International Journal of Engineering Science Invention (IJESI)
ISSN (Online): 2319 – 6734, ISSN (Print): 2319 – 6726
www.ijesi.org || PP. 49-55

Magnetic Nanoparticles: A Novel Approach In Tumour Targeting

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Abstract: *Nanotechnology could be defined as the technology that has allowed for the control, manipulation, study, and manufacture of structures and devices in the"nanometre"size range. These Nano-sized objects, e.g.,"nanoparticles",having small size, customized surface, improved solubility, and multi-functionality will continue to create new biomedical applications i.e.ability to interact with complex cellular functions in new ways that can target, diagnose, and treat devastating diseases such as cancer, leprosy and used in DNA, ocular and brain drug delivery. Magnetic iron oxide nanoparticles with a long retention time, biodegradability and low toxicity have emerged as one of the primary nanomaterial for biomedical applications in vitro and in vivo. Targeting specific sites in vivo for the delivery of therapeutic compounds presents a major obstacle to the treatment of many diseases. One targeted delivery technique that has gained prominence in recent years is the use of magnetic nanoparticles. In these systems, therapeutic compounds are attached to biocompatible magnetic nanoparticles and magnetic fields generated outside the body are focused on specific targets in vivo. The fields capture the particle complex resulting in enhanced delivery to the target site.*

Keywords: *Cancer treatment, magnetic Iron Oxide nanoparticles, Magnet, Nanotechnology, Tumor targeting.*

I. Introduction

1.1. Nanotechnology:

The engineering, characterization, synthesis, and use of materials and devices of 100 nanometers or less is called nanotechnology. The application of nanotechnology to medicine, designated as nanomedicine has greatly accelerated the diagnosis, imaging and treatment of many diseases. In cancer medicine, nanotechnology has become a potential application for the development of nanoparticles asdrug delivery systems. Classical very potent chemotherapeutic agents, including camptothecin, taxenes, platinating agents, doxorubicin, and nucleoside and nucleotide analogs have been used against several tumor types for several decades. However, they have the disadvantage of affecting both tumor cells and normal cells, with the concomitant secondary effects including, cardiotoxicity, cytotoxicity, neurotoxicity, nephrotoxicity, and ototoxicity. Some of these chemotherapeutic-associated problems have been solved by the use of nanoparticle formulations of these drugs. The most important advantage of these novel formulations is that they preferentially target tumor cells by the enhanced permeability and retention (EPR) phenomenon exhibited by solid tumors compared with normal tissues. In addition, nanoparticles as therapeutics carriers have other unique properties of higher therapeutic efficacy, lower toxicity and the ability to encapsulate and deliver poorly soluble drugs.

1.2. Nanoparticles:

Nanoparticles (NPs) have been of significant interest over the last decade as they offer great benefits for drug delivery to overcome limitations in conventional chemotherapy. They can not only be formed in a range of sizes (1-1000nm) but also be made using a variety of materials including polymers (e.g. biodegradable polymeric nanoparticles, dendrimers), lipids (e.g. solid-lipid nanoparticles, liposomes), inorganic materials (e.g. metal nanoparticles, quantum dots), and biological materials (e.g. viral nanoparticles, albumin nanoparticles). In addition, they can be tailored to simultaneously carry both drugs and imaging probes and designed to specifically target molecules of diseased tissues. Nanoparticles for anti-cancer drug delivery had reached the first clinical trial in the mid-1980s, and the first nanoparticles (e.g. liposomal with encapsulated doxorubicin) had entered the pharmaceutical market in 1995. Since then, numerous new nanoparticles for cancer drug delivery have been approved and/ or are currently under development due to their many advantages. Their advantages include enhancing solubility of hydrophobic drugs, prolonging circulation time, minimizing non-specific uptake, preventing undesirable off-target and side effects, improving intracellular penetration, and allowing for specific cancer-targeting.

