ISSN 2521-0521

JOURNAL OF CONTEMPORARY PHARMACY
Volume 3: Issue 1: 2019

PREPARATION, COMPONENTS AND APPLICATION OF MAGNETIC NANOPARTICLES: A REVIEW

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Submitted 19 June 2019, accepted 8th July 2019

ABSTRACT

In the recent past, the targeted drug delivery has gained attention for various advantages. Among which magnetic nanoparticles are most important offering local drug delivery, reduced side effects and controlled drug release for prolonged period of time minimizing problems of healthy tissue damage, drug wastage. An approach was made here to review the concept of magnetic nanoparticles, their components, coating material used, there methods of preparation and characterization techniques. This review also deals with the routes of administration as well as the biomedical applications of magnetic nanoparticles. Challenges faced in magnetic drug delivery due to limitations of magnetic nanoparticles have also been addressed.

Keywords: magnetic nanoparticles, preparation, components, applications

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INTRODUCTION

Magnetic nanoparticles are of size less than 100 nm that can be manipulated under the magneticfield **[1]**. They have controllable sizes which are smaller or comparable to cell, protein, virus or gene. Because of which they can come closer to biological entities **[2]**.

They have two essential features: Nano-scale dimensions and Magnetic properties. Nano-scale dimensions of particles allow them not only to pass through the narrowest blood vessels but also penetrate through cell membranes when necessary. Their magnetic properties allow them to be manipulated by an external magnetic field, which can drive them to the target organs where the active biomolecules, bound to the surface of these nanoparticles, can then be released **[3]**. Magnetic nanoparticles offer the advantage of super paramagnetism, not keeping magnetized after the action of magnetic field, which reduces the chances of particle aggregation. Drug targeting through nanoparticles decrease the wastage of drug, drug administration frequency as well as reduce the side effects by providing prolonged and sustained drug release **[1]**.

Magnetic nanoparticles have wide variety of biomedical applications like a) cellular therapy b) targeted drug delivery c) tissue repair d) magnetic resonance imaging and d) hyperthermia treatment of cancer. To make the therapeutic treatments effective, transition metals (e.g. Fe, Co, Ni) or metal oxides (e.g. Fe3O4, g-Fe2O3) are used to achieve magnetization. Small iron oxide nanoparticles are used for in vitro diagnosis for about 50 years. Nanoparticle surfaces must be modified to improve biocompatibility and reduce aggregation **[4]**.

COMPONENTS

Magnetic nanoparticle consists of following parts: 1) A magnetic core 2) Protective coating 3) Organic linker 4) Active molecule

Magnetic Core

At the center is the magnetic core which is responsible for the magnetic properties of these particles. The composition of the magnetic core is dependent on the application. For medical applications, we use ferromagnetic materials because they are strongly attracted by a magnet as well as it shows super paramagnetism at room temperature **[3]**.

Ferromagnetic Materials

These materials are strongly attracted by the magnet when placed under a magnetic field and preserve magnetic properties even after the magnetic field is removed e.g. Iron, cobalt and nickel **[5]**.

Super Para Magnetism

When the size of a ferromagnetic material is reduced below a critical value, it will become single domain means all the magnetons will be aligned in a single direction. When the size of single-domain particles is

further reduced, particles become superparamagnetic means they become magnetic in the presence of an external magnet, but revert to a nonmagnetic state when the external magnet is removed giving magnetic nanoparticles unique advantage of working in biological environments **[5]**.

Classes of Ferromagnetic materials

There are three classes of ferromagnetic materials that are mostly used as core. There pros and cons which are discussed in table 1 **[6]**.

