# Chapter 7
# Surface Modification of Magnetic Nanoparticles in Biomedicine


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**Abstract** Nanobiotechnology is proven for its advantage in several applications including applied biomedicine. The application of nanobiotechnology is possible in many aims such as drug and diagnostic test developments. Many new nanoparticles are developed and applied at present to serve those purposes. In this specific chapter, the author will focus on the surface modification of magnetic nanoparticles which pose specific properties of nanoparticle and magnetic property.

The application of surface modification of magnetic nanoparticles for pharmaceutical process as well as diagnostic test development will be summarized and presented in this article. Summary on important reports on the mentioned specific topics is also given in this article.

**Keywords** Nanobiotechnology · Surface · Modification · Magnetic · Nanoparticle

## 1 Introduction

Nano means the very small level at $10^{-9}$. At this level, the substance will have many interesting nanoproperties, which can be useful for usage. At present, nanobiotechnology is proven for its advantage in several applications including applied biomedicine. In general, nanomaterials that are very small will have significant increased surface area compared to the same material in big size. Also, the nanomaterials have specific change of electric and biochemical properties. In addition, the extremely small size lets the particles to be able to freely cross the cellular barrier into intracellular environment and further affect the cell. It is proven that the

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nanoparticle can successfully enter in several cells including white blood cell [1], lymphocyte [2], or renal cells [3]. The change of the cells after getting nanomaterials inside is the important physiological change, and this is the principle of application of nanomaterials in nanomedicine. In biomedicine, the application of nanobiotechnology is possible in many aims such as drug and diagnostic test developments. For pharmaceutical purpose, the nanomaterials can help in drug transfer and targeting the pathological site. In diagnostic medicine, the nanoparticles can help stimulate diagnostic reaction and help analytical process.

Many new nanoparticles are developed and applied at present to serve those purposes. Of several presently available nanoparticles, magnetic nanoparticles are specific nanoparticles which have specific dual properties of nanoparticle and magnetic property. This dual property is very interesting and becomes very useful for application in biomedicine. The application of surface modification of magnetic nanoparticles for pharmaceutical process and well as diagnostic test development will be summarized and presented in this chapter. Summary on important reports on the mentioned specific topics is also given in this article.

## 2 What Is a Magnetic Nanoparticle?

Before a further discussion on using magnetic nanoparticle in biomedicine, the details about this kind of nanomaterial should be mentioned. Generally, a magnetic substance means a substance that can present magnetic property. Due to the intrinsic electric current and magnetic moment, the ferromagnetism is the basic characteristic of a magnetic substance. Basic interaction test for magnetic property can be done and helps confirm the magnetic property of a substance. The examples of magnetic materials are iron, nickel, and cobalt. It is no doubt that there are some extremely small magnetic substances and if the substance is at nanolevel, it will be called a nanomagnetic substance or magnetic nanoparticle.

Magnetic nanoparticle is a specific group of nanoparticle that has magnetic property and can be manipulated by magnetic fields. There are usually two main components of a magnetic nanosubstance, the magnetic part and nonmagnetic part. Hence, the magnetic nanosubstance is usually a nanomaterial complex. In that complex, the magnetic parts might be a magnetic material such as iron or cobalt or other specifically designed chemical component with magnetic property. Since the magnetic nanoparticles are usually complex, the size of the complex is usually larger than a simple nanoparticle. The average size of the magnetic nanoparticle is usually 50–100 nm. The nanomagnetic complex is sometimes presented in the form of magnetic nanobead that is an important nanosubstance in the present day. The magnetic nanobeads become widely used in several purposes such as catalysts in industry or applications in biomedicine. For biomedical application, the magnetic nanosubstance can be used for both diagnostic and therapeutic purpose. Similar to other nanosubstances, the usefulness of application of magnetic nanosubstance is usually for the disease that is very hard to manage in clinical practice such as cancer [4].