1.3.Tumour Targeting:

Cancer, a disease characterized by the uncontrolled growth and spread of abnormal cells, is still the second most common cause of death in the U.S. According to the American Cancer Society, about 571,950 Americans are expected to die in 2011 due to cancer, and that means more than 1,500 deaths per day. Current treatments for various cancers include surgery, radiation, hormone therapy, and chemotherapy. Although these conventional therapies have improved patients' survival, they also have several limitations. For example, conventional cancer chemotherapy has the cancer therapeutic agents distributing non-specifically in the human body, thus these drugs affect both cancerous and normal cells. This non-specific distribution of drugs limits the therapeutic dose within cancer cells while providing excessive toxicities to normal cells, tissues, and organs; and thereby causing several adverse side effects including hair loss, weakness, and organ dysfunction, leading to a low quality oflife for cancer patients. Nanoparticles (NPs) have been of significant interest over the last decade as they offer great benefits for drug delivery to overcome limitations in conventional chemotherapy. They can not only be formed in a range of sizes (1-1000nm) but also be made using a variety of materials including polymers (e.g. biodegradable polymeric nanoparticles, dendrimers), lipids (e.g. solid-lipid nanoparticles, liposomes), inorganic materials (e.g. metal nanoparticles, quantum dots), and biological materials (e.g. viral nanoparticles, albumin nanoparticles). In addition, they can be tailored to simultaneously carry both drugs and imaging probes and designed to specifically target molecules of diseased tissues. Nanoparticles for anti-cancer drug delivery had reached the first clinical trial in the mid-1980s, and the first nanoparticles (e.g. liposomal with encapsulated doxorubicin) had entered the pharmaceutical market in 1995. Since then, numerous new nanoparticles for cancer drug delivery have been approved and/ or are currently under development due to their many advantages. Their advantages include enhancing solubility of hydrophobic drugs, prolonging circulation time, minimizing non-specific uptake, preventing undesirable off-target and side effects, improving intracellular penetration, and allowing for specific cancer-targeting

1.4. Magnetic Nanoparticles:

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).Interest in nanotechnologies and nanoscale materials, particularly magnetic nanoparticles (MNPs), has grown recently and their applications have attracted the attention of both the research and industrial communities in the chemical, environmental and medical sectors.In the medical fields, the inspiration for integrating nano-technology has been expanding exponentially, particularly in the areas of drug delivery with the objective of directing the drug to the disease site with minimal side effects and reducing the dosage through more localized and efficient targeting. This involves magnetic drug targeting, whereby an external magnetic field gradient is applied at the target tissue to deliver the drug through active targeting using high-affinity ligand attachment, as well as therapeutic strategies.

