

Magnetic nanoparticle drug delivery systems for targeting tumor

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Abstract Tumor hypoxia, or low oxygen concentration, is a result of disordered vasculature that lead to distinctive hypoxic microenvironments not found in normal tissues. Many traditional anti-cancer agents are not able to penetrate into these hypoxic zones, whereas, conventional cancer therapies that work by blocking cell division are not effective to treat tumors within hypoxic zones. Under these circumstances the use of magnetic nanoparticles as a drug delivering agent system under the influence of external magnetic field has received much attention, based on their simplicity, ease of preparation, and ability to tailor their properties for specific biological applications. Hence in this review article we have reviewed current magnetic drug delivery systems, along with their application and clinical status in the field of magnetic drug delivery.

Keywords Magnetic nanoparticles ·
Iron oxide nanoparticles · Magnetic drug delivery ·
Magnetic gene delivery

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Introduction

Hypoxia is a pathological condition in which the whole body or specific tissues are deprived of an adequate oxygen supply. This mismatch between oxygen supply and its demand at the cellular level can be due to various reasons such as cardiac arrest, strangulation, high intake of carbon monoxide, exercise, or reduced vasculature as seen in tumor cells (Brahimi-Horn et al. 2007). Of various types of hypoxia discussed above, tumor hypoxia is one of the most important pathological conditions for tumor therapy and diagnosis. In general, a tumor environment is characterized by a highly proliferating mass of cells that grows faster than the vasculature creating an avascular environment deficient in oxygen (Brahimi-Horn et al. 2007). Such hypoxic zones have been postulated to have a reduced response to radiotherapy due to a decrease in oxygen free radicals that are required to produce enough DNA damage result in cell death (Moeller et al. 2007). In addition, cells of these regions are considered to be chemotherapy-resistant due to limited delivery of drugs via the circulation (Brahimi-Horn et al. 2007). In such cases, the delivery of nanoparticles or drug loaded nanoparticles via angiogenesis is also not much effective due to the formation of neo-vessels which are often distorted and irregular and thus less efficient in oxygen, nutrient transport and drug delivery. This lack of efficient transport system in the body to deliver drug to the tumor cells has recently attracted lot of consideration and lot of delivery vehicles has been postulated. Of which magnetic nanoparticles as a drug delivery system has received considerable attention.

Magnetic drug delivery system works on the delivery of magnetic nanoparticles loaded with drug to the tumor site under the influence of external magnetic field (Fig. 1). However, development of this delivery system mandates

that the nanoparticles behave magnetic only under the influence of external magnetic field and are rendered inactive once the external magnetic field is removed. Fortunately, such magnetic properties are usually acquired by very small nanoparticles within the size range of less than 10 nm, due to the presence of single domain state. In contrast, large magnetic particles are well known for their multidomain structure. These multidomain states are separated by domain walls, as depicted in Fig. 2. This formation of the domain walls is energetically favorable if the energy consumption for the formation of the domain walls is lower than the formation of single domain states (Gubin 2009). As the dimensions of the particles are reduced, it costs more energy to create a domain wall than to support a

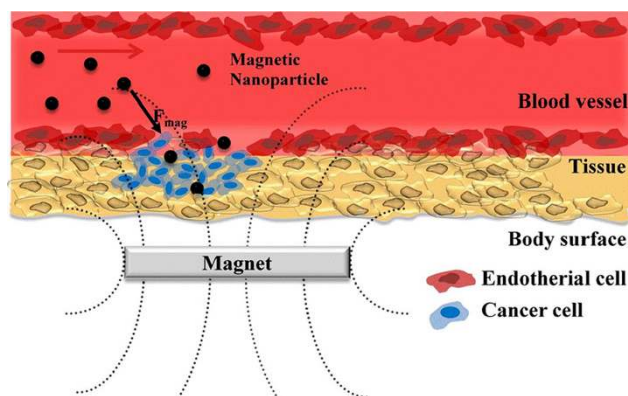


Fig. 1 Schematic representation of Magnetic drug delivery system under the influence of external magnetic field. F_{mag} is direction of external magnetic field are targeted. Copyrighted from reference (Park et al. 2010)

