REVIEW

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Magnetic nanoparticles for antimicrobial drug delivery

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Received December 18, 2011, accepted January 23, 2012

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Pharmazie 67: 817–821 (2012) *doi: 10.1691/ph.2012.1163*

Magnetic nanoparticles (MNP), fabricated by loading a therapeutic agent into a magnetic nanoparticle through encapsulation or adsorption, have gained particular interest during the last decade because of their intrinsic magnetic nature as well as enhanced physicochemical properties. Using their superior specifications MNPs can address the shortcomings of traditional therapeutic agents especially antimicrobials. The aim of this review, therefore, is to focus on the properties, fabrication and most recent finding in the application of MNPs for antimicrobial delivery.

1. Introduction

Alexander Fleming started the antibiotics era with the discovery of penicillin in 1928. Before the early 20th century, traditional medicine played a key role in the treatment of infectious diseases by means of natural remedies. Fleming found that a fungus of the genus *Penicillium* could inhibit the growth of bacteria assuming that this effect could be attributed to the antibacterial compound, he named it Penicillin. He, further, postulated that the antibacterial properties could be applied for treatment of infectious diseases (Fleming 1980; Berton et al. 2001). Despite these outgoing discoveries and contrary to what the US surgeon, William H. Stewart, reported in 1967, "That we had essentially defeated infectious diseases and could close the book of them [infectious diseases]." this book has not been closed so far (Verhoef 2003; Overbye and Barrett 2005). In fact, many infectious diseases, especially intracellular infections, remained difficult to be treated. This is a complicated issue; however the main reasons in this regard can be categorized as the problems of antimicrobial delivery to the active site, their lower activity and stability in the active site as well as their toxicity in healthy tissues. All these problems lead to a significant limitation in antimicrobial use and produce low inhibitory or bactericidal effects against the target bacteria. To overcome these problems, novel drug delivery systems are one of the procedures that have been successfully applied to, so far (Takemoto et al. 2004), among which nanoparticles (NPs) have gained lots of interest over the last few decades.

"Nanotechnology concerns the understanding and control of matters in the 1–100 nm range, at which materials have unique physicochemical properties including ultra small size, large surface to mass ratio, high reactivity, and unique interactions with biological systems" (Zhang et al. 2008). Beside their enhanced and unique properties, nano sized particles have got lots of applications in various eras from electronic devices to medical and pharmaceutical sciences. Indeed NPs, as one of the most fascinating novel drug delivery systems, offer numerous advantages over their ancestors including targeting the drug into the potential active site (Cheng et al. 2007), thus decreasing its side effect, controlling and sustaining the release of the drug at the active site and improving solubility of the drugs (Peer et al. 2007; Zhang et al. 2008). Moreover, pharmaceutical bearing NPs can by the target cells via endocytosis and then release their loads. Also, enhanced and superior surface characteristics of NPs produce some excellent pharmacokinetic properties, which have led to the development of efficient drug delivery systems. These different properties make NPs ideal drug delivery systems for management of severe diseases such as intracellular infections or cancers, thereby overcoming some of the limitations of traditional therapeutics. In fact, a number of NP-based antibiotics and anticancer delivery systems including liposomes, polymeric NPs, solid lipid NPs and dendrimers, and magnetic nanoparticles toward the infected or malignant cells, are currently under various stages of investigation (Heller 1980; Barrera et al. 1993; Mbela et al. 1993; Jain 2000; Murakami et al. 2000; DÃez and Tros de Ilarduya 2006; Hindi et al. 2009; Mohammadi et al. 2010; Chen and Wang 2011). Magnetic nanoparticles (MNP), fabricated by the attachment of a therapeutic agent on or its encapsulation within a magnetic nanoparticle, have gained particular interest during the last decade among other nanoparticle versions. These nanoparticles with their intrinsic magnetic properties address the shortcomings of traditional diagnostic and therapeutic agents (Veiseh et al. 2010).

Having set the ground, this paper provides a review on the properties, preparation procedures as well as application of magnetic NPs for antimicrobial delivery and reports the most recent findings in this era.

