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Biogenic synthesized magnetic nanoparticles (MNPs) for medical nanotechnology:An review

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ABSTRACT

Magnetic nanoparticles (MNPs) are increasingly being considered for a number of biomedical applications due to their inherent ultrafine size, biocompatibility and super paramagnetic properties. The functional properties of the MNPs can be tailored for specific biological functions, such as drug delivery, hyperthermia or magnetic targeting MRI, cell labeling, sorting and immune assays. Among the MNPs, Iron oxide nanoparticles (maghemite γ-Fe_2O_3 or magnetite Fe_3O_4) are the popular formulations. This chapter represent biogenic synthesis of sustainable magnetic iron nanoparticles for application in biomedical field. The applicability of iron oxide nanoparticles depends upon size, functionality, stability, dispensabilityand interfacial surfaces of nanoparticles. Magnetic metal oxide nanoparticles are a major class of nanoscale materials with the potential to revolutionize current clinical diagnostic and therapeutic techniques. The Iron MNPs were synthesized and functionalized by use of natural curcumin biopolymer in aqueous non-toxic environment.The materials were synthesized by co-precipitation method followed by combustion of hydroxides. Due to their unique physical properties and ability to function at the cellular and molecular level of biological interactions MNPs are being actively investigated in MRI contrast agents, as carriers for targeted drug delivery. Iron MNPs may soon play a significant role in meeting tomorrow's health care needs.

Keywords: *Magnetic nanoparticles, Biomedicines, Drug delivery agent*

1. INTRODUCTION

The nanoscience and nanotechnology are a relatively recent developing trend and showing widespread activities in scientific research. They have their roots in the idea of some scientists of the last century. In 1959, Richard Feynman, the American physicist assertively delivered legendary talk entitled "There's Plenty of Room at the Bottom." It makes others inspired to bring new revelations in the field of the nanotechnology. The process which enables the manipulation of individual atoms and moleculesby using proper tools andtechniques resulting in another proportionally smaller set on the desired scalehad been described by Feynman(Bohara, Thorat and Pawar, 2016).

The term "nanotechnology" wasoriginally coined by the Japanese scientist, Norio Taniguchi of the Tokyo University of Science, in a 1974 (TANIGUCHI, no date). However, the term was unused until 1981,when Eric Drexler published his first paper on the nanotechnology.(Drexler, 1981) He wasunaware of the fact that the nanotechnology term was prior used by Taniguchi. The concept of nanotechnology had been developed and popularized by K. Eric Drexler. He founded the field of molecular nanotechnology, which includes engineered nano systems operating on the molecular scale and associates of the molecular assembler. His ideas about the nanotechnology can be quoted as; it is the principle of manipulation atom by atom, through control of the structure of matter at the molecular level, which entails the ability to build molecular systems with atom-by-atom precision, yielding a variety of nanomachines. With respect to this reality, in 1998 National Science and Technology Council (NSTC) of the USA created a working group of the nanoscience, technology, and engineering. Succeeding this, they also programmed the National Nanotechnology Initiative (NNI) in 2001 with the objective of initiation to create a common platform for the academic institute, industries, and private sector for working on this new technology. Following this example, nowadays, the field of the nanoscience and nanotechnology are being rapidly developed and getting heavily invested in most of the advanced countries in the world and many developing countries including China and India. The word 'Nano' originates from the Greek word - Nanos, which means dwarf or extremely small. The nanotechnology and nanoscience are defined by various means, which are often interchangeable. The nanotechnology could be defined as, "The science involving designing, synthesis, characterization, and application of materials which are characterized by at least one dimension in the nanometer range where 1 nm = 10-9 m." In the nanotechnology, two typesof perspectives named as, bottom-up and top-down are used. With the "bottom up" approach, nano scale materials are created by breaking down larger materials physically or chemically. While in the "top-down" perspective, nano scale objects are assembled atom-by-atom or molecule-by-molecule (Lavate et al,2020). The nanotechnology includes the production and application of physical, chemical, and biological systems at scales, which range from individual atoms or molecules to submicron dimensions. It is also concerned with the integration of the resulting nanostructures into larger system. By merging the nanoscience with technology, new, improved, and potential nano techniques are developed, replacing older ones. The nanotechnology has been tremendously interested since materials ranging in nanoscale possess novel functionalities leading to have many imminent technological applications(Sawantet al,2021). There is an expanding scope of creating new knowledge, which explains the size dependent evolution of various physical properties, and previously unnoticed features, and other things. Various basic and applied scientific disciplines have been holed promptly within the empirical discipline of nanotechnology. It has recently become one of the most cardinal areas having potentiality to aid existing technologies with more efficiency and better outcome. The nanotechnology shows great promise for providing us in the near future with many breakthroughs that will change the direction of technological advances in a wide range of applications. Improved and more desirable products can be made by using nano systems than conventional materials. The nanotechnology is surely going to have a strong impact in areas such as electronics, communication, medical device, medicine, cosmetics, architectural, textile, agricultural, food, metallurgy, defense and security, space, and many more(Roco, Mirkin and Hersam, 2011).