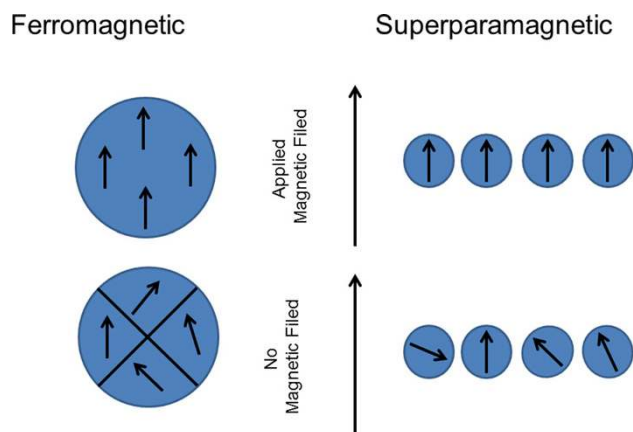


Fig. 2 Magnetic moment in both ferromagnetic and superparamagnetic materials. On application of the magnetic field the domain walls in ferromagnetic materials are washed away and aligned to the direction of the magnetic field. Whereas, in a superparamagnetic materials usually defined as the single domain structure has no domain walls, but magnetic moments align to the direction of the applied external magnetic field. The domain structure of the magnetic materials has been drawn for simplicity. Copyrighted from reference (Mody et al. 2013)

single-domain state. Thus below a critical size all the domain walls are washed away and the particle becomes a single domain particle (Lu et al. 2007). In practice, as the particle size is reduced, the coercivity increases to a maximum and then decreases toward zero. Below a critical diameter the coercivity becomes zero. Such particles are termed superparamagnetic (Fig. 3) (Jun et al. 2007). Here coercivity is defined as the force applied to reduce the residual magnetic field left in the magnetic particles to zero after the removal of an external magnetic field (Fig. 4). Therefore, when the particle size is small the spin-flip barrier for the reversal of the magnetic moments is very small, and the energy at the room temperature for small particles is enough for simple magnetization reversal energy i.e. $Ms^2V \sim k_B T \sim 25$ meV at room temperature (Gubin 2009; Krishnan 2010). Thus when typical ferromagnets obtain a critical diameter of about 5–10 nm it paves the way to become superparamagnetic nanoparticle. The superparamagnetism of any magnetic nanomaterial is basically caused by thermal effects where the thermal fluctuations are strong enough to spontaneously demagnetize a previously saturated assembly; therefore these particles have zero coercivity and have no hysteresis (Krishnan 2010). As a result, superparamagnetic nanoparticles become magnetic in the presence of an external magnet, but revert to a nonmagnetic state when the external magnet is removed. This avoids an ‘active’ behavior of the particles when there is no applied field. This behavior of superparamagnetic materials results in potential advantages to deliver therapeutics onto specific sites under the influence of external magnetic field and can be reverted to their nonmagnetic states by removing external magnetic field to allow them to be excreted (Park et al. 2010).

Ferrite oxide—magnetite (Fe_3O_4) is the naturally occurring minerals on earth which is widely used in the form of superparamagnetic nanoparticles for diverse biological applications, such as MRI, magnetic separation, and magnetic drug delivery. However, the use of magnetic nanoparticles in vivo needs lot of surface modification so as to protect them from reticuloendothelial system and increase the stability of molecule in vivo. Organic ligands such as polyethylene glycol, dextran, aminosilanes are commonly used to stabilize the magnetic nanoparticles (Laurent et al. 2008; Reddy et al. 2012). Unfortunately, these surface protectants modulate the magnetic properties by modifying the anisotropy and decreasing the surface magnetic moment of the metal atoms located at the surface of the particles (Paulus et al. 1999; van Leeuwen et al. 1994). This reduction has been mainly associated to the existence of a magnetically dead layer on the surface of particles (Kodama 1999). Thus the effect of size and surface coating of magnetic nanoparticles are both very important for the fabrication of nanomaterials for their role

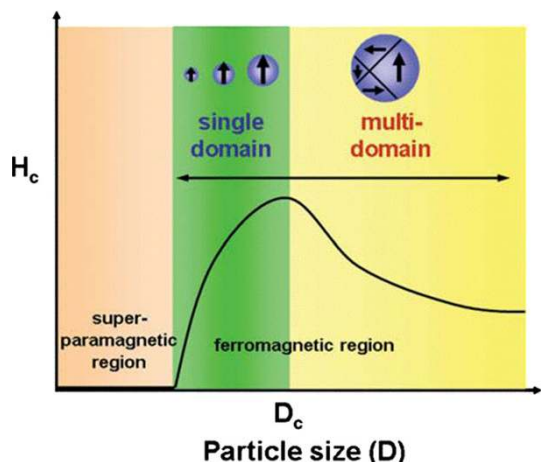


Fig. 3 Schematic illustration of the coercivity–size relations of small particles. Copyrighted from reference (Jun et al. 2007)

