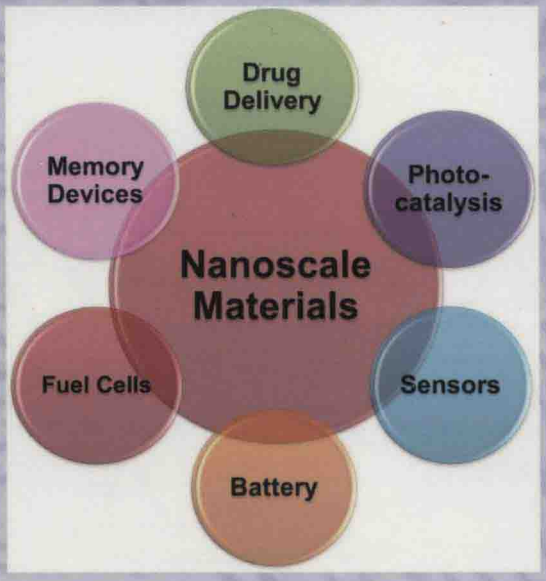
# Multi-Functional Nanoscale Materials and their Potential Applications




Edited by
Alagarsamy Pandikumar, Huang Nay Ming
and Lim Hong Ngee

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*Edited by*

**Alagarsamy Pandikumar, Huang Nay Ming and Lim Hong Ngee**

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# Preface

Nanotechnology is now ubiquitous and deeply embedded in our day-to-day lives. Unknowingly, it has weaved seamlessly into various applications, making it impossible to look passed its importance. This volume is a compendium of review as well as research articles, providing a wide spectrum of bottom-up fabrication approaches and their utilization on multiple fronts. This volume will be valuable to scientists, academicians, engineers and students who are keen to discover the advances in nanotechnology for favorable materials construction techniques and applications in relation to human health, environment and engineering.

The first three papers of this volume comprise review articles. Two of them discuss comprehensively on using nanomaterials as drug carriers and drug sensors. The magnetism of nanomaterials enhances the drug delivery efficacy by improving the target of drug to specific areas. Meanwhile, carbonaceous materials such as graphene and carbon nanotubes have been widely used to modify electrodes due to their excellent electron mobility. Energy storage is another noteworthy area of research in the face of depleting oil and gas. The review paper on the behavior of nanocomposite polymer electrolytes upon complexation with lithium ions provides an insight of their significant contribution in lithium ion batteries.

The subsequent four papers relate to photocatalytic degradation of sacrificial reagents. Metals oxides have been employed to oxidize and mineralize these harmful molecules to harmless components. A combination of metal oxides has shown to increase the efficiency of photodegradation, leading to improved kinetic rates of disintegration of pollutants. Doping of semiconductors with foreign elements shifts the photocatalytic activity from the ultraviolet to visible range and reduces the electron-hole recombination, as manifested in the paper that reports on hybridizing zinc with cadmium selenide using a facile method, which results in a narrow distribution of nanomaterials.

This volume also unveils some up-and-coming research on dielectric relaxation, nanofluids, non-volatile memory, polymer electrolyte membrane fuel cells, and solvatochromism and electroabsorption studies of drug carriers. These papers are evidence of the importance of interdisciplinary among the branches of science.

Last but not least, we would like to express our thanks and gratitude to the authors for their generous contributions of knowledge in nanoscience, consequently materializing this volume for the benefits of interested parties in nanomaterials synthesis, processing and applications. The editors are grateful to contributors for manuscripts and regret if any copyright is being infringed unknowingly. We acknowledge the sincere efforts of Mr. Thomas Wohlbier, TTP publishing authority, for bringing the Special Topic Volume in its final shape.

**Alagarsamy Pandikumar**
**Huang Nay Ming**
**Lim Hong Ngee**

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# Magnetic Nanoparticles as Drug Carriers: Review

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**Abstract**

Magnetic nanoparticles are made up of magnetic elements such as iron, nickel, cobalt and their oxides. Their unique physical and chemical properties, biocompatibility and their ability to be manipulated by external magnetic fields have made them as popular drug carriers in recent years. They offer various advantages such as ability to carry drugs to the desired areas in the body, and the ability to release the drugs in a controlled manner which in turn help in reducing side effects to other organs and in providing correct dosage of drugs. However, the complexity of the drug delivery system is a challenge in further improving the efficiency of magnetic nanoparticle drug delivery. In order to overcome this challenge, computational tools help in understanding the complexity of the drug delivery process and to design magnetic nanoparticles which are more efficient in drug delivery. In this chapter we propose to review various properties of magnetic nanoparticles, applications of magnetic nanoparticles as drug carriers, challenges in using them for drug delivery, various computational tools which aid in modeling magnetic nanoparticle drug delivery and in designing magnetic nanoparticles for efficient targeted drug delivery.

