Magnetic Nanoparticles for Targeted Drug Delivery

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Abstract. The development of nanoscale technologies has been advancing rapidly over the past few decades, and this has made a significant impact on biomedical fields. Their use as a revolutionary diagnostic and therapeutic approach in many diseases is gaining popularity. Nanostructures represent a successful solution for improved efficacy of established drugs that offer controlled release in a specific targeted area. Nanoscale drug delivery systems (NDDS) have been studied for several decades, and many of the characteristics that make them attractive drug carriers are well known. The potential application of magnetic nanoparticles based on energy storage, catalysis, sensing devices and more has long attracted the interest of scientists. Due to their biocompatibility, non-toxicity, chemical and mechanical stability, and ability for controlled transport, many opportunities are being revealed in the biomedical sector. These types of nanosystems comprise a large class of nanoscale materials with revolutionary potential in diagnostics and therapeutic practice. However, in a considerable number of cases, there are difficulties in mastering the process of creating them and achieving the expected result. The insolubility in aqueous media and the tendency to agglomerate, for example, limit the widespread use of these structures for biomedical purposes. The present review deals with the types of magnetic nanoparticles, the various functional materials and the techniques for their preparation. An analysis of the literature data on the influence of various physical factors and technological variables on the therapeutic potential of the constructed materials, as well as some approaches to improve their effectiveness, has been performed.

Keywords: magnetic nanoparticles, target therapy, drug delivery system, cancer treatment

1. INTRODUCTION

One of the major problems in the treatment of many diseases is the delivery of therapeutic compounds to the targeted site. The conventional application of drugs is characterized by no selectivity, poor biodistribution and limited efficacy. These drawbacks can be overcome by using controlled drug delivery systems (DDS), through which the drug is transported to the site of action with minimized influence on vital tissues and little or no manifestation of side effects (Nevozhay et al., 2007).

Cell-specific targeting can be achieved by attaching drugs to individually designed carriers. The last few decades nanoscience has proved the great potential of nanoparticles as drug carrier. They exhibit unique biological and physico-chemical properties that make them a successful modern tool for therapy and diagnostics.

The interest in nanotechnologies and nanoscale materials, particularly in magnetic nanoparticles (MNPs), is growing due to the possibility for fine tuning and functionalization for specific applications. They allow easy handling with the aid of external magnetic field and expose the possibility for passive and active drug delivery targeting. MNPs provide better uptake by the targeted tissue resulting in effective treatment at therapeutically optimal doses (Aruebo et al., 2007).

Iron oxide NPs and magnetite (Fe_3O_4), due to their biocompatibility, non-toxicity, chemical and mechanical stability and facile synthesis have become popular in oncology. They can be used as cancer therapeutics via drug delivery, biotherapeutic transport, magnetic hyperthermia, photothermal ablation and photodynamic therapy. MNPs occupy important place in personalized medicine as nanoscale modules with specific roles for cancer theranostics, indivi-

dualized NP formulations exhibiting a full-suite of treatment and diagnostic capabilities may be created in an efficient and effective manner. Fig. 1 reveals the multitude of diagnostic and therapeutic features (Revia et al., 2016).

However, in large percentage of cases where MNPs have been used, many difficulties arise in achieving a stable effective drug delivery system. These problems are most likely associated with the tendency of MNPs to aggregate into larger clusters and the impossibility of the magnetic force to overcome blood flow and accumulate drugs only in target tissues.

There are various approaches (chemical and physical) to create more optimized magnetic nanoparticles and enhance their stability, as well as physical methods to improve the action of the magnetic field. One of the most interesting and studied methods recently is to combine several therapies to create one more save, stable and effective therapeutic system.

2. MAGNETIC NANOPARTICLES

According to the definition given by the National Nanotechnology Initiative, nanoparticles are structures of size ranging from 1 to 100 nm in at least one dimension.

It is a well-known fact that nanoscale systems exhibit very good physicochemical and biological properties, making it easier to be absorbed by the cells than larger molecules. The basic core of nanoscale systems can be organic (lipids, liposomes, DNA, viruses, micelles), inorganic (magnetic, gold nanoparticles, quantum dots, carbon nanotubes and fullerenes) or hybrid (a combination of organic and inorganic molecules to which they can more components will be included).