## 3 How Can a Magnetic Nanoparticle Be Applied in Biomedicine?

An important basic question in nanomedicine is "How can a magnetic nanoparticle be applied?" This question can be easily answered in the following. First, there must be a magnetic nanoparticle that is appropriate for application. For using in pharmaceutical process, the specific magnetic nanoparticle must have specific biochemical property that can be useful in disease management. The developed magnetic nanoparticle will be conjugated with drug to form the nanodrug. That finalized magnetic nanoparticle is hereby called a nanodrug. The nanodrug usually has a very small size to allow its biochemical reaction on cells when it is applied for pharmacological purpose. The second step that requires for completing the usage of magnetic nanoparticle as drug is the nanoparticle administration. Generally, there are many ways for nanoparticle administrations of drug such as oral intake, inhalation, dermatological application, or direct injection into blood vascular or body space. This is a requirement for using any nanodrug. If the administration of the nanodrug into the body is not possible, it will be useless. Hence, there must be a good preparation of the magnetic nanoparticle in order to allow feasibility of administration. Similar to any drugs, the next concern is on the bioavailability of the magnetic nanosubstance. There must be a trial to confirm that the newly developed magnetic nanosubstance-based drug can be effectively absorbed, distributed, and targeted at the drug target (Fig. 7.1).

For using in diagnostic medicine, the similar first step is there must be the appropriate magnetic nanoparticle. The nanoparticle must be adaptable to be used in the diagnostic tool formation. The next concern is the durability of nanoparticle. The good nanoparticle should last long, and there should be no decreasing of properties after usage. In addition, there must be no or very little interference on using the nanoparticle. These are basic concerns in development of any diagnostic tools in investigative medicine. The next step for consideration is the actual application of the nanosubstance to be a composition of the newly developed nanodiagnostic tool. The attachment of the nanoparticle must be easy, and there should be very little loss during the process. The standard method for evaluation of the new medical diagnostic test is needed for verifying the acceptability of any new nanodiagnostic tool [5–6]. The standard evaluation for diagnostic properties (threshold sensitivity, accuracy,

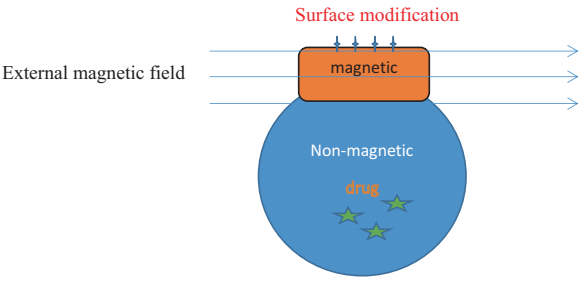


**Fig. 7.1** Figure showing a magnetic nanoparticle complex (graphic drawing by Wiwanitkit V, 2018)

precision, interference, reproducibility, etc.) and clinical application properties (diagnostic sensitivity, specificity, false positive, false negative, etc.) is needed.

## 4 Preparation of Magnetic Nanomaterials for Use as Nanodrug

As already mentioned, magnetic nanomaterials are considered as useful nanoparticles for application of the clinical therapy [7, 8]. The main required pharmacological reaction of a magnetic nanosubstance is its magnetic property. This action is aimed at the target cell. The effect of external magnetic field is used as important part in therapeutic process [7]. The remote control of the nanoparticles accumulation by mean of an external magnetic field is the basic concept [7]. For targeting the pathological cell for treatment, the magnetic drug targeting (MDT) by effect of an external magnetic field to target is the main process [7]. Additional technology can also be used to help increase effectiveness in drug targeting. The good example is the controlled-release technology for allowing the magnetic nanodrug to have its pharmacological action at the diseased site. Nevertheless, there is still an important precaution on the unwanted adverse effect of the newly designed nanoparticle. There are some toxicological concerns including unpredictable cellular responses and induction of signaling pathways, induction of unwanted oxidative stress, aberrant gene expression profiles, and disturbance in biometal homeostasis [9]. Hence, there must be the good modification of the developed particle to get the final nontoxic magnetic nanosubstance for nanodrug development. For modifying, the surface modification is proven effective. The surface modification might be by several techniques. However, there are only three main processes, increasing the surface structure by adding additional parts (such as antibody conjugation, surfactant coating, polymer coating, ligand anchoring, adsorption), decreasing the surface structure by removing some parts, and substitution of the old structure with the new one. Nevertheless, the most widely used approach is the increasing structure parts. The modification might be by chemical, biological, or physical reaction. The advantages from modification include decreased unwanted side effect and increased stability or addition of new desired property of the molecule (such as ligand binding or immunological linkage).