## 1.Introduction

Nanomedicine is one of the emerging applications of nanotechnology which exploits the unique properties of nanoparticles for medical applications. Nanomedicine provides greater benefits and can revolutionize the health care industry in the near future [1]. Nanoparticles, in particular, magnetic nanoparticles (MNPs) have been widely used in nanomedicine. MNPs are particles which are 1-100nm in length in at least one dimension. MNPs are mainly made up of magnetic elements such as iron, nickel, cobalt and their oxides. The unique properties of MNPs which make them to be widely used for medical purposes are their surface to mass ratio, quantum properties, chemical, electrical and magnetic properties. In recent years, MNPs are widely studied for the applications in drug delivery. Drug delivery systems using magnetic nanoparticles as carriers are based on the fact that nanoparticles become magnetic in the existence of an external magnetic field [2]. This property makes them to be targeted to a specific location under the influence of an external magnetic field. The therapeutic agents are attached to the surface of the MNP or embedded within a mixture of polymer and MNP. This complex is injected into the patient through intravenous or intra-arterial injection. After the MNPs reach the target site, the drug is released through changes in pH, osmolality, temperature or through the enzymatic activity [3]. The usage of MNPs for drug delivery has many advantages such as i) ability to deliver the drugs to the specific target locations in the body ii) decrease in the quantity of the drug used for treatment iii) minimization of side effects of drugs on the non-target sites and iv) protection from rapid degradation or clearance of the drug [4, 5].

In order to further improve the development of drug delivery using MNPs, new tools are required to understand the mechanism of drug delivery. Computational approaches help us to model the complex processes of the drug delivery system at the nanoscale and this helps us to understand and

predict the phenomenon at nanolevel [6]. Various techniques such as Molecular Dynamics (MD), Ab Initio methods and Monte Carlo simulations (MC) are available to obtain the information and predict the mechanical, chemical, electrical, optical and biological properties of nanoparticles [7]. Modeling and simulation can be used to predict the compatibility between nanoparticles and drug [8]. They can also be used to model a complete drug delivery system [9]. They help in designing novel MNPs as drug carriers and in identifying optimal drug material combinations. Computational modeling and simulation help in studying the complex drug delivery systems and they help in understanding the properties and substructures of MNPs. Modeling and simulation can help us in relating the nanoparticle structural properties and their biological performance. This relationship will help in designing efficient drug delivery systems and in evaluating the performance of the drug delivery systems [10].

Recently MNPs are widely studied and various research activities are being carried in order to study their behavior in drug delivery and in optimizing their properties so that they can be commercially available for clinical purposes. Still there are many challenges in efficiently utilizing MNPs for nanomedicine. Extensive study on the MNP based drug delivery system is very essential in order to bring advancements in diagnosis and treatment of diseases. This chapter gives a brief review of various properties of MNPs, applications of MNPs as drug carriers and challenges in using them for drug delivery. Further this chapter highlights on various computational tools which aid in modeling MNP-based drug delivery and in designing MNPs for efficient targeted drug delivery. This review is not exhaustive but provides an overview of MNPs in drug delivery and some of the computational approaches available for designing and modeling MNPs for drug delivery.

## 2. MNPs for drug delivery

### 2.1.Properties of MNPs.

MNPs have become promising candidates in nanomedicine because of their biological function, including distribution and elimination patterns in the body, is dictated mainly by their controllable physiochemical properties such as size, shape, hydrophobicity and surface charge. Particle size and size distribution are essential characteristics of MNPs which have control over in vivo distribution and the ability of MNPs to load, target and release the drug. MNPs are smaller in size compared to their microparticle counterpart [11]. Hence they have higher intracellular uptake and can carry drugs to different types of organs [12]. The size of MNPs also affects drug release. MNPs are smaller in size, hence their surface area is more and this makes most of the drug available on the surface of the MNPs. As most of the drug is on the surface of MNPs, it leads to faster release of drug [13]. Greater surface area also supports in faster dissolution of the drug. It is estimated that the ideal size of the nanoparticles is in the range 10nm-100nm for in vivo applications as these have the optimal pharmacokinetic properties [5]. 40nm-50nm MNPs coated with PEG (polyethylene glycol) were quite well taken up by endocytosis [14]. Smaller nanoparticles are victims of tissue extravasation and renal clearance. Larger particles are quickly opsonized and removed from the bloodstream through the macrophages [15].