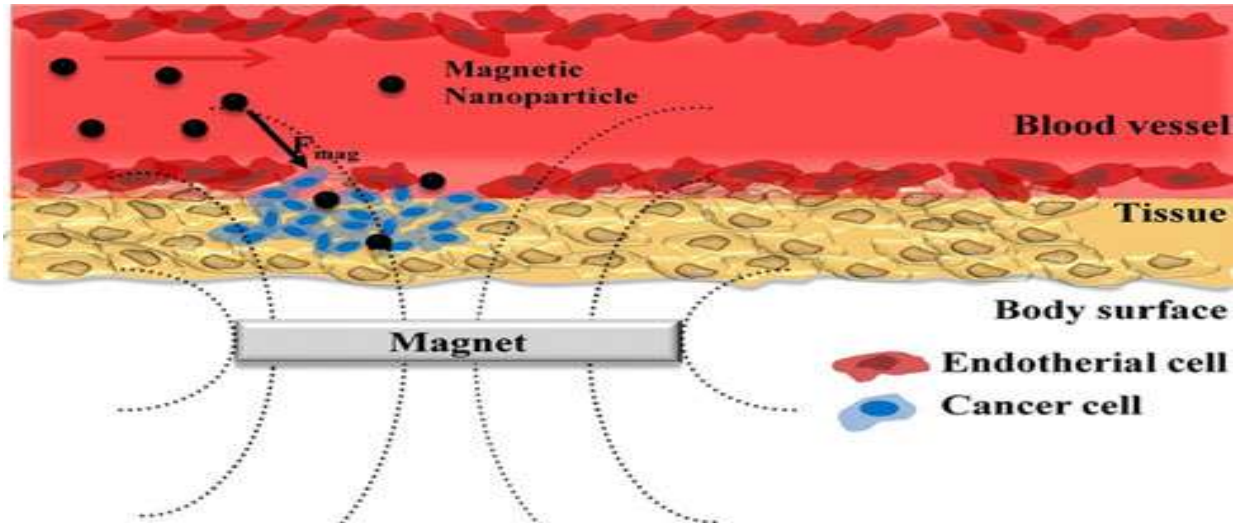


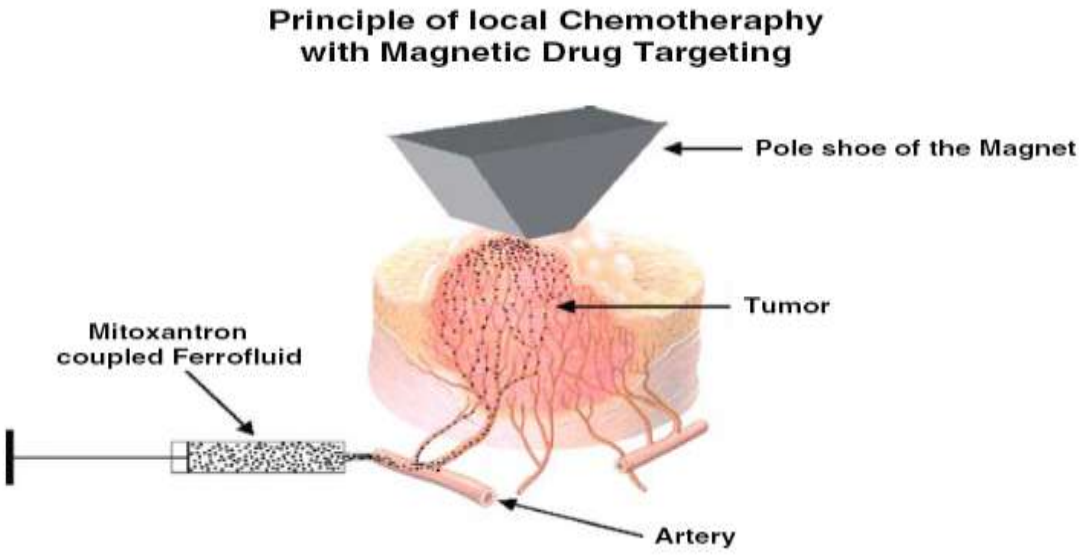
Fig.1 Schematic representation of Magnetic drug delivery systemunder the influence of external magnetic field. Fmag is direction of external magnetic field is targeted. Copyrighted from reference
(Park et al. 2010)

Ferrite oxide—magnetite (Fe3O4) 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 roleiwal et al. 2010). Any change in size and surface coating will modulate the magnetic properties such as Coercivity (Hc) 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 andcarry out its function.

II. Magnetic nanoparticles for drug delivery

An external magnetic field gradient will produce a force on magnetic nanoparticles. There is considerable interest in using this effect for targeted drug delivery by attaching the drug to the magnetic nanoparticles, then applying a large magnetic field to the desired region (e.g. a cancerous tumor or damaged joint), which will attract the magnetic nanoparticles, hence also attract the attached drug.This illustrates one of the recurring themes of many possible biomedical applications for nanoparticles: it is (believed to be) safe to apply relatively large static dc magnetic fields to patients. Furthermore, even ac magnetic fields may be safe, as long as the frequencies are not too high nor the field amplitudes too large.This application requires attaching the drug to the magnetic nanoparticles without (strongly) deteriorating the magnetic response of the composite or the efficacy of the drug.While detailed hydrodynamic modeling is difficult, this magnetic localization is expected to require very large field gradients, on the order of tens of T per m for even relatively low blood flow rates and large magnetic particles.