With surface modification, the adverse effect due to magnetic property of nonmodified magnetic nanoparticle can be managed. For example, Strehl et al. recently proposed for a cross-linkage to reduce the unwanted cytokine induction due to magnetic nanoparticles [10]. The hybrid polymeric-magnetic nanoparticles resulting from surface modification is proposed as the present safe generation of magnetic nanoparticle [11] (Table 7.1).

The good examples of magnetic nanoparticles that are used in therapeutic process are metal oxide nanoparticles. A widely used nanoparticle includes superparamagnetic iron oxide nanoparticle (SPION). Structurally, a SPION has an iron oxide core, which is usually coated with organic materials such as polysaccharides, fatty

**Table 7.1** Some important hybrid polymeric-magnetic nanoparticles

| Hybrids | Details |
|---|---|
| Dendrimer-based magnetic iron oxide nanoparticle [12] | Dendrimer-based magnetic iron oxide nanoparticle is a nanohybrid that has both functional organic and inorganic properties. It can be used in several biomedical applications, such as magnetic resonance (MR) imaging, drug and gene delivery, and protein immobilization [12] |
| Multifunctional magnetic iron oxide nanoparticles/ mitoxantrone-loaded liposome [13] | The multifunctional magnetic iron oxide nanoparticles/ mitoxantrone-loaded liposome is a new hybrid that is used for both diagnosis and treatment (such as for both MR imaging and targeted cancer therapy). This hybrid can serve the need in present new concept of theranostics [13] |

acids, or polymers. The coating is aimed at increasing colloidal stability and reducing separation between particle and carrier medium [7].

Some important reports in development of SPION are presented in Table 7.2.

There are many interesting reports on preparation of magnetic nanomaterials for using nanodrugs. The important application in several fields of clinical medicine will be hereby summarized.

(a) Reports in oncology

The development of new magnetic nanodrug usually aims at management of presently untreatable diseases, especially for cancers. The development of the magnetic nanomaterial for management of cancer is widely done at present. For example, Klein et al. reported the use of magnetite and cobalt ferrite nanoparticles for enhancing reactive oxidative stress formation in radiation cancer therapy [18]. Zhang and Song reported the use of combination therapy using an injectable, biodegradable, and thermosensitive polymeric hydrogel. In this system, a complex based on positively charged tumor necrosis factor-related apoptosis-inducing ligand and hydrophobic SPIONs complexed with negatively charged poly(organophosphazene) polymers via ionic and hydrophobic interactions is used in hyperthermia cancer therapy [19]. Based on the given examples, it might conclude that the magnetic nanomaterials are effective option for cancer management. The good design of magnetic nanodrug is the important determinant to achieve safe and effective magnetic anticancer nanodrug.

**Table 7.2** Some recent publication on development of superparamagnetic iron oxide nanoparticle

| Authors | Details |
|---|---|
| Singh et al. [14] | Singh et al. reported on development of SPIONs via direct conjugation with ginsenosides [14] |
| Miranda et al. [15] | Miranda et al. reported on development of inhalable SPIONs in microparticulate system for antituberculosis drug delivery [15] |
| Silva et al. [16] | Silva et al. reported on development of a new antitumor compound based on rhodium(II) succinate associated with SPIONs coated with lauric acid/albumin hybrid [16] |
| Muzio et al. [17] | Muzio et al. reported on development of a new SPIONs coated with silica and conjugated with linoleic acid which has an antitumor property [17] |

(b) Reports in neurology

There are also some interesting reports on preparation of magnetic nanomaterials as new nanodrugs in neurology. Most applications are also the same as the already mentioned one in the topic of clinical oncology, the treatment of brain malignancy. For example, Babincová et al. reported on application of albumin-embedded magnetic nanoheaters for release of etoposide in combined hyperthermia and chemotherapy of glioma [20].