According to the form they are nanospheres, nanorods, nanocubes, nanostars, nanodisks and nanoplates. Each core has specific physicochemical properties, size, shape, surface loading, hydrophobicity, and material properties that can be controlled within certain limits. This makes it possible to optimize the action of the nanoparticles depending on their use (Fig. 2).

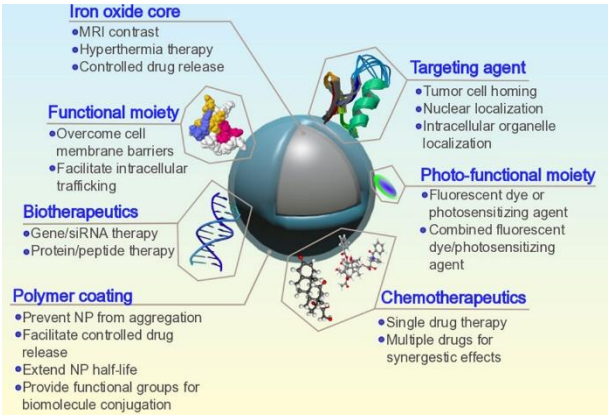

Fig. 1 Schematic illustration of diagnostic and therapeutic features of MNPs; (Revia et al., 2016).

According to the magnetic properties of their cores, MNPs can be separated into pure metals (Co, Ni, Mn, Fe), their alloys and oxides. As an approach to improve the characteristics associated with their application ad drug transport systems, in modern practice, MNPs are encapsulated in substances of different origins - silane, polymers, dendrimers, gold and other. Concerning their biomedical application, the choice of magnetic material is significantly restricted for most of them have a negative effect on the human body. Iron oxide nanoparticles have high potential in anticancer therapy due to their biocompatibility, biodegradability, easy synthesis (facile single step synthesis by alkane co-precipitation of Fe 2+ and Fe 3+), chemical stability in physiological states, and magnetic state. Magnetite and magemite are contained naturally in the human heart, spleen and liver, which is an indicator of biocompatibility and non-toxicity at physiological concentrations (Wilczewska et al., 2012). Some studies have argued that pure Fe and Co metals have advantages over Fe_3O_4 because of their stronger magnetic properties. Unfortunately, pure Fe and Co have poor oxidative stability, they are incompatible with non-aqueous systems and have high toxicity.

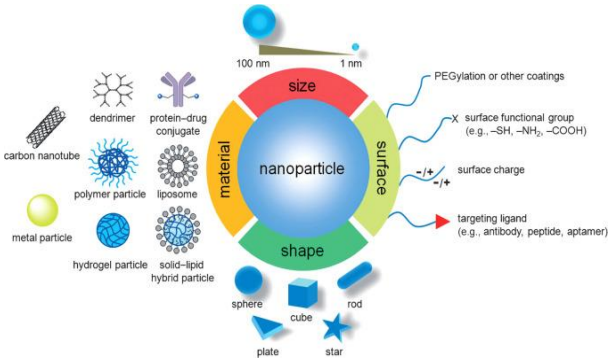

Fig. 2 Types of NPs and their structure.

1. 1. Structure and magnetic characteristics

Iron oxide is found in many pure phases in nature, but the most preferred MNPs are the nanoscale zero-valent iron (nZVI), Fe_3O_4 and γ-Fe_2O_3. They have different iron oxidation states and capability of contaminate removal. Magnetite is the most extensively studied state because of the presence of Fe^{2+} with the potential of acting as an electron donor.

Figure 3 shows all the magnetic states that can occur during iron crystallization (Kodama 1999, Teja and Koh, 2009). The paramagnetic crystal produces randomly aligned magnetic moments and the overall structure has zero net magnetization. When the magnetite in the paramagnetic state is under the influence of an external magnetic field, all the magnetic moments are aligned and weak net magnetization is observed. In the ferromagnetic and antiferromagnetic states, the moments are arbitrarily aligned without the presence of an external field.

The mass of a ferromagnet contains magnetic domains in which uniformly magnetized regions exist. Each domain is separated by non-homogeneous domain-walls with different magnetically polarized vectors. Weak net magnetization is due to the unmatched vectors of each domain (Mohammed et al., 2017).

Many of the benefits of magnetic nanosystems are due to the ability to control their properties using a magnetic field. The importance of the particle magnetic moment and the field gradient is of great importance. Ferromagnetic magnetite is preferred due to the presence of a Fe 2+ state with the potential to react as an electron donor. Spherical nanomagnetite (SPION) with sizes below 20 nm exhibits supermagnet behavior, a feature that is highly sought after in magnetic resonance diagnostics.