Magnetic nanoparticles will be attracted to regions of high field gradients.



The field gradients are largest close to the magnet, so this approach is most readily used to accumulate nanoparticles near external surfaces.

Using Fe^{2+} ions to cross-link the alginate leads to a non-magnetic material. The individual Fe ions do not order ferromagnetically.

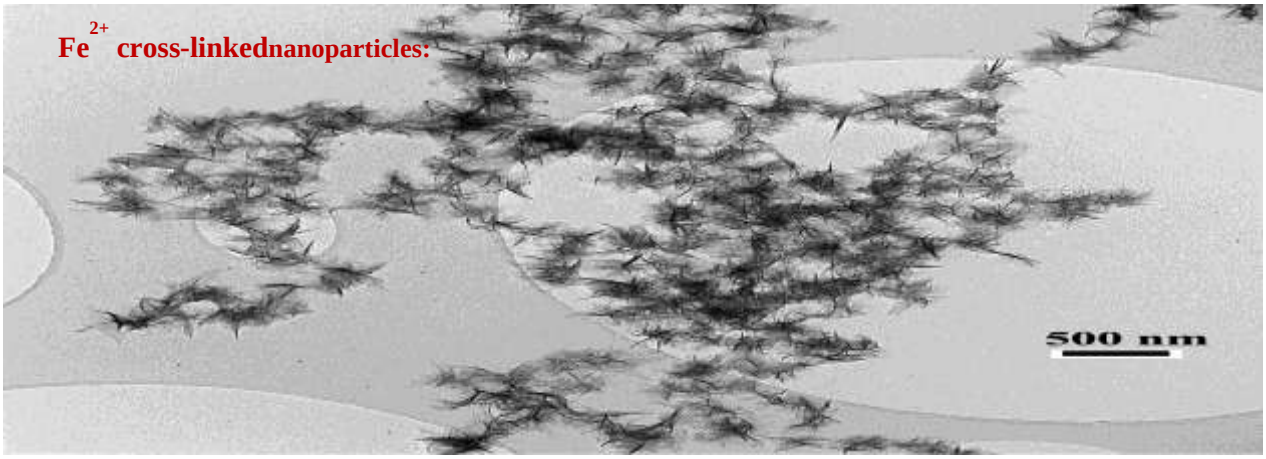


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Table I. Basic Mechanisms and Types of NPs Used for Different NP-Based Diagnostics and Therapy

Diagnostic/Therapy	Basic Mechanism	Type of NPs	Action of the NPs
MRI	Magnetic disturbance of 1H nuclear spin	Superparamagnetic. Large magnetic moment	Contrast agent
Chemotherapy	Biochemical affinity	Inert. Biocompatible. Surface functionalized	Drug delivery
Chemotherapy	Thermal activation, Time-dependent desorption	High specific surface area Specific chemical binding	Controlled release of drug
Neutron Capture Therapy	Nuclear capture and fission	Large neutron cross section (10B and 157Gd)	Neutron capture
Magnetic Hyperthermia	Electromagnetic absorption	Magnetic. Large magnetic moment	Heating
Photodynamic therapy	Photon emission. Photon internal conversion	Polymeric	Activation of photosensitizers. Production of cytotoxic species

and out of phase at a rate directly proportional to the magnetic field strength (Schick *et al.*, 1991). Clinicians then use radio frequency pulses to force protons into a high-energy, in-phase state; thus, the net magnetizable vector turns 90° towards the transverse plane. Ultimately, protons relax to their normal state via spin-lattice (T1) and spin-spin (T2) relaxation as protons transition back to their original longitudinal out of phase state, respectively (Houmard, Smith and Jendrasiak, 1995; Hsu and Lowe, 2004). In reality, protons de-phase much quicker than T2 because of inhomogeneities in the magnetic field; the combination of T2 relaxation and these inhomogeneities is termed T2* (Kamada *et al.*, 1994). It is the relaxation of protons from the transverse plane to the longitudinal plane that produces fluctuations in the net magnetic vector that is then used to image tissues.

