimeris, coated on IONPs was removed completely from the aqueous phase by a magnetic field while their nano sizes were synthesized through nucleation following controlled thin films growth onto iron oxide nuclei-gelatin (Skaat and Margel, 2009; Skaat *et al*., 2009). Magnetite IONPs may be functionalized also with silane, organosilane or oleic acid (Chen *et al*., 2008; Cai *et al*., 2007) while silanes having many amino groups form an ideal system for tuning the NPs-surface functionality to conjugate protein.

In this aspect, synthesized IONPs are coated with PEG by the alkaline co- precipitation method while ferrous chloride tetrahydrate and ferric chloride hex ahydrate are used as iron source (Xu *et al*., 2009). These NPs are then modified with 3-aminopropyltriethoxysilane to provide a $-NH_2$ functional group for application in the lysozyme immobilization promoting solubility, reducing toxicity and decreasing enzymatic degradation (Chertok *et al*., 2009), and increasing *in vivo* half-life of the drug. IONPs are also synthesized by ferrous chloride chemical reduction with sodium borohydride solution, grafted with amine-terminated PEG for biological applications (Balakrishnan *et al*., 2009). A nanocomposite composed of superparamagnetic IONPs / aminosilane core / shell functionalized with cyclodextrine are used in magnetic drug delivery applications (Cao *et al*., 2009). Gold coated IONPs are also synthesized from oleic acid, ferric acetylacetone, oleylamine, trioctyl amine and hydrazine monohydrate while IONPs are coated by gold with gold acetate (Lim *et al*., 2009).

Characterizations: For understanding the surface properties of IONPs-composite, the comprehensive surface characterizations -techniques are utilized to monitor their chemical composition, surface morphology, and spatial functional groups distributions. For investigating, the fundamental techniques for metal NPs-composite demonstrate transmission electron microscopy and scanning electron microscopy for particles' morphological features -study, x-ray diffraction analysis for evaluating different phases of the synthesized samples, fourier transform infrared spectroscopy for the study of the mode of interaction of stabilizer / coating material with IONPs-surface and their structure, dynamic light scattering technique for the measurement of size distribution, hydrodynamic radius and surface charge in term of zeta potential, uv-vis spectrophotometry for studying the surface plasmon resonance properties, atomic absorption spectrophotometry for estimation the concentration of metal present in the synthesized IONPs.

Mechanism of action: Metal-based NPs, due to their nanosize and high surface to volume ratio, can overcome multi-drug resistance (Singh *et al*., 2014; Cavassin *et al*., 2015) of cells and biofilm resistance (Chifiriuc *et al*., 2012) by penetrating and disrupting the cells or layer through oxidative stress inductions (Gurunathan *et al*., 2012), non-oxidative mechanisms (Leung *et al*., 2014) and metal ion releases (Nagy *et al*., 2011). These NPs also can cross the membrane barriers and easily absorbed into the blood stream (Sing *et al*., 2011). The oxidative stress is initiated due to contact of NPs-surface with cell membrane through electrostatic attraction (Li *et al*., 2015), hydrophobic interactions (Luan *et al*., 2016), van der Walls forces (Armentano *et al*., 2014) and receptors-ligands

(Gao *et al*., 2014) to produce ROS for damaging the microbes and / or diseased cells and their capabilities to bind to DNA or RNA following replication and translation processes (Arvizo *et al*., 2012; Zain *et al*., 2014). The another mechanism is that metal ions are slowly liberated from their oxide form and absorbed via the cell membrane following the direct interactions with the functional groups of nucleic acids, proteins e.g. mercapto (-SH), carboxyl (-COOH) and amino (-NH) groups to damage enzyme activity, alter the cell construction, affect the normal physiological activities and ultimately kill the microorganism or diseased cells. The other non-oxidative mechanisms especially relate to cellular metabolic disorders i.e. significant reduced metabolisms of carbohydrate, energy, amino-acids and nucleotides that inhibit the growth of cells-survival (Leung *et al*., 2014).

For the application of IONPs, ROS are produced following the Fenton or Haber-Weiss reactions. In this concern, a toxic hydrogen peroxide (H_2O_2) oxidant that causes protein and DNA damage, is produced by all aerobic organisms (Gonzalez-Flecha and Demple, 1995; Kumar and Imlay, 2013). In the presence of IONPs and H_2O_2, various oxido-reduction reactions occur involving both Fe^{3+} and Fe^{2+} to generate several more potent ROS (Kumar and Imlay, 2013; Auffan *et al*., 2009) which include the following reactions:

$$Fe\ (III) + H_2O_2 = Fe\ (II) + OH^- + OH^0 \quad (1)$$

$$Fe\ (II) + H_2O_2 = Fe\ (III) + HO_2{}^0 + H^+ \quad (2)$$

The reactive species, OH^0 and $HO_2{}^0$, formed in these processes are potent free radicals. Iron in magnetite (Fe_3O_4) NPs is completely oxidized to form maghemite (γ-Fe_2O_3) via a series of reactions to cause oxidative stress to the cells resulting deaths. In this aspect, wholly oxidized maghemite becomes relatively stable as it loses further possibilities of ionic and electronic transitions and forms itself an insignificant end product for cytotoxic prospensity (Auffan *et al*., 2009). However, the amounts of free radicals generated in the oxido-reduction procedure are adequate for putting strain on viable cells to cause death through membrane and other components damages.