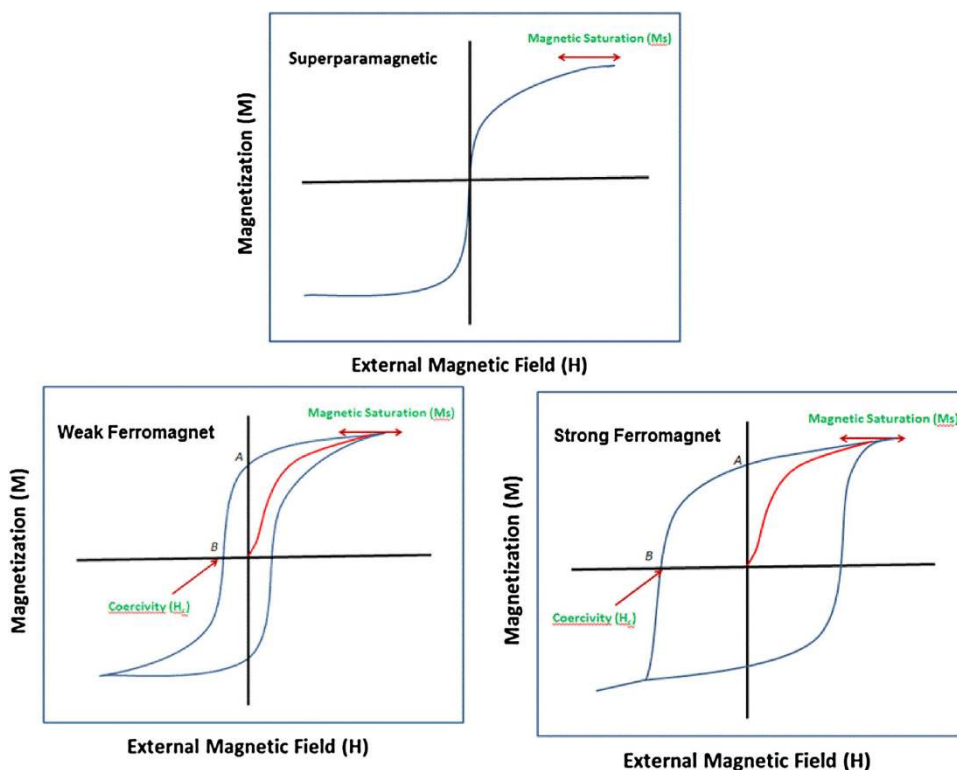
as diagnostic and therapeutic agents (Liu et al. 2011; Palwal et al. 2010). Any change in size and surface coating will modulate the magnetic properties such as Coercivity (H_c) of these nanospheres of the nanoparticles and hence can vary the effectiveness of these diagnostic as well as therapeutic agents. It is imperative to mention that the design of novel MNPs for biomedical application requires careful evaluation of the effect of surface modification, size, shape on its magnetic properties. A thorough consideration of each design parameter must be evaluated to produce MNPs that can overcome biological barriers and

carry out its function. Additional information on the effect of change in shape, size, and surface coating of nanoparticles on its magnetic properties is beyond the scope of this review and readers are requested to refer book titled “Magnetic Nanoparticles” by Dr. Sergey P. Gubin and a review by Krishnan (Gubin 2009; Krishnan 2010). In particular, it must be concluded that the magnetic response of a nanoparticle to an inert coating is rather complex and system specific; the effect of coating cannot be predetermined before the actual magnetic measurements have been performed. Even with limited information on the behavior of these systems various attempts have been made to bio-engineer magnetic nanoparticles so as to utilize them for magnetic drug delivery. In the following section, we have tried to outline few of these applications followed by their current status in clinical trials.