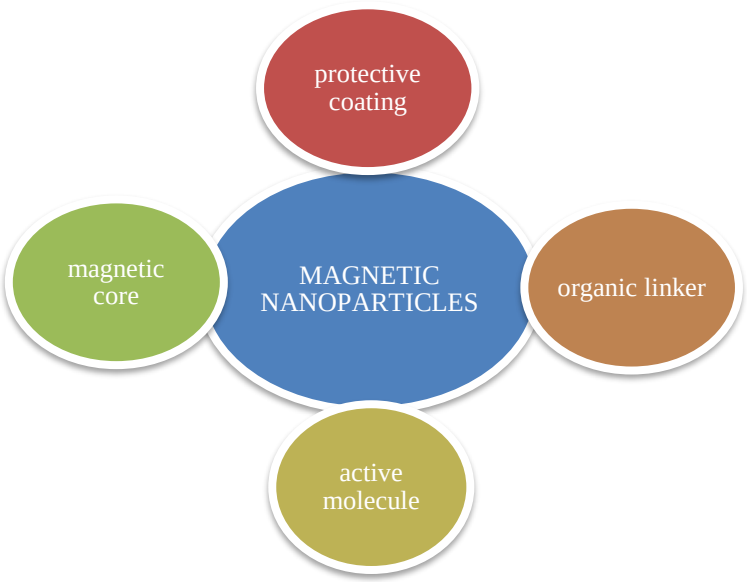

Figure 1: Components of magnetic nanoparticles.

Table 1: Classes of ferromagnetic materials used.

Material	Description
Metals	The only metallic elements showing ferromagnetism at room temperature are iron, cobalt, and nickel. They show promising magnetic behavior for medical applications but they are prone to oxidation as well as they are highly toxic and unlikely to be used as biomedical agents in vivo without a protective coating with high mechanical strength.
Alloys	This group includes CoPt, Fept, FeNi, or FeCo. The preparation of magnetic nanoparticles by ferromagnetic alloys is described in the literature but none has found access in medical applications mainly due to two facts 1- Potential agglomeration of the particles 2- Contain toxic components (e.g., Ni or Co)
Oxides	They include magnetite (Fe_3o_4), maghemite (γ-$Fe_20_{3)}$ and barium-, strontium- or cobalt-ferrite. First two are safe and are in use and one of the most suitable materials because they are least likely to cause health hazards. Whereas barium, strontium or cobalt-ferrite exhibit strong magnetic properties similar to magnetite and can be used as magnetic cores but they are highly toxic.

Protective Coating

Magnetic core nanomaterials need to be coated; To stabilize magnetic nanoparticles, protect the magnetic core against oxidation, enable chemical functionalization of MNPs prevent the leaching of potentially toxic components into the body during invivo applications.

There are three classes of coating materials, each class has its own pros and cons as mentioned in table 2. Choice of a coating material depends on the nature of the coating and the ease of further functionalization to suit specific applications **[7]**.

Organic Linkers

Without surface modification, biomolecules may not bind to the magnetic nanoparticles. Even if they do, the interaction between biomolecules and the surface of nanoparticles can be very weak, resulting in instant release of these molecules during the delivery with little control. As a result, surface modification is necessary. Modification through organic linkers is commonly used, as organic linkers provide a wide range of surface properties to suit various biomolecules in many conditions. Common organic linkers used are amines, carboxylic acids, aldehydes and thiols **[3]**.

Table 2: Classes of coating materials used**.**

Class	Names	Description
Polymeric	Polyethylene glycol (PEG) Polyvinyl alcohol (PVA) Poly lactic-co glycolic acid (PLGA), Gelatin, dextran, chitosan	Polymeric coating enhances the blood circulationtime, increases the colloidal stability, prevents from the coagulation and most important improves the biocompatibility.
Non-polymeric	Oleic acid Stearic acid Lauricacid	Polymer coating increases the thickness of the surface layers. So, researchers used non-polymeric coatings to produce homogeneous coatings.
Inorganic materials	Gold Silica	Helps in binding the various biological ligands at the nanoparticle surface along. With providing stability to the MNPS in solution.

Table 3: Comparison of methods of preparation.