Delivery system as drug carrier: Magnetic drug delivery has currently gained more attention as the magnetic NPs exert their possibility of systemic administration but direction towards the specific target in the body while the residuals are confined by the application of magnetic field. Normally, therapeutic ingredients are anchored to the magnetic NPs-surface or encapsulated within the nanocomposite mixture i.e. the magnetic NPs and the polymer / gold / silica / carbon. One group of researchers developed a drug delivery system while doxorubicin (DOX) was anchored chemically to IONPs coated with PEG-functionalized porous silica shell for protecting drug-escape, creating barriers for drug release and escaping reticuloendothelial system -uptake, and thus allowing drug for a sustained release to the target site (Chen *et al*., 2010). Another group developed epirubicin-bonded IONPs encapsulated with the polymer poly [aniline-co-N-(1-one-butyric acid)] aniline for higher targeting to the brain tumor compared to control animals overcoming BBB with the applications of both ultrasound and external magnetic field (Liu *et al*., 2010). Similarly other group of researchers investigated the exposure of 5-fluorouracil-attached IONPs coated with polyalkylcyanoacrylate against both resistant and non-resistant cancer cells resulting improved therapeutic efficacy and reduced drug toxicity supported by Phase I and II clinical trials (Arias *et al*., 2008; Merle *et al*., 2006). In order to enhance the targeting ability of the magnetic NPs, several targeting moieties such as proteins, antibodies and hormones have also been utilized to attach them to the IONPs-surface. Epidermal growth factor (EGF) has been anchored to the IONPs for the treatment of breast and colorectal cancers (Creixell *et al*., 2010). HER2 antibody has been attached to the glycerol mono-oleate coated IONPs showing their increased uptake efficiency in human breast carcinoma cells (MCF-7) (Dilnawaz *et al*., 2010). LHRH-hormone conjugated with IONPs has shown their improved capability for targeting both the lung metastases and the primary breast tumor cells (Zhou *et al*., 2006). In relation to the targeting characteristics, few shortcomings appear such as 1) quick burst release of drug from NPs- surface upon *in vivo* administration and 2) the digestion of NPs-coating influencing the overall cellular integrity.

To overcome these problems, the other investigators prepared tamoxifen conjugated IONPs coated with cross-linked poly (ethylene glycol)-co-fumarate (PEGF) and studied the reduced burst effect of PEGF-coating compared to non cross-linked tamoxifen-IONPs suggesting cross-linked unsaturated aliphatic polyesters (PEGF) as useful potent coating material for developing novel vehicles for drugs or other components - delivery applications (Mahmoudi *et al*., 2009). Recently, one group of investigators has synthesized gold-coupled core-shell IONPs by constructing a gap between the core and the shell as a new nanoprobe for signal augmentation in surface Raman spectroscopy owing to their jagged- shaped gold shell coating for use in future cancer therapy (Mahmoudi *et al*., 2011; Jin *et al*., 2010). One of the pivotal limitations with magnetic IONPs is that limited amount of NPs arrives the tumor site associated with insufficient temperature resulting a risk of proliferating cancer cells that survive during thermotherapy (Hergt and Dutz, 2007). To overcome this issue, few specific tumor receptor targeting moieties have been encapsulated to anticancer drugs bearing NPs-surface to induce enhanced cell apoptosis associated with hyperthermia treatment as a simultaneous driving force using thermo-sensitive polymers (Laurent *et al*., 2011).

Delivery system as gene carrier: Gene and antisense therapies have been the areas of the current research owing to their potency to develop a significant implication on medicines (Sun *et al*., 2008). Magnetic NPs technology offers its potentiality to get efficient and selective delivery for therapeutic genes applying external magnetic field for cancer treatment (Li *et al*., 2012). The conjugation to microspheres shows the higher transduction efficiencies to target cells than free vector delivery as it moves via the tissue vasculature (Mah *et al*., 2002). The cationic polymeric gene carriers e.g. polyethylenimine (PEI) augment the cellular magnetofectins uptake via endocytosis under the influences of magnetic fields (Huth *et al*., 2004). Magnetic NPs-gene based system focuses the target cells / site through the application of high gradient / field magnets to be rapid and more efficient transfection *in vitro* with lower dosages and shorter transfection times in comparison to both the cationic lipids and the stable field techniques (McBain *et al*., 2008b). Generally, gene delivery through magnetic NPs is utilized to diminish the needed time for transfection or minimize the vector dosage. The study also

has been conducted to improve the overall transfection efficiencies of this technique by utilizing the dynamic magnetic fields generated from oscillating array of eternal rare earth magnet to greater than 10 folds enhancement in contrast to the static magnetic field (McBain *et al*., 2008a).

