Pharmacokinetics and Applications of Magnetic Nanoparticles

Runyi Mao*a, Jing Wangb#, Jiao Peic, Songtao Wu*, Jie Fenga, Yunfeng Lin* and Xiaoxiao Cai*a

aState Key Laboratory of Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, P.R. China; bDepartment of Stomatology, Shanghai Tenth People’s Hospital, Tongji University School of Medicine, Shanghai, P.R. China; cDepartment of Medical Statistics, West China School of Public Health, Sichuan University, Chengdu, Sichuan Province, P.R. China

Abstract: Nanomaterials possess enormous potential for biomedical applications, while some of the most promising nanomaterials currently under investigation demonstrate prolonged tissue retention and contain heavy metals. This article investigates the pharmacokinetics of magnetic nanoparticles (MNPs) to help identify promising candidates with optimal pharmacokinetics and clearance from the body for biomedical use and synthesize nanomaterials ideal for biomedical use. The term ‘magnetic nanoparticles’ (MNPs) refers to nanoparticles with ferromagnetism. Such nanoparticles have special characteristics, and many in the field of biological field have undertaken research involving, e.g., immobilized enzymes and proteins, biological cells, macromolecular separation, drug carriers, and targeted, immune, biological sensors.

Keywords: Nanomaterial, magnetic nanoparticles (MNPs), drug delivery system, hyperthermia, cancer, targeting.

1. INTRODUCTION

In recent decades, some of the most promising nanomaterials currently under investigation have demonstrated prolonged tissue retention and contain heavy metals. Magnetic nanoparticles (MNPs) have recently received considerable attention, since they offer unique advantages over traditional drug delivery systems (Table 1). Since the 1970s, magnetic nanoparticles have shown application prospects, due to their particularly large surface-to-volume ratio, quantum size effect, and magnetic character, as well as their potential applications in the areas of bioscience and medicine [1, 2]. Magnetic nanoparticles employ iron oxide particles such as magnetic Fe3O4 or magnetite γ-Fe2O3 [3-5]. Cobalt and nickel have also recently been added to the chemical composition [6]. However, the toxicity of these compounds is of concern and should be further studied.

Recently, magnetic nanoparticles have been used more and more frequently in biomedical and biotechnology studies, including targeted drug delivery, tumor magnetic hyperthermia therapy, contrast enhancement of magnetic resonance imaging, biosensors, rapid separation in environmental biology, and concentration tracing of specific targets, such as bacteria, leukocytes, and proteins [7-11]. Magnetic nanoparticles currently being used for biology must be superparamagnetic; not only will they have directional movement to affect targets in the magnetic field, but also, depending on magnetic nuclear particle size, crystal morphology will influence magnetic behavior [12-16]. Among the family of magnetic materials, the superparamagnetic materials and ferro- or ferrimagnetic materials are of special interest in clinical applications. The largest iron oxide nanoparticles belong to the class of massive materials.

Smaller-sized magnetic particles constitute the ‘superparamagnetic’ class. The core of these particles is composed of ferric oxide particles 3–15 nanometers in diameter. The outer layer is coated with a dispersant of dextran, starch, or polyethylene glycol (PEG) to avoid agglomeration of naked nanoparticles. The magnetic ferric oxide particles coated with dextran are approved for clinical use by the US FDA. The major factors which determine the toxicity and biocompatibility of these materials are the nature of the magnetically responsive components, such as magnetite, iron, nickel, and cobalt, and the final sizes of the particles, their core, and the coatings. Iron oxide nanoparticles such as magnetite (Fe3O4) or its oxidized form maghemite (γ-Fe2O3) are by far the nanoparticles most commonly used for biomedical applications. Highly magnetic materials such as cobalt and nickel are susceptible to oxidation and are toxic; hence, they are of little interest. In previous studies, MNPs such as Fe3O4 have been demonstrated that, combined with chemotherapeutic drugs, are capable of inducing tumor cell apoptosis. The pharmacokinetics of magnetic nanoparticles depends on surface-to-volume ratio, quantum size effect, and magnetic character [17,18]. Iron is a common trace element in humans, and one of the advantages of MNPs is their biodegradability. Following treatment with MNPs, serum iron levels increase transiently, which suggests that the intracellular degradation of nanoparticles is a part of physiological iron metabolism [19]. Nanoparticles, because they are small, easily pass through various physical barriers and reach specific organs. Previous studies have shown that nanoparticles are able to be distributed in the liver, spleen, lung, and bone marrow, to the reticulo-endothelial system via macrophages, and passively targeted to organs, with most of them deposited in the liver.