2. Magnetic nanoparticles for nano-bio applications

Among the different types of nanomaterials, magnetic nanoparticles (MNPs) are tremendously being focused due to their various exciting properties that make them useful in a wide range of biomedical applications(Nguyen and Kim, 2014; Shete *et al.*, 2014; Su *et al.*, 2015; Truong *et al.*, 2015). The use of MNPs through the nanotechnology for biomedical applications is currently gaining huge attention since the MNPs have the immense potential for applications in diverse areas of biology and medicine. Scientific communities are widely reporting the potentiality of MNPs for diagnostic and therapeutic applications. Comparable size scales of MNPs and biological materials promote their self to be used in biological and biomedical applications.(McNeil; Arruebo *et al.*, 2007; N. D. Thorat, Patil, *et al.*, 2013; Patil *et al.*, 2014) At the nanometer scale, the properties of materials seem to be different from those at the macro scale. The distinctive physical and chemicalcharacteristics of nanomaterials like a high surface area to volume ratio, tunable optical emission, unique electrical and magnetic behavior, and many more other novel properties can be exposed to gain wide spectrum of nano-bio applications. However, some drawbacks have limited the use of MNPs in nano bio applications, like potential toxicity, immunogenicity, decreased efficacy, and cost of production. To overcome these drawbacks and enhance the efficiency of MNPs, functionalization and proper designing of synthesis are key parameters(Richards and Ivanisevic, 2012).

3. Functionalization of magnetic nanoparticles:

3.1. Synthesis of Magnetic nanoparticles:

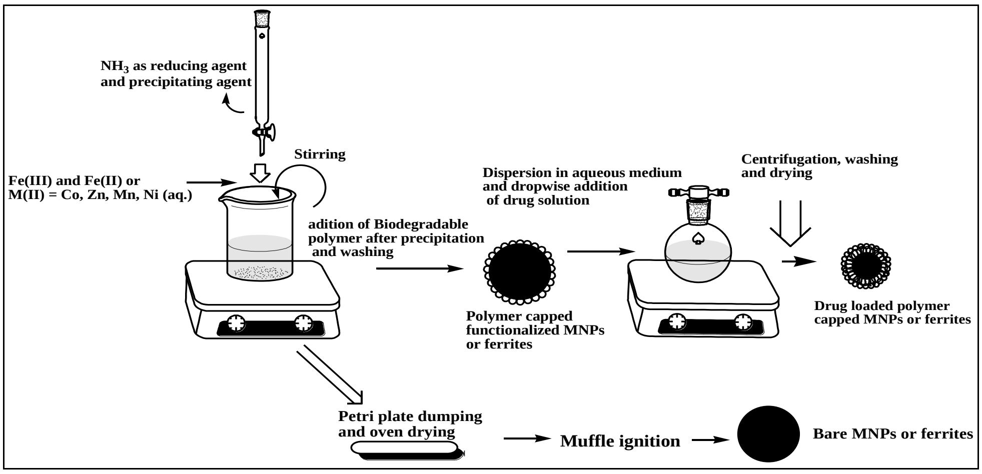
Iron oxide and ferrite nanoparticles are the most commonly used magnetic nanoparticles (MNPs) and their applications are promised in biomedical fields. Many researchers have got attention and great interest for magnetic nanoparticles of transition metal oxide popularly intended towards iron oxides as maghemite γ-Fe_2O_3 or magnetite Fe_3O_4, or ferrite MFe_2O_4 (M = Fe, Co, Ni, Mn and Zn) during the last few decades due to their interesting physicochemical properties and nano biotechnological applications.(Khot*et al.*, 2013; Thorat, Bohara, Tofail, *et al.*, 2016) Severalsynthesis protocols have been developed for to produce monodisperse magnetic nanoparticles of size ranging from single domain to super paramagnetic domains(Thorat *et al.*, 2012). Most of them consist bottom up synthetic approaches and fewer methods are based on top down approach. Few of these synthetic methods for MNPs includes solvothermal, hydrothermal, sol gel path, combustion, wet chemical co precipitation, mechanical milling, bacterial synthesis, sonochemical and microwave irradiation(Lu, Salabas and Schüth, 2007). Among these methods, most famous methods based on bottom up approach are co precipitation, sol gel methods and green bacterial synthesis and light irradiation methods. The most convenient routes for synthesis of MNPs are co precipitation or combustion. These methods facilitate the production of magnetic ferrite nanoparticles with plausible biocompatible surface engineering and functionalization due to minimal agglomeration, good stability and uniform particle sizes and morphologies. Applying the recent advances of nanotechnology, the parameters like composition, particle sizes, morphology and surface interactions of magnetic nanoparticles can all be tailored, furthermore in combination with their nanoscale magnetic phenomena facilitates them desirable in therapy and diagnosis(Holzinger, Le Goff and Cosnier, 2014). The maghemite and magnetite nanoparticles are main biocompatible, surface active and less toxic magnetic nanoparticles, which can be synthesized mainly by co precipitation or combustion methods. In combustion method iron salts homogenized by milling and amino acid or amide fuels are added in stoichiometric proportions and finally contents are ignited to get magnetic nanoparticles by combustion of iron salts. In co precipitation method Fe(II) and or Fe(III) salts oxidized at basic pH and then at neutral pH there hydroxides are precipitated and separated to convert them in to stable oxide forms by drying and ignition(Gao, Gu and Xu, 2009). Such dried magnetic nanoparticles can be dissociated to iron at acidic pH, but are stable at neutral pH and basic blood pH=7.4. Such calcinated MNPs of maghemite, magnetite or ferrite contain electron spin oriented magnetic domains resulting in to super paramagnetic. This property shows uniqueness of MNPs from other oxide nanoparticles in biomedical applications. Because as superparamagnetic can be utilized in biomedical fields for heat generation, magnetic targeting, contrast agent and probing in to cells by use of external magnetic field on MNPs(Laurent *et al.*, 2008).