Magnetic nanoparticles for drug delivery

Magnetic nanoparticles offer the possibility of being systematically administered but directed towards a specific target in the human body while remaining ultimately localized, by means of an applied magnetic field. Even though the concept of using magnetic particles for drug delivery was proposed as far back as 1970, the field of magnetic drug delivery has only recently received much attention (Senyei et al. 1978; Widder et al. 1978). Usually

Fig. 4 A typical hysteresis loop such as that obtained from superparamagnetic and ferromagnetic materials. Figure modified and copyrighted from reference (Mody et al. 2013)



therapeutic agents are attached to the surface of magnetic nanoparticles or encapsulated within a nanocomposite mixture of a polymer and magnetic nanoparticle. In this case they can be operated under the influence of very low values of applied magnetic field. Ideal properties for the nanocomplexes which are to be used must be those with high values of magnetization at the operational temperature. Magnetic particles from iron, cobalt, and nickel are favorable in such situations due to their specific magnetic properties but the control of the particle size and shape, and the matrix or medium in which the particle is embedded is also critical. More commonly, these particles may have magnetic cores with an external coating of a polymer or other metals and nonmetals such as gold or silica. They can also be nanocomposite mixtures consisting of magnetic nanoparticles encapsulated within a porous polymer. Presence of the polymers or various metal/nonmetal coating provides an opportunity to anchor various therapeutic drugs or DNA for targeted gene delivery (McBain et al. 2008b). Another approach lies in encapsulating a cytotoxic drug along with magnetic nanospheres inside the polymer matrix. Once targeted to the site of action, the sustained delivery of the drug molecule at the site of action will provide its therapeutic effect.

Once the therapeutic moiety has been loaded on to the nanoparticles and placed in vivo these magnetic nanocomplexes are often directed on a target site using high-field rare earth magnets. The presence of high gradient field which is focused over a specific site onto the body forces and captures the particles at the targeted tissue. Although this may be an effective strategy for targets close to the body's surface the effect wears off for applications deep within the body as the magnetic field strength falls off rapidly with distance and inner sites become more difficult to target. Some groups have recently proposed to circumvent this problem by implanting magnets in the body near the target site (Kubo et al. 2000; Yellen et al. 2005). Ideally, the magnetic particles should not retain any remnant magnetization once the magnetizing field has been removed. This avoids aggregation of the magnetic nanoparticles due to dipolar interactions between their respective magnetizations and facilitates their excretion from the body.

An optimum magnetic response has been achieved using magnetic ferrofluids and the most common coating or encapsulating materials for in vivo applications are polysaccharides like dextran, and polymers such as polyethylene glycol and polyacrylamide. Recently carbon coating has been used as biocompatible material. One of the advantages of using carbon is its high capacity of adsorption. Chen et al. developed a magnetic drug delivery system in which doxorubicin (DOX) was chemically bonded to Fe_3O_4 nanoparticles (Chen et al. 2010). This complex

was then embedded in a polyethylene glycol (PEG) functionalized porous silica shell ($\text{Fe}_3\text{O}_4\text{-DOX/pSiO}_2\text{-PEG}$) (Fig. 5). The presence of a porous silica shell is not only provided a protective layer for drug molecules and magnetite nanoparticles, but also created a thin barrier for the DOX release from the carrier. Hence this composite magnetic drug delivering system exhibited a slower of DOX than seen in DOX-conjugated Fe_3O_4 nanoparticles alone (Fig. 6). In addition, biocompatible polymer PEG, allowed this complex to escape reticuloendothelial system, thus allowing drugs to be administered over prolonged periods of time.

Magnetic nanoparticles can also be of enormous potential for the diagnosis and therapy of brain tumors. One of the most common ways to target nanoparticles across blood brain barrier (BBB) is via enhanced permeation and retention effect (EPR). However, EPR can be limited by environment of the tumor, such as hypovascularity, fibrosis, or necrosis even when pathologic processes compromise the integrity or function of the BBB (Kreuter 2001; Lockman et al. 2002; Pardridge 2002). Towards this end, Liu et al. developed MNPs of iron oxide (Fe_3O_4) by encapsulating them within the polymer poly[aniline-co-N-(1-one-butyric acid)] aniline (SPANH) (Liu et al. 2010). The anticancer agent epirubicin was immobilized on the surface of these MNPs. This novel magnetic drug delivery system was targeted to the brain using focused ultrasound and magnetic targeting as a synergistic delivery system. Both ultrasound and an externally applied magnetic field actively increased the local MNP concentration. The results demonstrated that the control animals showed no MNP accumulation in the tumor region even 6 h after MNP administration. However, on application of external magnet, approximately 15-fold higher than the therapeutic range of epirubicin per gram of tissue were taken up by tumor cells. The confocal and fluorescence microscopy and Prussian blue staining further confirmed the presence of more epirubicin-MNPs at the tumor site than in the contralateral side (Liu et al. 2010).