III. Contrast agents

Contrast agents are used to enhance the quality of MRI images and are classified based on their ability to impact T1 or T2/T2* relaxation times. T1 contrast agents alter the longitudinal (T1) relaxation times of water protons to produce bright positive signal intensity in images and increase the conspicuousness of cells. T2/T2* agents alter the transverse (T2/T2*) relaxation times of water protons producing dark negative signal intensities in images. SPN-based contrast agents principally impact T2* relaxation, allowing regions to be identified as hypo-intense signals on the obtained image, although SPN-based contrast agents are also known to impact T1). Given that the ability for SPNs to impact T2 and T2* relaxation time is proportional to their ability to disrupt the local magnetic field; SPN-based contrast agents with high magnetic susceptibility and relaxivity are preferred. In addition to imaging tissues and cell clusters, SPNs have been used to label and subsequently track individual cells. Several non-specific SPN-based contrast agents are available for general imaging purposes; however, these non-specific SPNs are unable to efficiently accumulate in restrictive microniches, such as tumour sites. Targeted delivery of SPNs, using tumour-specific targeting moieties attached to the SPN outer shell, can facilitate their accumulation in cancer sites improving MRI resolution; for example, conjugation of anti-α-

fetoprotein and anti-glypican antibodies to the SPN shell can be used to selectively target hepatocellular carcinoma. Unfortunately, only a small number of SPN-based specific contrast agents have been produced to-date, principally due to the lack of highly specific biomarkers Nevertheless, non-specific SPN-based contrast agents have arguably revolutionized tissue imaging and diagnostics; future research into targeted contrast agents will augment the availability of MRI as a non-invasive and robust system for imaging specific pathologies.

IV. Magnetic hyperthermia

Magnetic hyperthermia is a term used to describe the generation of heat by MNPs in response to the application of an external alternating magnetic field.

5.1.Magnetic hyperthermia in cancer therapy:

Tumour vasculature has been shown to possess distinctive anatomical and biochemical characteristics arising from a lack of adequate perfusion leading to the generation of hypoxia and acidosis rending cancerous cells thermally sensitive. Tumour growth can be halted by heating cells to 40°C for 30 min or more; however, it is difficult to raise whole body temperature without also promoting adverse biochemical side effects. In 2010, Balivada *et al.* demonstrated the production of a localized thermo-ablative effect that did not induce systemic hyperthermia in vivo. Here, the researchers reported an increase of 11°C–12°C in C57/BL6 mice mediated by the accumulation and subsequent activation of MNPs. In addition, demonstrated that as the iron concentration of the magnetic nanocomposites increased from 5 μg/ml to 25 μg/ml, the number of viable tumour cells decreased from approximately 480 000 to 150 000 indicating the increase in iron concentration had an in vivo cytolytic action.

Other studies have demonstrated the effectiveness of magnetic hyperthermia as a prospective cancer treatment . Initial work by Yanase *et al.* (1998b) used magnetite-based cationic liposomes in the *in vivo* treatment of brain gliomas in F344 rats. Here, the researchers found that the average tumour volume decreased from 30 377 to 2 684 mm^3 with three rounds of treatment. Interestingly, one case from the test group did not appear to respond to treatment as a result of abnormal tumour morphology that had metastasized. This particular case seems to suggest that the application of magnetic hyperthermia in the treatment of multi-site and metastatic cancers may be more technically demanding.