The hydrophobicity of the surface of MNPs controls how much of blood components especially proteins are adsorbed. The proteins are mainly opsonins and the binding of opsonins to the surface of nanoparticles is called opsonization. If opsonization is more, the nanoparticles will be removed easily by the macrophages of mononuclear phagocytes system rich organs [16]. In order to minimize opsonization and to circulate the nanoparticles for a longer period of time in vivo the surface of the nanoparticles can be coated with hydrophilic polymers/ surfactants [12].

Various experiments also have been conducted on the shape of the nanoparticles and their biodistribution. Studies done by Geng et al. show that as the length-to-width aspect ratio increases,

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the in vivo circulation time of the nanoparticles also increases [17]. The appropriate length-to-width aspect ratio of MNPs can be determined so that their biodistribution is appropriate for nanomedicine. Hydrophobic and charged nanoparticles circulate in the blood stream only for shorter duration as they have the tendency of opsonization which makes them to be removed from circulation [18].

The magnetic properties of the nanoparticles are highly dependent on the size and surface features [19]. Magnetic targeting is very useful for carrying drugs to the desired areas especially to tumors. When the size of the nanoparticle is less than 10 nm, they become single domain particle and become superparamagnetic [20]. An external magnetic field is applied and a translational force is exerted on the MNP carrier and drug complex to attract it towards the magnet. These particles show their magnetic behavior only in the influence of external magnetic field and become inactive when the external magnetic field is removed. If the MNPs do not become inactive after the external magnetic field is removed, the MNPs tend to aggregate with each other. Superparamagnetism is observed in small ferromagnetic or ferrimagnetic nanoparticles [21]. The advantages of superparamagnetic iron oxide nanoparticles based drug carriers are currently in clinical trials and experimental studies. Some of them have been permitted for therapeutic applications [22].MNPs are very useful for diagnosis and treatment of brain tumors. Blood brain barrier (BBB) are more restrictive barriers. They allow only very small MNPs which are less than 500 DaMW [23].

The coating on the surface of the MNP also plays an important role in preventing agglomeration, interaction with proteins (opsonization) and filteration by reticuloendothelial system. MNPs which are coated with biocompatible materials show lower toxicity due to the coating and lesser number of adsorption sites [24]. The coating around the MNP is also determined in such a way that they carry the drug and release it in a desired way. MNPs have the ability to heat the particles with changes in external magnetic field. This effect is called hyperthermia. The MNPs are used to generate this hyperthermia effect to locally heat the cancerous cells without disturbing the healthy cells surrounding the tumor [25].

### 2.2.Challenges in using MNPs for drug delivery.

Although MNPs are widely being considered as efficient drug carriers, there are many challenges in using MNPs for drug delivery. These challenges are mainly due to the small size of the MNPS and the dynamic nature of drug transport & delivery process. The MNPs tend to aggregate into clusters due to which they lose some properties associated with small dimensions and become difficult to handle [5]. Targeting the drug to specific sites becomes difficult as the magnetic force is not strong enough to overcome the force of blood flow [26]. The external magnetic field gets dampened with increasing depth in the biological environment during in vivo magnetic targeting. It is necessary to hold the MNP/ drug complex in the target site for which the externally applied magnetic field gradient has to be strong. The drug does not respond to the external magnetic field. So even if it is released very near to the target site it may reach the target or may flow with the blood to the near by regions. Sometimes, these MNP drug carriers may get accumulated in the bloodstream and may block the blood flow [27]. The rate in which the drug is released is controlled by the external magnetic field. The superparamagnetic nanoparticles have to be small enough so that they don't get agglomerated after stopping magnetic field and so that they can remain in the body without getting filtered by organs such as liver or immune system [28].

### 2.3.Applications of MNPs for drug delivery.

The unique properties of MNPs make them to be widely used for disease diagnostics and therapeutics. These properties of MNPs are considered thoroughly in order to design efficient MNPs so that they are biocompatible and carry out targeted drug delivery appropriately.

- Dextran coated or silane coated paramagnetic nanoparticles were explored for the treatment of cancer [29]. It is also demonstrated that magnetic fluid hyperthermia affects mammary carcinoma cells in vitro and in vivo [30]. The superparamagnetic particles can be endocytosed by cells and then are excited with alternating current magnetic fields leading to hyperthermia in the cells.