Furthermore, cells impregnated with magnetic nanoparticles (MNP) are being explored for a range of therapeutic and diagnostic applications, including magnetic resonance imaging [20,21], magnetically driven endothelialization of vascular grafts and injured blood vessels [22-26], vascular tissue engineering [27], and cancer treatment.

Magnetic iron oxide nanoparticles have currently been shown to be suitable for use as theranostic agents, especially as intrinsic diagnostic agents in the context of MRI. Among all imaging diagnostic methods, magnetic resonance imaging (MRI) has the advantages of real time, low cost, and high safety. Magnetic nanoparticles offer targeting strategies in cancer imaging and therapy [28]. Due to the difficulties associated with drug delivery across the brain-blood barrier (BBB) to tumors, the capability of targeted magnetic/optical nanoprobes to accumulate selectively in brain tumors via chlorotoxin (CTX) offers us an opportunity to overcome one of the most formidable challenges in the treatment of malignant brain tumors [29]. It has also been demonstrated in a system that uses ‘tumor homing’ cells to actively carry iron/iron oxide nanoparticles into tumor tissue for alternating magnetic field treatment [30].
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2. PHARMACOKINETICS OF MAGNETIC NANOPARTICLES

2.1. Absorption and Distribution of Magnetic Nanoparticles

In recent years, magnetic nanoparticles have usually been administered intravenously. However, in the study by Wang et al. [33], Fe$_3$O$_4$ MNPs at 600 mg/kg were given intra-gastrically in mice. Their results showed that the concentration of MNPs peaked 6 h after administration (about 439 μg/mL) and then declined, but another concentration peak was noted 5 days after administration (about 436 μg/mL). The mononuclear phagocyte system is the main component in the clearance of macromolecules. Thus, the ability of phagocytes to take up MNPs is a main determinant of plasma clearance and drug distribution. The way in which phagocytes take up MNPs depends on the size of nanoparticles. Raynal et al. reported that intraperitoneal macrophages in mice could endocytose dextran MNPs (100 nm) in a scavenger receptor A (SR-A)-dependent manner [34]. However, the 20-nm MNPs are phagocytosed [35]. Moreover, the opsonization of MNPs by plasma proteins may facilitate the phagocytosis of macrophages (Fig. 1) [36]. As a result, passivation through PEGylation may avoid the opsonization of MNPs and increase the retention of MNPs in the circulation. However, the interaction between MNPs and biomolecules (protein, lipid, carbohydrate) requires further study.

Fe$_3$O$_4$ MNPs are considered ideal drug carriers and can inhibit tumor proliferation and induce apoptosis of tumor cells in a dose- and time-dependent manner. In the studies of Fe$_3$O$_4$ MNPs, it has been demonstrated that, following intravenous injection of oleic-acid/pluronic-coated MNPs (mean size, 190 nm) in rats, 55% of particles may accumulate in the liver [37]. Wang et al. [33] also found the distribution of MNPs in the heart, liver, spleen, lung, kidney, bone marrow, brain, stomach, and small intestine, but the content of MNPs was highest in the liver and spleen (237 μg/g and 211 μg/g, respectively). In the liver, the MNP concentration presented two peaks. The first peak was present 1 day after administration, and the second occurred 7 days after treatment. In addition, these investigators also found that the content of MNPs in the brain was markedly higher than that in the control group. Although the mechanism underlying the penetration of MNPs across the brain-blood barrier is still unclear, the findings demonstrate that MNPs have the potential to become excellent drug carriers. The experiments on magnetic particle diffusion in tissue have shown migration in gel in a steady magnetic field [38], and evaluated magnetic nanofluid transport and heat distribution in an agarose gel.

It is well-known that kinetic models in combination with graphical or other methods have been put to use to analyze the time-AR$_2$ curve. Jae Boem Na et al. used the three-compartment method to describe the kinetics of iron oxide. This model includes plasma, extracellular interstitial space, and Kupffer cells in the liver [39].

In Kin et al. study, MNPs are distributed in diverse organs. They also showed that MNPs were administered to mice through the intraperitoneal route. Thus, the majority of the MNPs would be taken up by the liver via the first-pass effects and then redistributed from the liver to the other organs. Our results show that MNPs are rapidly and widely redistributed in the body except in the case of the lungs. He et al. used the Stable Ni nanoparticles of 24–200 nm in size pre-pared by a thermal decomposition method and their result showed that with the increase of particle size, the saturation magnetization increases monotonically, and the coercivity decreases at first and then increases. These results provided evidence for the existence of size effect and shape anisotropy in Ni nanoparticles [40,41-43].