5.2. Magnetic hyperthermia in the treatment of infectious diseases:

Magnetic hyperthermia has emerged as a promising technique for the treatment and control of infectious diseases. Given that hyperthermia leads to the physical destruction of pathogenic organisms, efficacy is expected to be independent of the drug-resistance status of the pathogen. Studies by Park *et al.*(2011) showed that iron oxide-based MNPs could be used to inactivate bacterial biofilms in vitro. Furthermore, they demonstrated that magnetic hyperthermia (using 20–60 mg/ml SPN solutions) is capable of severely disrupting the membrane integrity of *Pseudomonas aeruginosa* PA01 biofilms in vitro. Thus, even if treatment by magnetic hyperthermia fails to completely destroy the target biofilm, through disrupting the cell wall it may render drug-resistant bacteria susceptible to bactericidal compounds.

V. MNPs and targeted drug delivery

The use of therapeutic cells, proteins and nucleic acids in the treatment of various conditions is an highly active area of research (Mok and Zhang, 2013); their innate specificity make such biotherapeutics attractive potential treatments. Unfortunately, ineffective delivery systems often hamper the application of biotherapeutics. To address this, novel magnetically driven delivery systems have been developed to facilitate the fast, efficient, and site-specific delivery of biotherapeutic interventions.

VI. Therapeutic viruses

Therapeutic viruses have been touted as a potential cancer therapy for decades with adenoviruses considered one of the most powerful gene-delivery systems. However, several challenges relating to non-specific immune responses to their application and low transfection efficiency have meant clinically viable virus-based treatments are still in development. The conjugation of adenoviral particles to MNPs using electrostatic interactions can protect the virus from inactivation by cells of the immune system. In addition, through the application of an external magnetic field, virus conjugated MNPs can be targeted to specific sites improving gene transfection efficiency; this process is otherwise known as magnetofection. SPNs in complex with adenovirus particles have an approximately 3–4-fold higher transfection rate in vivo(of NIG-3T3 cells) compared to adenovirus particles lacking SPN functionalisation. This result, among others, presents a case for the potential utilization of therapeutic viruses in clinical treatments.

VII. Nucleic acid and protein delivery

Nucleic acid and protein-based treatments are largely dependent on successful cellular uptake. Given the concerns surrounding viral safety and costly production methods, non-viral vectors, such as the use of MNPs as vectors, are highly sought after. Here, external magnetic fields are used to manipulate SPNs into promoting the accumulation and deposition of nucleic acid-based therapies often leading to the expression or suppression of a gene; for example, through the functionalisation of MNPs with synthetic silencing RNA (siRNA) molecules, via ionic interactions, researchers have demonstrated significantly reduced gene expression rates in vitro . Similarly, Wang *et al.*(2011) conjugated Polyethylenimine-coated MNPs and lipofectamines with plasmid DNA expressing short-hairpin RNA which targeted the Type 1 insulin-like growth factor receptor (IGF-1R). They recorded an approximately 2-fold higher gene suppression rate following a 72-h incubation time using magnetofection in vivo.

In addition, SPNs have shown promise as potential vectors for improving the delivery of nucleic acid-based vaccines ; for example, nanoparticles conjugated to a nucleic acid–base vaccine that encoded for the *Plasmodium yoelii* merozoite surface protein ($MSP1_{19}$) were able to transfect African green monkey kidney cells at a higher rate than comparable chemical-based methods in vitro.

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). Usuallytherapeutic 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 highfield 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.

VIII. Conclusion

In the past decade MNPs, specifically SPNs, have proved a useful tool in promoting the deposition of therapeutic compounds; mediating the destruction of cancer cells and biofilms; and, improving the sensitivity of MRI techniques. Production of specialized encapsulation strategies has shown that MNPs can now be targeted to specific tissues, including cancer cells, revealing the possibility for a novel personalized approach to MNP-mediated treatment. Similarly, developments in the field of magnetic hyperthermia have mediated near complete tumour regression and the re-senitization of drug-resistant bacterial strains to antibiotics. These features characterize MNPs as versatile and adaptable tools for use in a broad range of biomedical contexts. There are still limitations to the use of MNPs in the diagnosis and treatment of cancer and infectious diseases, however, progress in this field is evident and it is likely the use of MNPs will become a staple component in the treatment of both infectious diseases and cancer in the future.

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