Table.1.1. List of methods with their principles, benefits, and drawbacks

Type of Method	Principle	Benefits	Drawbacks
Chemical method			
Co-precipitation	Salt solution of the required metallic element is reduced by alkali solution.	Simplest and most efficient, large amount of NPs can be synthesized	Particle size cannot be controlled
Hydrothermal	Hydrothermal conditions: hydrolysis and oxidation or neutralization of mixed metal hydroxides	Ultrafine MNPs, monodispersed in Nature	Rate dependent method, requires strict control on reaction conditions
Combustion	Exothermic redox reaction	Itself act as a powerhouse, low cost	Easily influenced by small changes in process parameters
Biological method			
	Physiochemical intracellular or extracellular synthesis	Promising method with well desired powder characteristics	Size cannot be controlled, Polydipsersity

3.2. Need for functionalization of MNPs :

The major problem associated with direct use of bare MNPs in to cells is their hydrophobicity and low aqueous solubility, which restricts and limits their direct use in biomedical fields. So there is need for functionalization of MNPs and their surface engineering(Thorat *et al.*, 2014). Lot of attempts are going on for surface functionalization and engineering of MNPs, for to increase their aqueous solubility and make them bioavailable and hydrophilic. The magnetic metal oxide surfaces have extremely high surface energies greater than 100 dynes/cm^{-1}, that make the functionalization of MNPs very challenging. In addition, magnetic dipole–dipole attractions between particles enhance the difficulties experienced in their production and agglomerations in comparison to non-magnetic NPs(Sapsford *et al.*, 2013).



Cartoon 1 : Surface engineering of MNPs using bottom up wet chemical co precipitation.