Similarly, Chertok et al. also successfully delivered polyethyleneimine (PEI)-modified magnetic nanoparticles (GPEI) with a magnetic saturation of 93 emu/g Fe to brain tumors. The results in vitro showed high cell association and low cellular toxicity. However, initial investigation conducted in vivo in the absence of the magnetic field did not successfully accumulate magnetic nanoparticles onto tumors of rats harboring orthotopic 9L-gliosarcomas, due to poor pharmacokinetic properties (Chertok et al. 2010). However, intra-carotid administration in conjunction with magnetic targeting resulted in 30-fold ($p = 0.002$) increase in tumor entrapment of GPEI compared to that seen with intravenous administration (Fig. 7). Figure 7 shows the

Fig. 5 Synthetic Scheme for the development of Doxorubicin loaded magnetic drug delivery system. Copyrighted from reference (Chen et al. 2010)

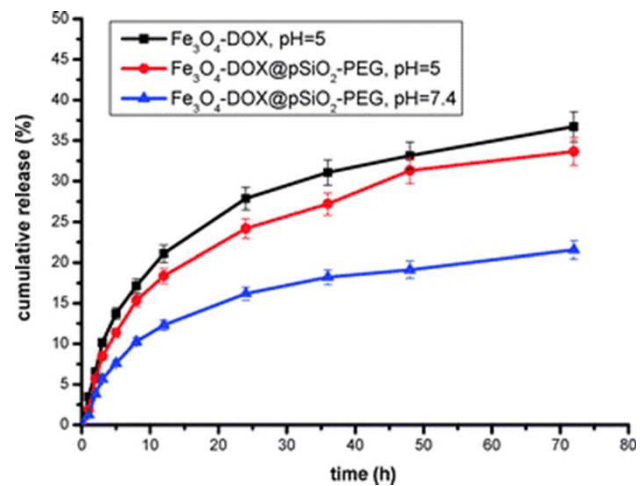
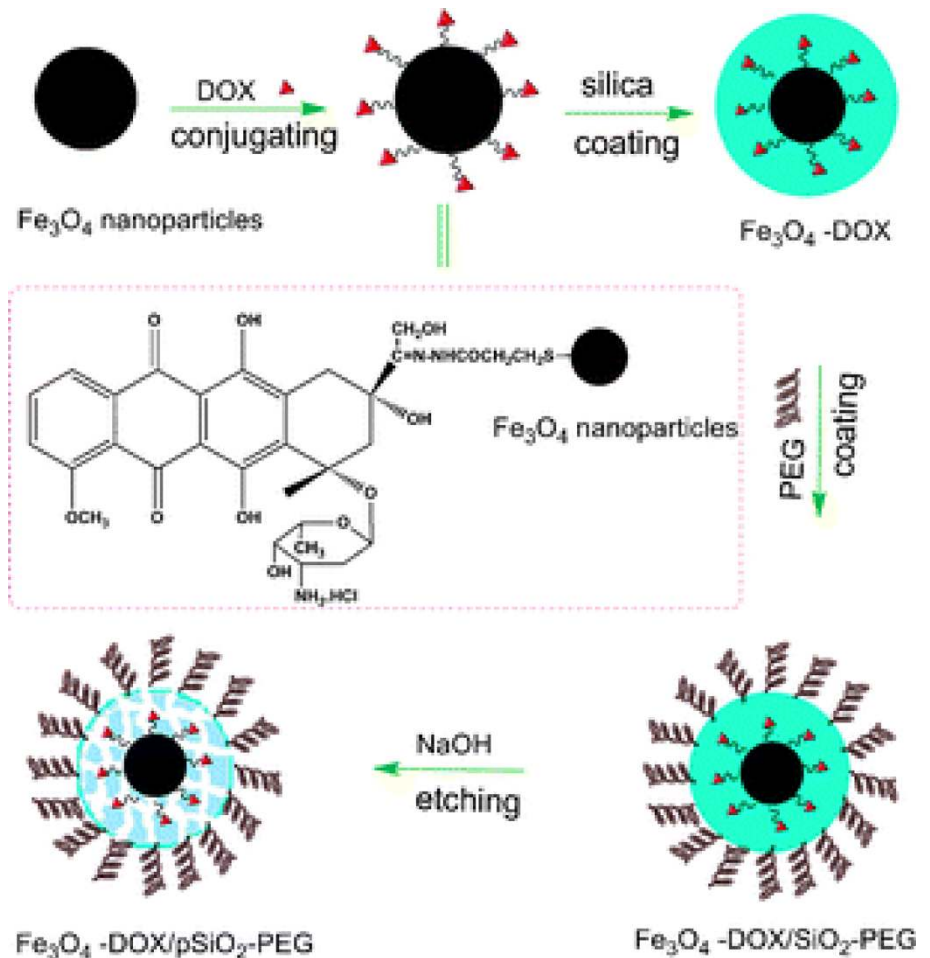