- 5-flurouracil, an antimetabolite, is very effective for the treatment of a wide range of solid tumors. Arias et al. have proposed a technique for the preparation of 5-flurouracil loaded core/ shell particles for drug delivery [31]. They have demonstrated that embedding 5-flurouracil with MNPs during the emulsion solvent evaporation process resulted in higher drug loading and a slower drug release profile. These results indicate that iron/ ethylcellulose nanoparticles are potential carriers for efficient delivery of 5-flurouracil for cancer.

- Bajpai et al. have proposed a method for magnetic nanocomposite hydrogel preparation by in situ synthesis of homogeneously dispersed superparamagnetic nanoparticles in a hydrogel matrix prepared by copolymerization of methyl methacrylate (MMA) onto polyvinyl alcohol [32]. They have used antibiotic drug ciprofloracin, which is diluted with appropriate amount of phosphate buffer saline (PBS) as the drug. They have analyzed the chemical integrity of the drug/ carrier complex and have found that the carrier MNP seems to be a promising carrier for targeted drug delivery applications.

- Hua et al. have prepared three types of MNPs with different proportions of poly-[aniline-Co-N-(1-one-butyric acid) aniline] (SPAnH) shell and $Fe_3O_4$ core and have investigated their drug capacities [33]. They have used these particles to enhance the therapeutic capacity of 1,3-bis(2-chloroethyl)-1-bitrosourea (BCNU) which is used to treat brain tumors. They have investigated the drug loading capacity, activity, stability and in vivo cytotoxicity of bound BCNU and have proved that MNP bound BCNU was more stable than free BCNU.

- Jingting et al. have synthesized $Fe_3O_4$-dextran-anti-β-HCG nanoparticles and have studied their configuration, diameter, iron content and cytotoxicity of the synthesized nanoparticles [34]. They have also examined the efficiency of absorbing DNA and resisting deoxyribonuclease I (DNase I) digestion of these MNPs by agarose gel electrophoresis. The results ensure that $Fe_3O_4$-dextran-anti-β-HCG nanoparticles have the potential as a secure, effective and choriocarcinoma specific targeting gene vector.

- Kempe et al. have synthesized octahedral MNPs using one-pot procedure by precipitation of ferrous hydroxide followed by oxidation to magnetite [35]. These MNPs were silanized with tetraethyl orthosilicate in the presence of triethyleneglycol and/or polyethylene glycol. They have studied the magnetization, hemolytic activity and in vitro evaluation of these MNPs. The results show that these MNPs may be useful for magnetically targeted lysis of in-stent thrombosis.

- Losic et al. have functionalized diatom structures with dopamine modified MNPs (DOPA/ $Fe_3O_4$) in order to introduce diatoms with magnetic properties [36]. They have controlled the motion of the modified diatom by an external magnetic field. They have also explored the drug loading and drug release behavior of DOPA/ $Fe_3O_4$ modified diatom structures to demonstrate their drug release characteristics.

- Wu et al. have evaluated the biocompatibility of self-assembled $Fe_3O_4$ MNPs loaded with daunorubicin (DNR) ($Fe_3O_4$-MNPs/DNR) by hemolysis testing, micronucleus assay and

detection of median lethal dose ($LD_{50}$) [37]. They have used hemolysis testing to evaluate the hemocompatibility of the MNPs. They have used micronucleus assay to evaluate the inherent toxicity of $Fe_3O_4$-MNPs/DNR. Their results suggest that $Fe_3O_4$-MNPs/DNR have good compatibility in mice and hence can be used for chemotherapeutics in clinical therapy in the future.

- Yang et al. have prepared magnetic poly epsilon-caprolactone (PCL) nanoparticles and have studied their surface and size properties [38]. The nanoparticles showed magnetic and superparamagnetic characteristics which were confirmed by transmission electron microscopy (TEM), Fourier transform infrared spectroscopy (FT-IR) and vibrating sample magnetometer. They have encapsulated anticancer drug in the MNP and observed their release behavior for 30 days. Their experiments showed that magnetic PCL nanoparticles have the potential to be used as drug carrier.

- Jain et al. have prepared oleic acid (OA)-pluronic-coated iron oxide magnetite nanoparticle loaded with water insoluble anti-cancer agent [39]. They have observed the release of the drug for two weeks under in vitro conditions. The experiments confirmed the sustained intracellular drug retention relative to drug in solution.