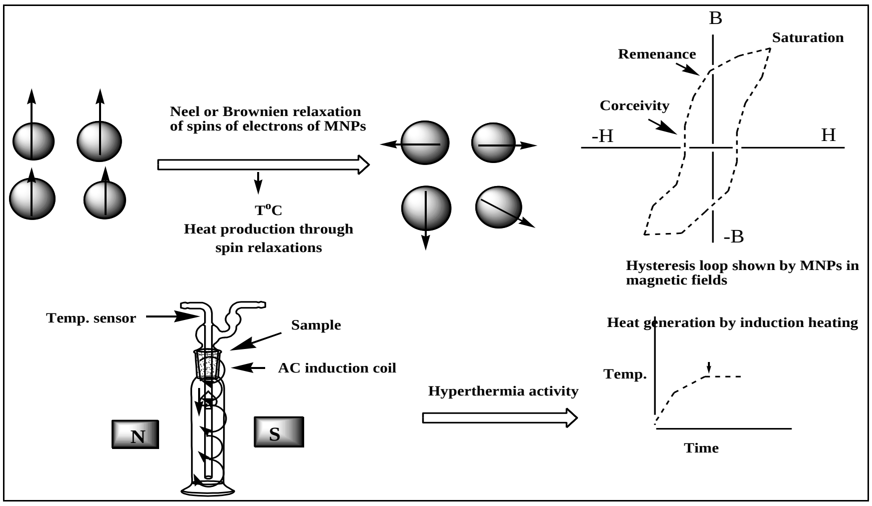
A wide range of monomers, surfactants, polymers and organic materials are used for stabilization and or functionalization purposes,where the balance between steric and electrostatic repulsive forces is important aspect in functionalization of MNPs. Control of the surface chemistry of MNPs is required to functionalize them for bio-related applications. Bare MNPs having large agglomerates reduce superparamagnetism(Hergt and Dutz, 2007). Surface engineering of MNPs must be performed using surfactants or water loving biodegradable polymers to prevent aggregation of the particles, leading to colloidal stability, and also to make them with water-soluble, biocompatible and for retaining their super paramagnetism. Polymers capping to MNPs surfaces enhance not only colloidal stability, bioavailability and hydrophilicity but also drug encapsulation ability over engineered surfaces of MNPs.

3.3. Enhancement in blood fluid retention of drugs:

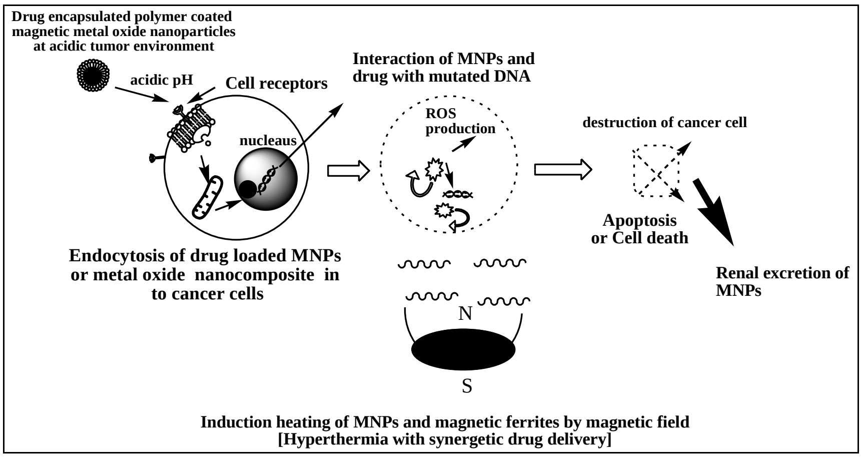
Functionalization of MNPs results in their improved pharmacokinetics and bio distribution profiles via the enhanced permeability and blood fluid retention effect(Berry *et al.*, 2003). Although this effect enhances the accumulation of MNPs within tumor tissues at acidic pH. The poor cellular internalization and insufficient targeting of bare anticancer drugs like Camphothecin, 5-fluorouracil, Gemcitabine, Cisplatin, Curcumin limits their dosages to levels below the optimum therapeutic value, and adversely affecting the efficacy of the chemotherapy(Maeng *et al.*, 2010). So pH responsive surface engineered MNPs as drug delivering vehicles are the solution for targeted and effective delivery of above hydrophobic anticancer drugs to cancer cells. The stimuli responsive and long term effective drug delivery systems for hydrophobic drugs can only be formulated using the MNPs. The polymers can be coated on the surfaces of MNPs by electrostatic interactions which also facilitates the drug encapsulation of MNPs over their surfaces with higher zeta potentials(N. D. Thorat, Khot, *et al.*, 2013).