Techniques	Principal	Product Morphology	Advantages	Disadvantages
Physical	Deposition of Gas phase	Spheres and irregular	Easy to execute	Problematic in controlling the size of particle
	Electron beam lithography	Spheres and rods	Well controlled interparticle spacing	Requires expensive and highly complex machines
Chemical	Co-precipitation	Spheres	Simple and effective	Nanoparticles are of broad size distribution.
	Thermal Decomposition	Spheres, cubes	Narrow size distribution Little solvent involved	Coating can be difficult. Control of particle size is difficult.
	Microemulsion method	Spheres	Narrow size distribution Good shape control	Low yield
Biological	Microbial Incubation	Small platelets, spheres or rod-like spheres, irregular spheres	Good reproducibility and scalability, high yield, and low cost	Slow and laborious

METHODS FOR PREPARATION

There are three methods of preparation of magnetic nanoparticles: 1. Physical, 2. Chemical, 3. Biological **[8].** In physical method, a solution of ferric salts and a reducing agent in organic solvent is sprayed into a series of reactors; where the aerosol solute condenses and the solvent evaporates. The resulting dried residue consists of particles whose size depends upon the initial size of the original droplets. Maghemite particles with size ranging from 5 to 60 nm with

different shapes have been obtained using different iron precursor salts in alcoholic solution. Electron beam lithography is based on the resonant interaction between laser photons and at least one gaseous species, reactant or sensitizer. A sensitizer is an energy transfer agent that is excited by absorption of CO_2 laser radiation and transfers the absorbed energy to the reactants by collision.

In Co-Precipitation method, $FeCl_3 \cdot 6H_2O$ (0.3 Mol) and $FeCl_2 \cdot 4H_2O$ (0.15 Mol) are dissolved in 50mL of deionized water. The mixture of Fe^{3+} and Fe^{2+}in solution is added slowly to a 2M NaOH solution while stirring, with the pH kept at less than 10 at room temperature. The solution is sonicated for a further 60 minutes at room temperature. The particles are filtered, washed three times with deionized water, and dried **[9, 10]**.

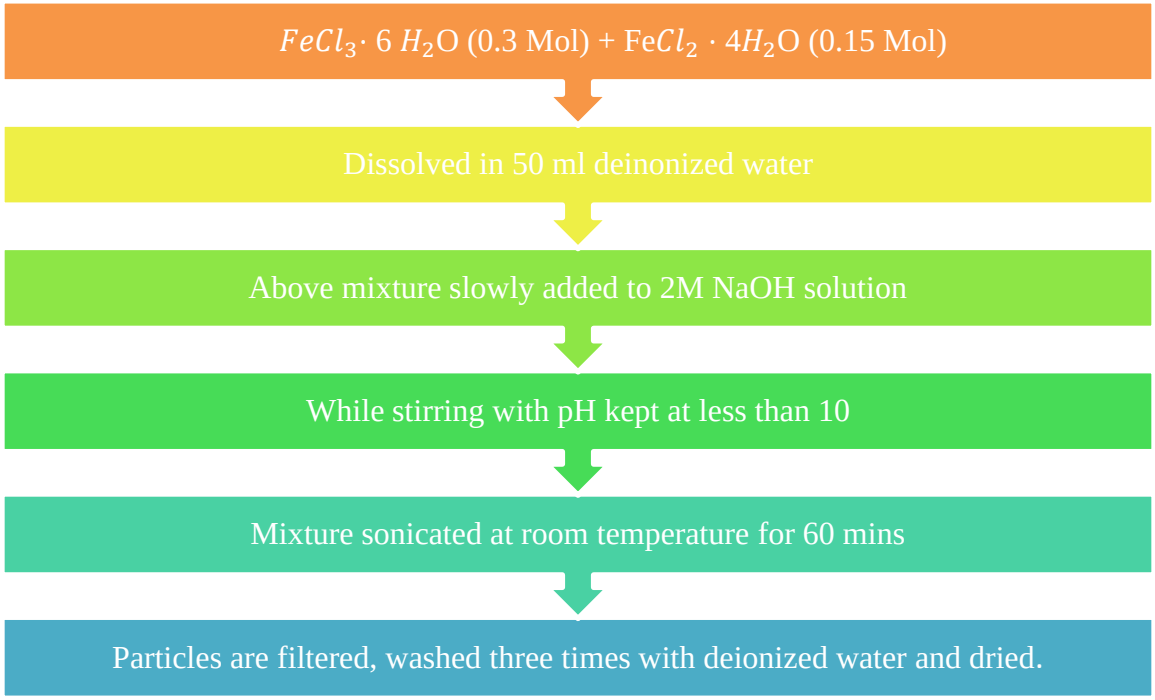

Figure 2: Co-precipitation technique to prepare MNPs.