Fig. 6 Comparative release profile of Doxorubicin in iron oxide conjugated DOX. Iron oxide conjugated dox in silica and PEG protected shell. Copyrighted from reference (Chen et al. 2010)

MRI head scans of 9L glioma bearing rats. This figure clearly indicates the presence of iron oxide nanoparticles in the tumor lesion (Chertok et al. 2010).

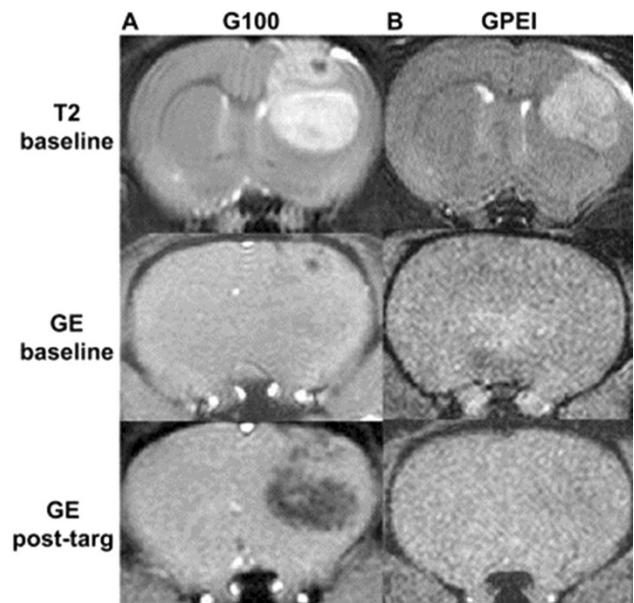


Fig. 7 Representative subsets of axial MRI head-scans of 9L-glioma bearing rats before (baseline) intravenous administration of a G100 or b GPEI and after magnetic targeting (post-targ). Figure copyrighted from reference (Chertok et al. 2010)

Ito et al. were the first to target esophageal cancer in rabbits by oral administration under the influence of a magnetic field in 1990 (Ito et al. 1990). The first clinical cancer therapy trials in humans using magnetic microspheres (MMS) was reported in Germany in 1996 and involved treatment of advanced solid liver cancer in 14 patients (Lübbe et al. 1996). These MMS had a diameter of approximately 100 nm and were filled with 4-epidoxorubicin. The results clearly showed that the MMS accumulated in the target area and were nontoxic. Similarly, Arias et al. investigated the capabilities of polycyanoacrylate nanospheres with a magnetite core as delivery systems for the antitumor drug 5-fluorouracil (Arias et al. 2008). By loading this hydrophilic drug onto a carrier system the therapeutic efficacy improved, while its undesired toxic effects were reduced. The choice of the biodegradable polymeric shell, namely polyalkylcyanoacrylates, was based on well-demonstrated therapeutic results in the treatment of both resistant and nonresistant cancers of a wide range of cell lines, and the low toxicity levels seen in Phase I and II clinical trials (Merle et al. 2006). In addition to this application, magnetic microspheres loaded with the γ -emitting radioisotope ^{90}Y have also been successfully used for a radionuclide therapy in the eradication of small subcutaneous B-lymphoma in mouse (Häfeli et al. 1997).

Bacterial magnetosomes (BMs) synthesized by magnetotactic bacteria have also been used as carriers for enzymes, nucleic acids and antibodies (Balkwill et al. 1980; Ota et al. 2003; Matsunaga et al. 2003). Their application as targeted drug carriers has been commended due to their unique features, such as paramagnetism, nanoscale, narrow size distribution and membrane-bound form (Grünberg et al. 2004).