In non-oncological neurological disorder, the magnetic nanoparticles are also applicable for management of degenerative diseases such as Alzheimer's disease. For example, Do et al. reported on using magnetic nanocontainers for treatment of Alzheimer's disease with use of electromagnetic, targeted drug-delivery actuator [21]. Nevertheless, most present applications for neurodegenerative disease are usually on imaging diagnosis.

(c) Reports in infectious medicine

There are also some interesting reports on the preparation of magnetic nanomaterials as new nanodrugs in infectious medicine. The good example is the use in management of tuberculosis. As earlier mentioned, Miranda et al. developed a new inhalable SPIONs in microparticulate system for antituberculosis drug delivery [15]. Another good example is the use in HIV management. Williams et al. recently proposed a new approach for radication of latently infected HIV-positive cells by using magnetic field hyperthermia and SPIONs [22].

The efficacy of magnetic nanomaterials in treatment of microbial infection is proposed to be due to the similar process as that seen in malignant cell management.

The main actions of the nanoparticles are damaging the cell wall or by generating reactive oxygen species [23].

Based on the mentioned application in clinical medicine, it can be summarized that the present trend of using magnetic nanomaterial preparation is for the management of pathology at deep hard-to-access organs or of the disease that can be presently cured by classical therapy. The magnetic nanocomplex is usually designed and prepared to serve the different specific needs in treatment of different clinical problems. Several attempts on clinical trials have been done for many years, and it is aimed at finding new nanodrugs based on magnetic nanomaterials. Although there is still no commercially available magnetic nanodrug, it might be available within the next few years.

## 5 Preparation of Magnetic Nanomaterials for Use as Nanodrug and Theranostics

As already mentioned, the application of magnetic nanomaterials in diagnostic process is possible. The interesting concept is the combined diagnosis and treatment. This is called theranostics. For single use in diagnosis, the application in

imaging investigation is well described. The magnetic nanoparticle is widely applied for MR imaging at present [24]. In addition to basic MR imaging, the advanced technology also allows the use of magnetic nanoparticles as tools for helping molecular imaging. The imaging of cells is presently possible with use of magnetic nanoparticles [25].

As a substance with magnetic property, it is no doubt that manipulation of magnetic nanoparticle during MR imaging is possible. Also, if the magnetic nanodrug is well prepared (including ligands design for targeted delivery and fluorescent or other chemical tagging) and used, the final theranostic property can be achieved [26].

## 6 Conclusion

The magnetic nanomaterials can be served as important basic materials for developments of new nanodrugs and nanodiagnostic tools. The application of magnetic nanomaterials is proven useful for management of several medical problems. The design of magnetic nanomaterials is an important step for further application. This process must be carefully performed, and there must be specific consideration during formation to focus on the desired final product and prevent possible unwanted toxicity. The effective nanoformulation can be useful in both pharmaceutical and laboratory diagnostic developments. For formation of an effective nanodrug, the well-designed magnetic nanomaterials can support nanodrug administration, nanodrug delivery, targeting, and pharmacological acting. The magnetic nanomaterial-based nanodrug becomes the present hope for management of uncurable disease (such as malignancies) and effective approach to hard-to-access pathological sites (such as central nervous system, ocular and joint spaces). The good magnetic nanomaterials are stable in extracellular environment and have the preferable pharmacological reaction in the targeted cells. There are many compositions of the new magnetic nanomaterial complexes that are proven for different advantages. Some newly developed magnetic nanomaterials are already registered and used as the main composition of the new commercially available drug for clinical usage. Similarly, the application of the magnetic nanomaterials in the development of new medical diagnostic analyzer is based on good design and formation of the nanomaterials. The good magnetic nanomaterials are stable and give accurate diagnostic result when applied for diagnostic purpose. Some newly developed magnetic nanomaterials are already registered and used as the main composition of the new commercially available medical diagnostic tool. Although there are many reports on the development and use of magnetic nanomaterials in clinical medicine, further researches and developments in this area are still necessary.Conflict of InterestNone.

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