2. Magnetic nanoparticles

2.1. Properties and categories

MNPs are one of the leading classes of nanosized materials with the potential to make a great progress in current therapeutic and diagnostic techniques, this great potential comes from their superior physical properties regarding their intrinsic magnetic nature and ability to function at the cellular and molecular level. The concept of MNPs application in biomedical field was first proposed in the late 1970 s (Senyei et al. 1978; Widder et al. 1978; McBain et al. 2008). Basically therapeutic agents attached to or encapsulated within biocompatible MNPs together with magnetic fields generated outside the body and focused on specific targets *in vivo* result in targeting of the particles to the sites intended (McBain et al. 2008; Arruebo et al. 2007).

In general, a MNP is composed of two main parts, an inorganic central core and a biocompatible surface coating which could be functionalized using multiple molecules at its surface for stabilization, under physiological conditions, or other functionalities.

A central core that provides the magnetic specification typically consists of iron oxide including magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), metallics (pure iron and cobalt metals) and Bi-metallic or alloys such as CoPt3 (Shevchenko et al. 2002), FePt (Sun et al. 2000), and FeZn (Grasset et al. 2002) nanoparticles (Sun et al. 2008; Veiseh et al. 2011).

Iron oxide nanoparticles including nanocrystalline magnetite (Fe_3O_4 and MFe_2O_4, where M is + 2 cation of Mn, Fe, Co or Ni) or maghemite (γFe_2O_3) represent a spinel crystal structure in which oxygen ions produce a cubic lattice and iron ions located at interstices. Various synthetic procedures are proposed for this class of MNPs ranging from traditional wet chemistry solution-based methods to laser pyrolysis or chemical vapor deposition (Sun et al. 2008; Tartaj et al. 2003; Gupta and Gupta 2005; Willard et al. 2004; McBain et al. 2008).

Furthermore in this category, superparamagnetic iron oxide nanoparticles (SPIONs) have become fascinating components for a broad range of biomedical applications, mainly due to their special features (Gupta and Gupta 2005; Gupta et al. 2007; Laurent et al. 2008; Mirsa 2008). Generally, when the size of the nanoparticles is below a critical value of typically around 10–20 nm, each nanoparticle becomes a single magnetic domain and represents superparamagnetic behavior above a so-called blocking temperature. Consequently SPIONs with a large constant magnetic moment behave like a giant paramagnetic atom with a fast response to applied magnetic fields which inhibit agglomerate formation at room temperature. In addition, highly reactive surface that can be readily modified with multiple functional molecules (Laurent et al. 2008; Mirsa 2008; McCarthy et al. 2007; Dobson 2006; Veiseh et al. 2010) is another privilege of MNPs that makes them suitable for a wide application in the biomedical field (McBain et al. 2008).

The second category of MNPs, metallics, is made of iron, cobalt, or nickel. The most important limitation of these metallic MNPs is their fast oxidation in the presence of water and oxygen, so they are typically protected by coatings, such as gold or silica, and form a core shell structure. In spite of their instability, some of metallic MNPs have specific properties like the relatively high magnetization capacity and the ability to maintain superparamagnetism at larger particle sizes in comparison with magnetics (Huber 2005; Sun et al. 2008).

Bi-metallic nanoparticles or alloys as the next category of MNPs consist of two different chemical species such as FePt. Due to the interactions between the two different metals, Bi-metallic nanoparticles show higher chemical stability in comparison with their metallic counterparts. In addition, due to the highly reactive surface properties bi-metallic nanoparticles, carboxylate- and amine-based surfactants can be attached to them inorder to improve their water solubility. Several synthetic processes have been explained for this category including vacuum-deposition or solution phase synthesis (Gubin et al. 2005; Sun 2006; Lu et al. 2005; Sun et al. 2008).

2.2. Protective coating

Agglomeration due to the high surface energy, adsorption to plasma proteins (opsonization), oxidation and corrosion are main problems related to the stability of MNPs that can be overcome by surface coating (Berry and Curtis 2003; Sun et al. 2008). Indeed the protective coating (shell) on a magnetic core (core–shell structure) isolates MNPs from their surrounding environment and makes them stable against the adverse reactions and it also reduces the cytotoxicity of these particles to healthy cells and adds some functionality to the prepared particles (Gubin et al. 2005; Lu et al. 2005; Kami et al. 2011).