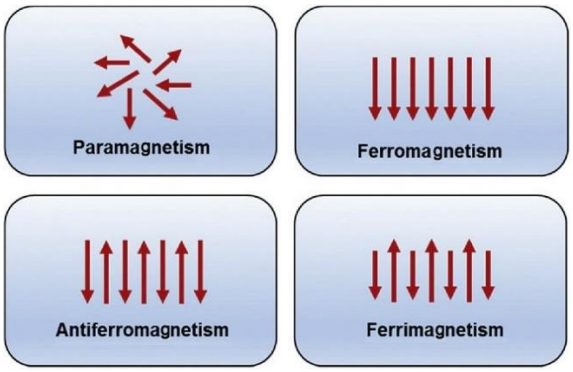

Fig. 3 Alignment of the magnetic moment of individual atoms of iron.

1. 2. Fabrication and modification methods. Connecting drug molecules to the MNP

There are many reviews that reveal various methods of fabrication and synthesis techniques for MNPs, basically classified into the following categories:

1) Physical methods: (a) size reduction to the needed nanometer range and dispersing in an aqueous medium (by classical colloidal routes) and (b) condensations of the precursor from either a liquid or gaseous phase (Charles, 2002). Very important disadvantage of the method is the difficulty of achieving the desired particle size and shape (DeCastro and Mitchell, 2002). A laser ablation or evaporation synthesis method prove to be an extremely effective method of creating powders with relatively uniform sizes of coarse materials and iron blocks (Amendola et al., 2011).

2) Wet chemical preparation methods: includes chemical co-precipitation, sol-gel and hydrothermal reactions, flow injection synthesis, polyol methods, electrochemical and aerosol/vapor methods (Gupta and Gupta, 2005, Veiseh, Gunn & Zhang, 2010), also sonolysys (Laurent et al., 2008), thermal

decomposition (Oh & Park, 2011), hydrolytic and nonhydrolytic methods, microemulsion and laser evaporation methods.

3) Microbial methods – MNPs form in a biomineralization process (Mohammed et al., 2017).

The effective use of MNPs for biomedical use in targeted therapy, for example, depends on many factors related to particle size and magnetic characteristics. Parameters such as physico-chemical properties of magnetic drug-delivery system, strength and geometrics of the magnetic field, depth of targeted tissue, blood flow rate, and vascular supply are extremely important to the efficiency of the method. Increase in magnetic polarization facilitates manipulation within the system.

Many applications of MNPs rely on the use of magnetic field. They depend on the effectiveness of particle magnetic moment and field gradient (Silva, Di Corato, Gazeau, Pellegrino and Wilhelm, 2012). MNPs should be of small size to exhibit supermagnetism, not to agglomerate after switching off the external magnetic field, and continue circulation in the bloodstream without being eliminated by the body's natural defense mechanisms. Supermagnetic nanostructures are preferred because of their ability to magnetize under the influence of an external magnetic field, but they do not retain this property long time after the magnetic field is turned off. Thermal effects in the material also trigger supermagnetism. In the supermagnetic particles, thermal fluctuation is strong enough to cause spontaneous demagnetization.

Coating MNPs with various materials such as amino groups, silica, gold, polymers, surfactants, etc. is another method of affecting physicochemical properties. (Fig. 4) Magnetic core packing improves dispersion, increases oxidation stability and enables the system to be loaded with noticeably larger amounts of drug (within the shell).

In order to avoid rapid clearance from the reticulate system, the particle sizes should not exceed 100 nm. In this regard, the size and surface area of the nanostructures are important for toxicity.

Linking of drug molecules to MNP can be accomplished by electrostatic interaction, covalent binding or encapsulation process (Wilczewska et al., 2012).