- Chertok et al. have performed surface modification of magnetic nanoparticles with cationic polyethyleneimine (PEI) moieties [40]. They have studied the interaction of these MNPs with 9L-glioma cells in vitro. They have also studied the in vivo benefit of intra-carotid and intravenous administration of these MNP to tumors of 9L-gliosarcoma bearing rats. They have proved that in vitro association of 9L-glioma cells with the synthesized MNPs was 100-fold higher than that with G100. There in vivo brain tumor delivery of MNPs may be promising to enhance the therapeutic potential of tumor specific cytotoxic agents.

- Alexiou et al. have loaded starch coated MNPs with chemotherapeutic agent mitoxantrone and have intra-arterially administered the drug/ carrier complex into tumor bearing rabbits with the help of external magnetic field [41]. They were able to show that with only 20% and 50% of the regular drug dosage they were able to reduce the tumor. They have also showed that there is a 7% fold increase in the concentration of the drug in tumor region compared to regular administration, which is confirmed by high pressure liquid chromatography analysis. The presence of MNPs was confirmed by X-ray imaging.

- Majeed et al. have proposed a method to prepare water soluble magnetic iron oxide nanoparticles (MIONs) using a polymer ligand didecanethiol polymethacrylic acid (DDT-PMAA) [42]. The developed MIONs show high dispersity and superparamagnetism which were characterized by nuclear magnetic resonance (NMR), TEM, X-ray diffraction (XRD) and other methods. The nontoxicity and biocompatibility of the MIONs have been confirmed by the MTT assay. They have also shown that the anticancer drug doxorubicin (DOX) embedded with these MIONs are more efficient than the free drug.

- Shleich et al. have developed paclitaxel/ superparamagnetic iron oxide (SPIO)-loaded PLGA-based nanoparticles for drug delivery [43]. The nanoparticles were approximately 240nm and their properties were characterized by TEM, dynamic light scattering and electron paramagnetic resonance spectroscopy, magnetic resonance and imaging and other techniques. They have also examined the in vitro cellular uptake, cytotoxity and in vivo anti-tumor efficacy.

- Kayal et al. have synthesized and characterized gold coated iron nanoparticles (Fe@Au) [44]. These Fe@Au nanoparticles have been bound to anti-cancer drug doxorubicin (DOX). They have studied the DOX loading and release profile of Fe@Au nanoparticle and in vitro targeting of the synthesized nanoparticles and have shown that DOX loaded gold coated iron nanoparticles are promising for targeted drug delivery.

### 3. Computational modeling and simulation for MNP based drug delivery

The properties of MNPs such as size, shape and the range of MNPs available demands the optimal selection of MNP and their properties which will make the MNPs and appropriate drug carrier. An optimal and efficient MNP based drug carrier design is very crucial for targeted drug delivery. The magnetic transport and MNP based drug carrier and delivery of drugs at the target site depends on a number of factors including magnetic force, interactivity, inertia, buoyancy, thermal kinetics and other characteristics. Issues such as cell selectivity and adhesion efficiency can be improved if appropriate MNPs are designed by controlling their size, shape and compositions. Designing these drug carriers using experiments is time consuming and a challenging task [45]. Hence computational modeling becomes crucial for designing the properties of the MNPs and in predicting their behavior as a drug carrier. The shape, size, surface and other properties of MNPs can be tuned through computational designing so that they are efficient in delivering the drug to the target site. But the drug delivery is complex and challenging due to complex vascular geometrics and physiological conditions at the target site.

A multiscale model is essential to associate physical/ chemical properties of ligand-receptor in nanoscale (particulate model) and to model the adhesion/ detachment rates in macroscale (continuum model) [9, 46]. Multiscale modeling can be used to optimize that parameters required for designing drug carriers based on MNPs. It can take into consideration the nanoscale effects and the behavior of the MNPs.

Computational fluid dynamics (CFD) is widely used to solve continuum scale equations. CFD enables us to qualitatively and quantitatively predict the fluid flows through mathematical modeling and numerical methods. Various methods such as finite difference methods (FDM), finite element methods (FEM) and finite volume methods (FVM) are used to solve CFD [47]. FEM is one of the widely used methods due to its boundary conditions and efficiency in handling irregular shapes [9]. Finite element model has been used to quantify the magnetic force and Stokes drag force [48] and to model the magnetic flux density as magnetostatic problem [49]. With regard to MNP based targeted drug delivery, CFD has been combined with in vitro release profile of drug transport [45].