Biodistribution and bioelimination: Shape, size and surface modification of IONPs determine their biological uptakes and distribution involving serum protein interactions i.e. opsonisations and NPs-cells interactions (Chouly *et al*., 1996; Owens and Peppas, 2006). Several biodistribution investigations show the probable localizations of the NPs in blood, liver, spleen and kidney, and preferentially in spleen and liver (Edge *et al*., 2016) while ultra-small IONPs have been used as potent MRI contrast agents for the visualization of bio-events such as metastasis and gene expressions at sub-cellular and cellular levels (Soenen *et al*., 2010; Shanehsazzadeh *et al*., 2013; Oghabian and Farahbakhsh, 2010). These studies for biodistribution demonstrate that liver and kidney take part in the elimination of NPs while after 6 h of injection, about >50% of iron is cleared by the uptakes of RES and macrophage to accumulate in liver mainly due to their higher vascularisation and permeability capability, supported by opsonisation from blood circulation (Jain *et al*., 2008; Edge *et al*., 2016; Hanini *et al*., 2011; Mejias *et al*., 2010; Brigger *et al*., 2012).

In other studies, magnetic IONPs have also been accumulated in the animal lungs for upto 3 months showing no toxicity owing to their monocyte-rich and vascularised nature (Edge *et al*., 2016; Chaves *et al*., 2005). Generally, the human body possesses haemoglobin, myoglobin, ferritin and transferrin at 65%, 4%, 15-30% and 0.1% of magnetic NPs respectively, while degradation of IONPs happens as for ferritins at molecular level (Edge *et al*., 2016). The degradations of IONPs lead to iron level enhancement in the organs which is controlled by two chief iron-protein complexes such as ferritin and transferrin, involved in shuttling and storing of iron ions, observed as degradation products (Ruiz, *et al*., 2013; Nissim and Robson, 1949; Richter, 1959). Mononuclear phagocytic system can degrade the intravenously administered larger IONPs (>15 nm), while nanosized particles (<5 nm) are eliminated through kidney filtration (Mandal, 2017b). Ferritin and hemosiderin can generate iron-protein complexes while transferrin can also be produced from ferritin and transported to bone marrow as the precursor of haemoglobin for the synthesis of red blood cells. Myoglobin, the other iron-protein complex, may be involved in muscular oxygen transport. Macrophages can metabolize haemoglobin into ferritin that may be stored in hepatocytes or converted to transferrin for participating in erythropoiesis. Thus, iron is required as trace element in the organism for some cellular processes such as energy metabolism, electron and oxygen –transports (Hatcher *et al*., 2009).

Conclusion

As IONPs are biocompatible having superparamagnetic characteristics, the synthesized colloidal nanosize particles can be surface-functionalized with multifunctional ligands associated with metallic / non metallic, liposomal / polymeric vesicular -coatings and / or attachment with sugars, proteins, peptides, antibodies and genes to bind and target desired receptors / cells / tissues in a sustained component release - manner under the application of hyperthermic external magnetic field by overcoming also the BBB, MDR and biofilm resistance. In this concern, the NPs (1-9 nm) can penetrate microbial cell membrane through channels such as porins (Neal, 2008) and also they may be endocytosed (Lai *et al*., 2015). The NPs may be processed through the complete disintegration of the cells and the removal of the lipo-polysaccharide layer protruding vesicular form for their binding to enter the cell by electrostatic attractions (Wang *et al*., 2017), while the NPs can also extravasate through enlarged pores of the capillary endothelium at tumor sites (Mandal *et al*., 2014). Thus, superparamagnetic IONP as a delivery system has created attention for the cancer therapy and the treatments of infections and other ailments.

Future perspectives

Monolayer polymers, organic ligands or other biomolecules - coatings have been converted successfully the hydrophobic IONPs as stealth NPs which are soluble in water and more biocompatible to gain approval from US, FDA for using mainly in the fields of target specific drug delivery, MRI, cancer treatments, gene therapy and in vitro diagnostics. Although IONPs exhibit many favourable features as delivery system, more toxicological investigations and criteria are needed to evaluate particles-toxicity for advancing this field. Furthermore, the biocompatibility of IONPs is correlated with their biodegradation and toxicity generating capabilities, especially due to NPs-surface modification with other molecules affecting variations of bioaccumulation and biodistribution. Therefore, the successful engineering of multifunctional IONPs would be of prime interest for the designing and developing the therapeutic nanomedicine. However, the challenge exists in the clinical translational work for NP probes and in the issues of toxicity, and *in vitro* and *in vivo* targeting efficiencies.

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