Magnetic nanoparticles for gene delivery

One of the promising applications of MNPs is their application to deliver therapeutics at local inflammatory process of the musculoskeletal system in humans. At present, many of the local inflammatory conditions which are currently treated with systemic nonsteroidal anti-inflammatory drugs are hampered by systemic side effects (Závišová et al. 2007). Hence, MNPs could serve a major purpose in drug delivery to inflammatory sites when directed by external magnetic field, thus reducing systemic side effects. Other studies have also shown the advantages of directing the magnetic drug delivering vehicle to the lungs, which can be done with a properly designed magnetic targeting system (Gonda 2000). Numerous attempts have been made to use immunotoxins for targeted treatment of malignant lung diseases (Ally et al. 2005). Finally, these novel formulations have been shown to increase the

drug accumulation in the stratum corneum and epidermis plus dermis, which clearly demonstrates the potential of MNPs for topical application (Lacava et al. 2002; Primo et al. 2007).

Magnetic nanoparticle technology also offers the potential to achieve selective and efficient delivery of therapeutic genes by using external magnetic fields. As compared to traditional gene delivery strategies, magnetic drug delivery system has been shown to significantly increase gene delivery to human xenograft tumors models. This implies that they therefore have potential to turn the challenge of gene therapy in vivo into a new frontier for cancer treatment (Li et al. 2012). Mah et al. were the first to demonstrate that the conjugation to microspheres results in a higher effective concentration of vector to target cells as it moves through the tissue vasculature. In fact, both in vitro and in vivo studies demonstrated that microsphere-mediated delivery of rAAV vector results in higher transduction efficiencies than delivery of free vector alone, when administered either intramuscularly or intravenously (Mah et al. 2002). Currently, in vitro magnetofection kits utilizing cationic polymer coated MNPs are commercially available (Mykhaylyk et al. 2007; Pan et al. 2007; Ryther et al. 2005; Schillinger et al. 2005). Huth et al. showed that the cationic polymeric gene carriers, such as polyethylenimine (PEI) increase the cellular uptake of magnetofectins (Huth et al. 2004). This increased uptake is shown to proceed by endocytosis with an increased rate of internalization under the influence of magnetic field. Similarly, McBain and Coworkers showed that an MNP-gene based system focused to the target site/cells via high-field/high-gradient magnets has been shown to be efficient and rapid for in vitro transfection. This MNP-gene based system compares well with cationic lipid-based reagents, producing good overall transfection levels with lower doses and shorter transfection times (McBain et al. 2008b). Their experimental results indicate that the system significantly enhances overall in vitro transfection levels in human airway epithelial cells, compared to both static field techniques ($p < 0.005$) and the cationic lipids ($p < 0.001$).

To date, gene delivery via magnetic particles is predominantly used to reduce the time needed for transfection or minimize the dose of vector. Work is also being conducted on improving the overall transfection efficiency of this technique by using dynamic magnetic fields produced from oscillating arrays of permanent rare earth magnets (McBain et al. 2008). The preliminary data from these studies suggests that this approach can improve the level of transfection >tenfold compared to static magnetic fields. This can be due to the extra energy inducted into the system, which improves particle uptake (McBain et al. 2008). However, targeting siRNA to specific tissues still has not lived up to its potential clinical application, and much more

work is needed via collaboration with bioengineers and scientists across various scientific disciplines (Sun et al. 2008).

Conclusion

The use of magnetic nanoparticles as a drug delivering system is still defined by its biocompatibility and selective targeting to the desired cell or tissue under the guidance of external magnetic field. Advances in current technologies and the development of magnetic nanoparticles as drug delivery systems to deliver drugs to tumor hypoxic zones have fast-tracked in the past decade and led to the development of various magnetic nano-formulations such as liposomes, metallic/nonmetallic, and polymeric nanoparticles. These novel drug delivery systems has increased the ability to deliver drugs for which conventional therapy has shown limited efficacy (Sun et al. 2008). This technology will not only minimize invasive procedures, but also reduce side effects to healthy tissues, which are two primary concerns in conventional cancer therapies (Sun et al. 2008; Veisheh et al. 2010). The field of magnetic drug delivery is still at infancy, and synthesis of better magnetic drug delivery system and integration of multifunctional ligands are being continuously investigated so as to carry it from the bench-top to the clinic (Wahajuddin 2012). Until then the concerns about their elimination and long term toxicity remain barriers to clinical entry.

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