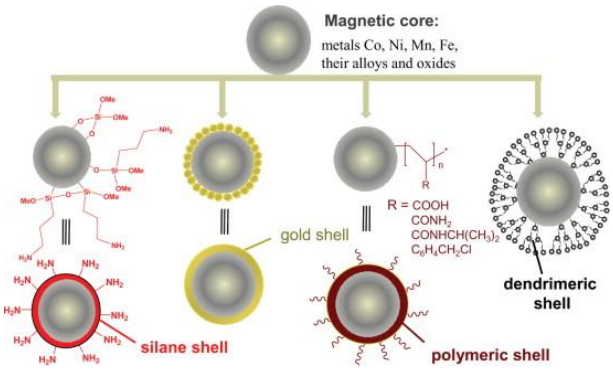

Fig. 4 Magnetic nanoparticles with various shells; (Wilczewska et al., 2012)

1. 3. Characterization of magnetic nanoparticles

Morphology and size of MNPs can be investigated by transmission electron microscopy (TEM) whereas surface characteristics can be examined by scanning electron microscope (SEM).

Fourier-transform infrared spectroscopy (FTIR) can be used to confirm the presence of particular functional groups, for example of Fe_3O_4 NPs. Mean particle size and size distribution, and zeta potential of MNPs can be determined by dynamic light scattering (DLS).

Magnetic properties are generally confirmed in the solid state of MNPs at room temperature using vibrating sample magnetometer (VSM). TEM images are unable to represent the core-shell structure of MNPs if the shell is golden, because the electronic density of gold is much higher than that of iron oxide (Zhou et al., 2012). In this case energy-dispersive X-ray spectroscopy may be used. Thermal properties may be measured by thermogravimetric analysis (TGA) technic under oxygen atmosphere.

3. INDUCED MAGNETIC HYPERTHERMIA

One of the non-invasive techniques used in the battle against cancer is conventional hyperthermia, which is highly effective in destruction of tumor cells but has low spatial selectivity and affects healthy tissues. To overcome this drawback, magnetic properties of Fe_3O_4 NPs could be used to induce localized hyperthermia with the aid of external magnetic field, enhancing Fe_3O_4 NPs efficacy even without functionalization. Temperature higher than 42^oC amends many structural and functional proteins within the cells causing necrosis (Steeves et al., 1992), (C. Christophi et al., 1998).

The combination of photothermal therapy and magnetic hyperthermia, mediated by Fe_3O_4 NP, can eliminate inflammatory macrophages, thus providing a new therapeutic strategy for the treatment of atherosclerosis and vascular stenosis.

Resulting in conversion of electromagnetic resonance energy into heat induction within tumor mass is enough to produce cancer cell apoptosis. Gold-coated magnetic nanostructures are used in the application of hyperthermia for the treatment of cancer. The combination of those three methods – MNPs as DDS, coating MNPs to provide better stability and hyperthermia, has its advantages:

1) The MNP nucleus acts as a magnetic field targeting drug system;

2) The golden flexible sheath can increase the temperature of the affected cells under the action of an IR laser and thus provide photothermal therapy;

3) Photothermal therapy itself facilitates the release of the anticancer drug – if the drug is encapsulated in a heat-labile coating, then we could achieve a controlled release with MNPs when they heat up due to the application of external magnetic field.

4. THERANOSTICS

There are many diseases such as cancer that are characterized by inability of early diagnosis, low prognosis and impossibility of predicting pathological pathways. These deficiencies put patients at increased risk of morbidity and mortality (Setyawati et al., 2013).

The indispensability of single agent that combines therapeutic and diagnostic capabilities with non-toxicity and biocompatibility is growing. The potential of IONPs is powerful due to their unique properties and easy surface manipulation.

They can be used as delivery systems for cell replacement therapy, gene delivery with the aid of external magnetic field or MRI-aided tumor detection or surgical removal. (Shubayev et al., 2009)

5. CONCLUSIONS

Magnetic nanoparticles show promising benefits for biomedical purposes as imaging contrast enhancement and targeted therapeutics for cancer treatment over conventional surgery, chemotherapy and radiation therapy.

Modern medicine strives to discover improved methods of treating various diseases, focusing on a highly personalized approach. The major issue holding back the clinical translation is the lack of control in the different stages of preparation and insufficient tissue selectivity.

In the name of biomedical progress, numerous modifications could be applied to therapeutic or diagnostic agents. The main purpose is to enhance their potential and overcome the limitations. There are improvements in controlling MNPs size, shape and surface modifications. Thanks to them, improved physical and biological properties are obtained, improved magnetic properties are gained, and tissue targeting is accomplished.

The challenge, therefore, is to develop multifunctional nanomaterials that can be integrated into different therapeutic modalities using one nanoplatform, which is considered a new trend in recent nanomedicine research.

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