There are various mathematical models available to demonstrate the drug release and dissolution such as zero order, first order, quadratic, Hopfenberg and Logistic models [50]. The simplest of these models is zero order kinetics model which assumes that the release rate is independent of the concentration of the drug and is a very slow process. In the case of first order kinetics model, the release rate is dependent on the concentration of the drug. Any one or more of the drug release models are used to model the MNP based drug release process [51]. The dynamic transportation and adhesion of MNPs can be simulated using Brownian dynamics method.

Any material structure can be modeled and simulated by solving the quantum-mechanical Schrodinger equation [6]. A number of modeling techniques such as ab initio methods, MD simulation and MC simulation are available to model the MNP structure and their properties. Ab initio methods are wide used to predict the properties of nanoparticle based drug delivery systems. The density functional theory (DFT) is a widely used method to simulate hundreds of atoms without any experimental input [9]. MD simulation is used to calculate the time-dependent behavior of the system such as the positions of particles and forces acting on them at different time intervals [6]. It

is based on integration of Newton's equations of motions. MC simulations are mainly used to obtain numerical results of a system which involves one or more probabilistic entity [52].

Quantitative structure-activity relationship (QSAR) models can be used to predict the biological activity of nanoparticles by considering their properties [53]. Recently nano-QSAR models are also being developed to model and predict the behavior of nanoparticles [54].

Following are some of the computational modeling and simulation work done using MNP:

- Wang et al. have developed a finite element model of MNP binding to the magnetizable stent for drug delivery [55]. They have used this model to study the effects of external magnetic field, MNP size and flow velocity on trapping MNPs. They have demonstrated the mechanism of magnetic force in certain regions and have shown that magnetic force can either attract MNPs towards or repel MNPs away from the stented surface.

- Kayal et al. have studied the deposition of polyvinyl alcohol (PVA) coated magnetic carrier nanoparticles (MCNPs) in a tube under the impact of an external magnetic field [56]. They have used time dependent CFD simulations to study the salient features of MCNP deposition mechanism. The results show that for a strong magnetic field MCNPs can undergo high shear forces as they move along the tube wall. The results also indicate that deposition of MCNP is less in targeted location and the loss is more when the flow rate is high or under a weak magnetic field.

- Han-dan et al. have simulated a three dimensional aneurysm blood vessel along with ferrofluids flow and have studied their characteristics using CFD [57]. They have performed numerical simulations in a water-soluble ferrofluid in a simplified tube with a bulge. The results indicate that ferrofluid flow rapidly and slow down near the aneurysm bulge region when no magnetic field is applied. The results also indicate that the enhancement of magnetic field intensity could slow down the velocity of ferrofluid and increase the retention of ferrofluids at the target position.

- Hoare et al. have observed that the drug release rate occurred according to zero order kinetics models across magnetically-triggered nanocomposite membranes containing nanogels and superparamagnetic nanoparticles [51].

- Nacev at al. have stated and solved the equations governing diffusion, convection and magnetic transport of nanoparticles in the blood and in the nearby tissue in order to model the behavior of nanoparticle in and around a single blood vessel [58].

- Shah et al. have combined Brownian dynamics method with adhesion kinetics model and have simulated the dynamic delivery process in different vascular flow conditions [59]. They have studied the adhesion processes, trajectories, binding probability of non-spherical nanoparticles.

- Mahmoudi et al. have used FEM to study the impact of the magnetic field on superparamagnetic iron oxide nanoparticle SPION) in a simulated blood vessel [60].

## 4. Summary

The unique properties of MNPs and the wide range of MNPs available are the main reasons to use MNPs for drug delivery. A lot of research work is currently being carried out to design MNPs in such a way that their features can be tuned to make them efficient drug carriers. Understanding the

properties and the behavior of the drug delivery system will enable us to design efficient MNP based drug carrier. This in turn will help in the diagnosis and proper treatment for a number of diseases. Computational tools help us in understanding the characteristics of MNPs and in tuning their properties to make them suitable for drug delivery. These tools are cost effective and less tedious compared to the experiments conducted on the MNPs. This chapter provided a brief review of various properties of MNPs, their applications as drug carriers and challenges in using them for drug delivery. Further this chapter provided some insights on various computational tools which aid in modeling MNP drug delivery and in designing MNPs for efficient targeted drug delivery.

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