4. Hyperthermia activity of MNPs:

The etymological meaning of the word "hyperthermia" is generation of heat and with respect to cancer therapy, the term is used to imply treatment based on generation of heat at the tumor site. The approach involves raising the temperature of local environment of a tumor resulting in changing the physiology of diseased cells finally leading to apoptosis. This treatment modality complements currently available treatments including chemotherapy, radiation therapy, surgery, gene therapy, and immunotherapy for cancer(Sanz *et al.*, 2017). Depending on the degree of temperature raise, hyperthermia treatment can be classified into different types. In thermo ablation, a tumor is subjected to high temperatures of heat 46 °C (up to 56 °C) causing cells to undergo direct tissue necrosis, coagulation or carbonization. Moderate hyperthermia (41 °C to 46 °C) has various effects both at the cellular and tissue levels. Diathermia uses lower temperatures (T_b41 °C) for the treatment of rheumatic diseases in physiotherapy. During moderate hyperthermia, which is traditionally termed as hyperthermia treatment, cells undergo heat stress in the temperature range of 41–46 °C resulting in activation and/or initiation of many intra and extracellular degradation mechanisms like protein denaturation, protein folding, aggregation and DNA cross linking. With a single heat treatment, permanent irreversible protein damage can occur resulting in protein aggregation and/or inhibition of many cellular functions(van den Tempel, Horsman and Kanaar, 2016). The other cellular effects of moderate hyperthermia include induction and regulation of apoptosis, signal transduction, multidrug resistance and heat shock protein (HSP) expression. The tissue level effects include pH changes, perfusion and oxygenation of tumor micro environment(Takahashi, 2016). The effectiveness of any hyperthermia treatment greatly depends on the temperatures generated at the targeted sites of action, duration of exposure and characteristics of particular cancer cells. Traditionally, hyperthermia treatment was administered by using external devices to transfer energy to tissues either by irradiation with light or electromagnetic waves. Currently available techniques for induction of hyperthermia are ultrasound, radiofrequency, microwaves infrared radiation, magnetically excitable thermoseeds, and tubes with hot water. However, each of these methods suffers from its own limitations. Oncologists often use the heat treatment in combination with radiotherapy or chemotherapy or both. The combined approach results in eliminating many cancer cells in addition to making the resistant cancer cells more vulnerable to other treatments. Some of the challenges in traditional hyperthermia treatment are: 1) unavoidable heating of healthy tissue resulting in burns, blisters and discomfort, 2) limited penetration of heat into body tissues by microwave, laser and ultrasound energy, and 3) thermal under-dosage in the target region, a nearly unsolved problem in the case of bone of pelvis or scull which shield deep tissues; often yielding recurrent tumor growth(Hayashi *et al.*, 2014). With the possibility to convert dissipated magnetic energy into thermal energy, the application of magnetic materials for hyperthermia treatment of cancer was first proposed in 1957. Since then the approach evolved into a well-researched field due to the introduction of magnetic nanoparticles (MNPs). MNP-based hyperthermia treatment has a number of advantages compared to conventional hyperthermia treatment. such as 1) cancer cells absorb MNPs thereby increasing the effectiveness of hyperthermia by delivering therapeutic heat directly to them, 2) MNPs can be targeted through cancer-specific binding agents making the treatment much more selective and effective, 3) the frequencies of oscillating magnetic fields generally utilized pass harmlessly through the body and generate heat only in tissues containing MNPs (Thorat, Bohara, Malgras, *et al.*, 2016), 4) MNPs can also effectively cross blood-brain barrier (BBB) and hence can be used for treating brain tumors, 5) effective and externally stimulated heating can be delivered at cellular levels through alternating magnetic field (AMF), 6) with the possibility to obtain stable colloids using MNPs, they can be administered through a number of drug delivery routes, 7) MNPs used for hyperthermia are onlyfew tens of nanometer in size and therefore, allows easy passage into several tumors whose pore sizes are in 380–780 nm range,8) compared to macroscopic implants, MNP-based heat generation is much more efficient and homogeneous , 9) MNP-based hyperthermia treatment may induce antitumoralimmunity, and 10) last but most important aspect is that MNP-based hyperthermia can also be utilized for controlled delivery of drugs and first such nanoconstruct for this purpose was made using layer-by-layer self-assembly approach.