Thermal Decomposition involves the chemical decomposition of the iron precursors at elevated temperature followed by the breaking of the chemical bonds. In this method we decompose iron precursors in high-boiling organic solvents with the help of stabilizing surfactants. Organic solvents used are benzyl ether, ethylenediamine and carbonyls. Surfactants used are oleic acid, poly vinyl pyrolidone, oleylamine and hexadecylamine **[11]**. In Microemulsion Synthesis two microemulsions containing desired reactants are made. These micro emulsions are then mixed. The micro droplets will continuously collide, coalesce and break again and finally a precipitate form in the micelles. Conceptually, when reactants A and B are dissolved in two identical micro emulsions, they will form an AB precipitate on mixing **[7]**.

CHARACTERIZATION

Following are some most commonly used analytical techniques for characterization:

Transmission Electron Microscopy

Magnetic nanoparticles are characterized for its size by TEM. Transmission electron microscopy (TEM) is used in the determination of particle core size. It reports the total particle size of the core. It provides details on the size distribution and the shape. However, this technique needs an analysis by image treatment, and must be performed on a statistically significant large number of particles. High-resolution transmission electron microscopy (HRTEM) gives access to the atomic arrangement. It can be used to study local microstructures and the surface atomic arrangement of crystalline NPs **[12].** A drop of an aqueous dispersion of magnetic nanoparticles is placed on a Formvarcoated copper TEM grid (300

mesh size) and allowed to air-dry. After that electron beam is passed through it and the image of the particles can be seen on fluorescent screen **[13]**.

Scanning Electron Microscopy

Scanning electron microscopy (SEM) used for the determination of morphology and size distribution of particles in the scales of micro to nano range. Resolution of the SEM is lower than TEM and it is not efficient for NPs with particles size lower than 20 nm **[12]**.

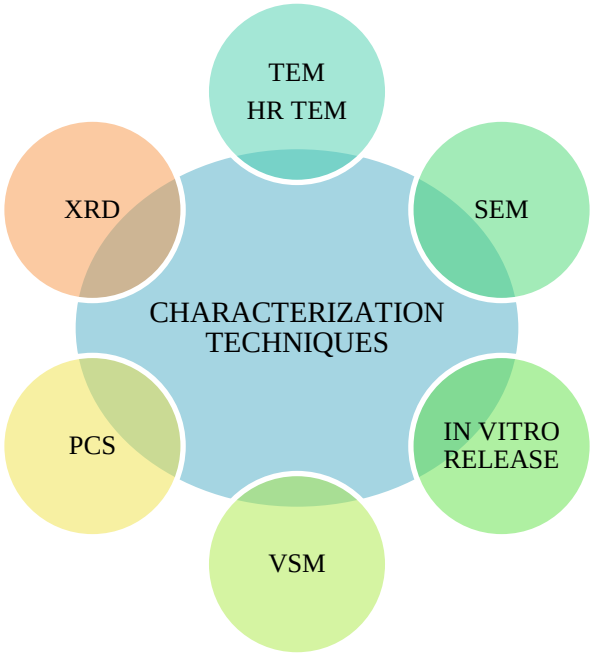

Figure 3: Various characterization parameters for MNPs.

CONCLUSION

Though progress in clinical applications of magnetically targeted carriers has been slow since first introduced in the 1970s but the potential for this technique remains great. Rapid developments in particle synthesis have enabled the use of new materials for more efficient targeting and novel strategies are being developed for applying magnetic fields which could lead to treatments for diseases such as cystic fibrosis and localized cancerous tumors. But there are only a few clinical trials. Magnetic nanoparticles overcome the problem of drug delivery, by addressing the problems of toxicity and localization. This field is still emerging and has a long way to go.

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