Basically the coating procedures can be categorized into two major groups: the first group includes coatings with organic shells of polymers (polyethylene glycol and poly-L-lysine, poly propylene and poly ethyleneimine, and poly-L-lactic acid) (Lee et al. 2009; Li et al. 2009; Gonzalez et al. 2011), polysaccharides (dextran, chitosan and heparan sulfate) (Corot et al. 2006; Kievit et al. 2009; Morishita et al. 2005), proteins (serum albumin, streptavidin) (Lee et al. 2009; Hashimoto and Hisano 2011) and surfactants (oleic acid, lauroyl sarcosinate, Pluronic F-127 (Mykhaylyk et al. 2007; Namiki et al. 2009; Pan et al. 2008) and lithium 3-[2-(perfluoroalkyl) (Tresilwised et al. 2010; Kami et al. 2011). The second category of coating material of inorganic components include silica (Kobayashi et al. 2003; Yiu et al. 2010), carbon (Lu et al. 2005) and precious metals such as Ag (Sobal et al. 2002) and Au (Liu et al. 1998; Lin et al. 2001; Lu et al. 2005).

2.3. Synthesis strategies

Various physical (Gubin et al. 2005) or chemical routes including one-step and multi-step procedures for MNPs fabrications have been reported so far (Li et al 2006; McBain et al. 2008). The fabrication procedures range from traditional co-precipitation of metal salts in basic solution to a high temperature organic phase decomposition, liquid phase reduction, reverse micelle mechanism, laser prolysis, and chemical vapor deposition. Overall, all of the mentioned methods have their advantages and limitations, and the method selection should be based on the ingredients, environment as well as available instruments and facilities (Taraj et al. 2003; Gupta and Gupta 2005; Willard et al. 2004; Sun et al. 2008; Chenjie et al. 2009).

3. Antimicrobial properties of MNPs

MNPs application as antimicrobial delivery system to the infected sites is of great importance due to the potential of MNPs in site specific delivery of the antimicrobials. However, another important point here is that most of the fabricated MNPs show intrinsic antimicrobial activity owing to the ingredients used in their fabrication without addition of antibiotics. In fact, there are several investigations regarding this phenomenon and its potential to be utilized for beneficial biological application. It was indicated that different bacterial groups exhibit various susceptibilities to MNPs (Kell and Simard 2007) but the mechanism for the controlling of the toxicity is not well understood yet. Moreover, various factors such as synthesis, shape, size, composition, addition of stabilizer and others can lead to different conclusions even for very closely related MNPs (Gubin et al. 2005).

Chatterjee et al. (2011) prepared iron oxide (Fe_3O_4) and gold (Au) nanoparticles and characterized them using Transmission Electron Microscopy (TEM) and Dynamic Light Scattering (DLS). The phase contrast microscopic study of the effect of the nanoparticles on the growth of *Escherichia coli* demonstrated antimicrobial efficiency of the prepared MNPs. Their results showed an abnormal increase in bacterial cell length, indicated that both Fe_3O_4 and Au nanoparticle extended up the cell division level and consequently inhibit their growth.

Inbaraj et al. (2011) synthesized MNPs modified with sodium and calcium salts of poly(γ-glutamic acid) (NaPGA and CaPGA) by the coprecipitation method. Both NaPGA and CaPGA coated MNPs are shown to have antibacterial activ-

ity against *Salmonella enteritidis*. NaPGA was effective against *Escherichia coli* and *Staphylococcus aureus*, whereas CaPGA was effective against *Escherichia coli* (Inbaraj et al. 2011).

Furthermore, MNPs based on ferrofluid (maghemite) were reported to be elaborated by inverse emulsion crosslinking of sodium salt of carboxymethylcellulose (CMCNa) and gelatin using glutaric aldehyde as a cross linker. The magnetic properties of the particles are demonstrated from saturation magnetization when their superparamagnetic character was shown by the absence of hysteresis on the magnetization curve. In this study also the bactericidal activity was observed for the prepared MNPs without toxicity (Tataru et al. 2011).