Generally, magnetic nanoparticles show good distribution in vivo. Depending on their characteristics, magnetic nanoparticles are phagocytosed from the blood by the reticulo-endothelial system.

2.2. Excretion of Magnetic Nanoparticles

The excretion of MNPs is slow. Following injection of dextran-coated MNPs (mean size, 80 nm) in rats, about 25% of MNPs were excreted through the urine and feces within 19 days [44]. Bourrinet et al. found accumulation of MNPs in the liver, spleen, and lymph nodes after intravenous administration to rats, mice, rabbits, dogs, and monkeys. About 20% of MNPs are excreted through the urine and feces within 7 wks [45]. Intravenous administration is the most effective method of reaching target organs through the blood circu-
3. APPLICATIONS OF MAGNETIC NANO PARTICLES

3.1. Magnetic Nanoparticles within Carriers for Drug Delivery

Drug targeting is a hot topic for study in the modern technologies for drug delivery. The development of magnetic nanoparticles for drug delivery has dramatically increased. As one of the modern technologies for drug delivery, drug targeting can offer the possibilities for the application of iron oxide. Magnetic nanoparticles in drug targeting have drastically increased in recent years. Moreover, MNPs in combination with an external magnetic field and/or magnetizable implants allow for the delivery of particles to the desired target area, where they can be fixed at the local site while the medication is released, and act locally (magnetic drug targeting).

In general, this process involves the attachment of a cytotoxic drug to a biocompatible MNP carrier (a.k.a. magnetic targeted carrier or MTC), intravenous injection of these MTCs in the form of a colloidal suspension, application of a magnetic field gradient to direct the MTC to the pathological site, and release of the therapeutic agent from the MTC. Although seemingly straightforward, there are many variables that complicate the execution of this technique. Parameters such as the physicochemical properties of the drug-loaded MNP, field strength and geometry, depth of the target tissue, rate of blood flow, and vascular supply, all play a role in determining the effectiveness of this method of drug delivery [40,45,49-53].

Most magnetic nanoparticles are modified with polymers or oxides to make them biodegradable and suitable for drug delivery. Magnetic nanoparticles can be used as drug carriers to selectively deliver the molecules not only to the target tissue, but also to tumor cells [54,55]. When MNPs enter the body, they rapidly achieve high concentrations in the bloodstream, where external high magnetic fields can be used to direct them to target tissue [56]. With self-assembled DNR/Br Tet MNPs as one of the potential antitumor agents, Wang et al. have studied the apoptotic mechanism of human leukemia K562/A02 cells induced by magnetic iron oxide nanoparticles co-loaded with daunorubicin and 5-bromotetrandrin (DNR/Br Tet MNPs), which have shown that the DNR/Br Tet MNP formulation may have potential application as an antitumor agent in the treatment of hematologic malignancies, and may effectively induce apoptosis of K562/A02 cells through elevating the ratio of bax/bcl-2, activating caspase 3, and inactivating K562/A02 cells surviving. Magnetic iron oxide (Fe3O4) nanoparticles are considered ideal gene vectors [57-59].

As one of the modern technologies for drug delivery, the use of drug targeting has drastically increased in recent years, with the possibilities for the application of iron oxide magnetic nanoparticles. MNPs, in combination with an external magnetic field and/or magnetizable implants, allow for the delivery of particles to the desired target area, where they can be fixed at the local site while the medication is released, and act locally.

Cai et al. have generated a new-generation choriocarcinoma-specific gene vector with magnetic nanoparticles containing Fe3O4-dextran-anti-β-human chorionic gonadotropin. In this study, with high transfection efficiency with good biocompatibility and low cytotoxicity, Fe3O4-dextran-anti-β-HCG nanoparticles could be considered as ideal gene vectors [60].

3.2. Magnetic Nanoparticles as Contrast Agents for MRI

With the development of nanomaterials, different kinds of nanoparticles have been used for diagnostic magnetic resonance imaging. Thus, depending on novel uses for in vitro and in vivo cellular and molecular imaging, and with a high degree of magnetic behavior in the magnetic field, magnetic nanoparticles are widely used in MRI [61]. MRI is an imaging technique that ‘interrogates’ the nuclei of atoms inside a living body. It is universally recognized as one of the most frequently used imaging tools in daily clinics.
allowing diagnosis to be performed in a non-invasive and real-time manner [62,63]. Superparamagnetic contrast agents have the advantage of producing an enhanced proton relaxation in magnetic resonance imaging (MRI) in comparison with paramagnetic ones. To achieve stable contrast agents, the magnetic nanoparticles, CLIO (cross-linked iron oxide) and SPIO (bonding dextran macromolecules and magnetic cores by coupling agents), have been applied to MRI [64,65]. CLIO nanoparticles consist of a superparamagnetic iron oxide core (3- to 5-nm monocrystalline iron oxide) composed of ferrimagnetic magnetite (Fe₃O₄) and/or maghemite (γFe₂O₃). Cross-linked iron oxide (CLIO) nanoparticles have been widely used for MRI, obviously because of their excellent stability and biocompatibility [66]. Amine-terminated CLIO nanoparticles have an average hydrodynamic diameter of 25–40 nm, approximately 40-80 amines per nanoparticle for bioconjugation, and an r₂ of ~50 s⁻¹ mm⁻¹ (Fe) [67,68]. The pharmacokinetics, toxicity, and biodistribution of another contrast agent, SPIO, have been studied, and the results have shown the potential uses of contrast agents [69,70]. SPIO decrease the signal in the liver and spleen within several minutes of administration [71].