Cartoon 2 : Hysteresis property and hyperthermia activity of MNPs

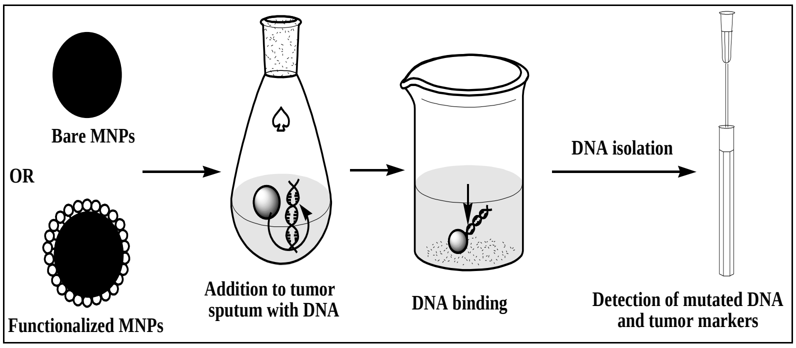


Cartoon 3: Hyperthermia and anticancer effects of drug loaded and polymer functionalized MNPs

This additional feature opens up possibilities for the development of multifunctional and multi-therapeutic approaches for treating a number of diseases(Chen *et al.*, 2016). Recently the research is shifting from use of MNPs to use of superparamagnetic nanoparticles in hyperthermia therapy. The concept of this is something what we can say that this material can acts as a magnetic switch. Hence beyond the certain temperature say Curie temperature of the material the material is shifts from paramagnetic to diamagnetic stage and heating ability of the material is seized. Such phenomenon will prevent the overheating of tissue. The most challenging job is to design and develop the material with appropriate Curie temperature designed material (Chu, Yu and Hou, 2015)

5. DNA isolation and early detection of tumor markers by MNPs:

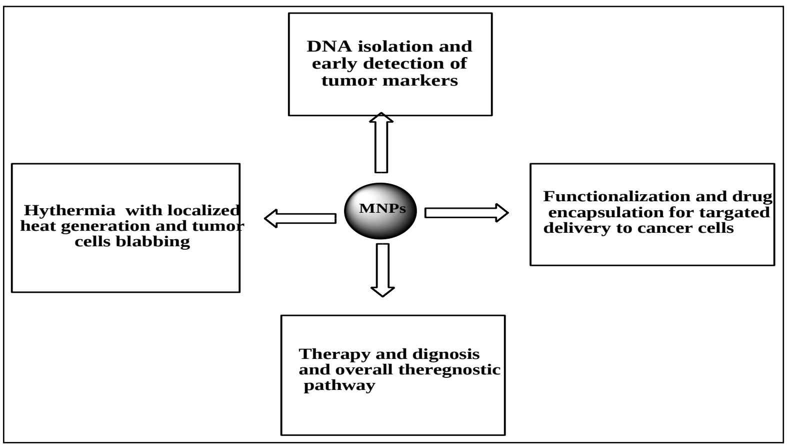
Highly sensitive and selective DNA sensors are of prior requirements regarding genetic engineering. These have a wide role in the diagnosis of genetic diseases, detection of infectious agents, gene therapy, and identification in forensic and environmental cases. In recent years, many studies have been devoted to develop DNA sensors due to the simplicity, specificity, exceptional sensitivity and selectivity for the detection of specific genes. Some conventional techniques like PCR and real-time PCR have the ability of amplification from small amounts of DNA into readable quantities and being applied mostly in the fields of biomedicine. However, these techniques demand more time, sample preparation, high-tech equipped apparatus and well educated operators. Unlike to this, nano-bio sensors have opened a perspective to overcome most of the disadvantages of the conventional detection methods for the applications in agriculture, clinics, drugs, environment, and food. Magnetic nanoparticles-DNA interaction can open up new possibilities in various biomedical applications, which are based on fundamental properties of DNA and magnetic nanoparticles.(Patil *et al.*, 2015)



Cartoon 4: DNA isolation ability of MNPs

6. MNPs as powerful material for theragnostic applications:

Theragnostic is a newly emerging concept which involves simultaneous execution of therapeutic and diagnostic approaches for personalized medicine. Nanoparticles (NP) can be designed to encapsulate a wide variety of chemotherapeutic and diagnostic agents for the delivery of these agents to tumor cells(Lammers *et al.*, no date). Nanoparticles can target tumors by a passive process. Passive targeting implies that nanoparticles are smaller than the fenestrations of endothelial cells and can therefore enter the interstitium to be finally entrapped in the tumor. The combination of leaky vasculature and poor lymphatic drainage results in the well-known enhanced permeability and retention (EPR) effect(Stylianopoulos, 2013). Paclitaxel (PTX), a major anti-cancer



Cartoon 5: Variety of medical and clinical applications of MNPs

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