In an *in vitro* study, Taylor and Webster (2009) explored the use of SPION to prevent biofilm formation in orthopedic implants. The results showed that the antibacterial activity of SPION alone or in couple with antibiotics against *Staphylococcus epidermidis* could decrease prosthesis infection. Also a lowered colony assembly as a result of SPION treatment could prevent biofilm formation and expansion.

Kong et al. (2010) reported the preparation of ferromagnetic gamma-Fe_2O_3/polyrhodanine MNPs with average diameters of 10 nm. Polyrhodanine encapsulated MNPs were fabricated by a one-step oxidation synthetic procedure and characterized by TEM and X-ray and applied as a recyclable antibacterial agent towards Gram-negative/positive bacteria.

A research team in Taiwan demonstrated a photokilling approach for pathogenic bacteria using MNPs as photokilling nanoprobes. The nanoprobes were composed of iron oxide/titania (Fe_3O_4/TiO_2) core/shell MNPs. The titanium layer on the magnetic nanoprobes was used as a photokilling agent and as an affinity substrate for pathogenic bacteria. According to the report, the prepared MNPs not only have the capacity to target several pathogenic bacteria, but they also can effectively inhibit the cell growth of the bacteria targeted by the nanoparticles under irradiation of a low-power UV lamp within a short period (Chen et al. 2008; Chen and Chen 2010).

Application of titania coated MNPs was also reported in another investigation. Sunkara and coworkers prepared tungsten doped and undoped titania coated nickel ferrite nanoparticles and reported the enhancement of antimicrobial activity of both the titania coated MNPs. They explained that coating of ferrite nanoparticles with titania maintains the superparamagnetic character and magnetic strength of them and leads to decreased deterioration of magnetic properties. It has been concluded that the prepared MNPs can be used as removable antimicrobial photocatalyst nanoparticles (Sunkara and Mirsa 2008).

There is another study about magnetic binary nanocomposites, two types of them including Ag@Fe_3O_4 and γ-Fe_2O_3@Ag, were synthesized and characterized and their antibacterial activities were tested. Based on the results, both synthesized nanocomposites exhibited very significant antibacterial and antifungal activities as well as non toxicity against mice embryonal fibroblasts at the related concentrations (Prucek et al. 2011).

4. Antimicrobial agent delivery by MNPs

MNPs have been developed for various applications in medicine ranging from imaging agents and tissue repair to immunoassay and detoxification of biological fluids. However, undoubtedly, MNPs application as a drug delivery strategy is considered as one of their main usages. Regarding the basic magnetic properties of MNPs as well as their improved physicochemical nature like higher surface per volume ratio, different categories of drug delivery applications can be proposed. For instance, the main problem of most chemotherapeutic agents is their non-specificity and consequently side effects to healthy tissues. To overcome this problem and to increase site specific delivery of chemotherapeutic agents, drug loaded MNPs using an external magnetic field can be applied (Pankhurst et al. 2003; Dobson 2006). In fact, a number of MNP-based antibiotics delivery systems toward the infected or malignant cells are currently under various stages of investigations (Veiseh et al. 2010), some of them are reviewed here.

Gupta and Bajpai reported the design of a superparamagnetic nanocomposite to deliver ciprofloxacin using a magnetic field. To this end, a polymer matrix of polyvinyl alcohol-γ-polymethyl methacrylate was prepared by a free radical polymerization process and iron oxide particles were impregnated by *in situ* precipitation method and then the prepared particles were characterized. Accordingly, ciprofloxacin was loaded onto the prepared particles and the chemical integrity of the drug and its antibacterial potential in the formulation were shown to be preserved. The authors showed that the prepared NPs were biocompatible and superparamagnetic in nature and could be used as a smart drug carrier for controlled and targeted drug delivery (Gupta and Baipai 2011; Baipai and Gupta 2010).

In a different investigation, Kell and Simard (2007) indicated that by modifying vancomycin architecture/orientation on the surface of MNPs, the ability of them to magnetically capture vancomycin-antibody modified polystyrene microbeads was extremely affected. According to their report, vancomycin can be selectively anchored to NPs comprised of an iron-oxide core surrounded by a silicon dioxide shell. This antibiotic could be selectively anchored to surface in two distinct orientations and one of the orientations caused a more expedient magnetic capture of vancomycin-antibody modified microbeads which shows the importance of controlling the molecular architecture of substrates anchored to surfaces for use in assays dependent on specific molecular interactions. Their research well emphasized the importance of being capable of controlling the molecular architecture of substrates on nanoparticles surfaces and demonstrated the power of utilizing small molecule probes for the capture of biomolecules.

Lin et al. (2005) employed vancomycin-modified magnetic nanoparticles as affinity probes to selectively trap Gram-positive pathogens from sample solutions by applying a magnetic field for isolation and characterization purposes by mean of Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry (MALDI-MS). The pathogen cell concentration in an infected sample is generally lower than the detection threshold of MALDI-MS. Taking into consideration the high affinity of vancomycin to the D-Ala-D-Ala units of Gram-positive bacteria cell walls, the designed probe can selectively trap and isolates the bacteria from sample solutions and consequently the isolated bacteria can be characterized by MALDI-MS. The authors concluded that their proposed method could effectively reduce the interference of protein and metabolite signals in the mass spectra of Gram-positive bacteria and can be employed for their characterization in biological samples.

Furthermore, Nădejde et al. (2010) reported the preparation of biocompatible magnetic fluids with Fe_3O_4 cores which were functionalized with rifampicin or chlortetracycline. The synthesis process consisted of coprecipitation of iron oxide in basic, as well as in acid medium. This was followed by the dispersion of the resulted MNPs in aqueous solution containing the antibiotics. In their method the intermediate organic coating in the MNPs preparation was neglected, however the TEM diameter analysis revealed good stability of their MNPs after 6 months.

Khuat et al. (2008) reported the preparation of Fe_3O_4 MNPs using a co-precipitation method with double layers of surfactants (core/oleic acid (OA)/sodium dodecyl sulfate (SDS)) coats. Consequently the double-layer-coated MNPs were fully loaded with chloramphenicol and the effect of the drug release

process against *Escherichia coli* was investigated in comparison with untreated chloramphenicol. According to their results, the authors indicated that the MNPs gradually released the antibiotic; hence stability of the drug and consequently its effect was maintained when compared to its water-soluble counterpart.

In a different investigation also recyclable antibacterial MNPs consisting of a magnetic Fe_3O_4 core with an antibacterial poly(quaternary ammonium) (PQA) coating were prepared in a four-step process. The magnetite properties of prepared nanoparticles led to easily removal of dispersed nanoparticles from water after antibacterial tests and antimicrobial activity tests indicated that the PQA-modified MNPs retained 100% biocidal efficiency against *E. coli* during eight exposure/collect/recycle procedures without washing with any solvents or water (Dong et al. 2011).

In an attempt Fe_3O_4/oleic acid/cephalosporins MNPs were fabricated by the Massart method using $FeCl_3$ and Fe^{2+} salts with oleic acid as the surfactant, under microwave conditions. According to the study, MNPs in dimensions of 5–20 nm range were achieved and they were characterized by High Resolution Transmision Electron Microscopy. The antibacterial activity of the obtained MNPs was observed in both, reference Fe_3O_4/oleic acid shell nanoparticles and adsorption shell cephalosporins case (Buteica et al. 2011).

5. Conclusion and future discussions

From the pharmaceutical point of view, one of the desirable approaches to combat infectious diseases is to develop efficient delivery systems targeting the infected sites. Basically due to their intrinsic magnetic nature as well as the improved physicochemical specifications, MNPs have been thoroughly investigated for the potential applications in biomedical era. MNPs based drug delivery has come up as a safe and effective drug delivery strategy thanks to the higher specificities and lower side effects of this strategy. Antimicrobial specifications of prepared MNPs with or without loaded antibiotics are promising; however *in vivo* studies in this regard are few and further investigations are critical for development of efficient MNPs based infectious fighting systems.

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