Currently, magnetic nanoparticles such as SPIO and CLIO are used for the diagnosis of malignant tumors, because of clinicians’ needs regarding which contrast agent could have a specific signal in tumor tissues.

For magnetic fluids to be applied to an MRI contrast agent, SPIO should be dispersed into a biocompatible and biodegradable carrier [72]. In the study by Wada et al., the lethal dose of the dextran-iron oxide complex was found to be 2000-6000 mg Fe/kg of body wt. The larger nanoparticles of SPIO can exhibit a high R₂/R₁ relaxivity ratio. Furthermore, compared with SPIO, USPIO shows that lower relaxivities are exhibited, along with a more favorable T₁/T₂ ratio, in which UPSIO can shorten the T₁ of blood during the first hours after injection. However, MRIs are not convenient for in situ monitoring, and the problem remains that the fluorescence of cell-specific or target-specific contrast agents’ signal is easily affected by background noise, so that diagnostic accuracy is affected. It is desirable to accelerate the development of magnetic nanoparticles as contrast agents.

### 3.4. Magnetic Nanoparticles as Mediators for Magnetic Hyperthermia

The application of ferrofluids for hyperthermia treatment was investigated in the work of Chan et al. [73] and Jordan et al. in 1993 [74]. This technique is a promising technique for cancer treatment because of ease in targeting the cancerous tissue and hence having fewer side effects than chemotherapy and radiotherapy. It is notable that the results of current/ongoing clinical trials show significant reduction in side effects. Recently, the generation of localized hyperthermia by using magnetic nanoparticles to absorb alternating magnetic field energy is one of many techniques used in oncology. Tumor cells showed higher sensitivity than normal tissue cells, in the range of 42-45°C (Fig. 2) [75]. In this condition, hyperthermia increases the rate of cell cycling, increased hypoxia, poor fluid exchange, and increased acidity [76,77]. Being combined with radiation therapy or chemotherapy would increase the efficiency for damaging tumor cells and for increasing the radiation sensitivity of tumor cells. In general, cancer cells possess a greater likelihood of dying when the temperature is above 42.5°C, and the rate of death drastically increases with increasing temperature [78-82].

Temperature is one of the important factors affecting the quality of cancer treatment. Whole-body hyperthermia is used clinically to take advantage of this differential temperature and toxicity to treat cancer. However, whole-body hyperthermia (41.5°C) can cause serious side-effects, which may limit its usefulness [83-87]. An ideal hyperthermia treatment should selectively destroy the tumor cells without damaging the surrounding healthy tissue. Depending on the specific selection of the target tissue, magnetic nanoparticles have great potential in hyperthermia, which can be performed by focusing laser, microwave, ultrasound, or magnetic energy to the infected regions. The research group of Basel et al. reported a new system whereby cell-delivered magnetic nanoparticles that caused hyperthermia could increase survival in a murine pancreatic cancer model. Paramagnetic core/shell iron/iron oxide magnetic nanoparticles were surface-modified for low-toxicity therapeutic use. The system is considered an ideal method for the further development of magnetic nanoparticle-generated localized hyperthermia [88]. It is worth mentioning that the heat induction in SPIONs can be en...
hanced by the creation of magnetic microspheres which consist of a polymer matrix randomly filled with MNP. During hyperthermia in comparison with other magnetic materials, it is surprising to note that most of both experimental and commercially available MNP for hyperthermia applications consist of SPION cores rather than other mentioned MNP [89-92].

Thermal dose has also been identified as one of the most important factors to influence the efficacy of hyperthermia. Golneshan and Lahnoian used the lattice Boltzmann method to analyze the effect of magnetic nanoparticle dispersion on temperature distribution in a spherical tissue in magnetic fluid hyperthermia [93]. In their study, they found that for 2*105 volume fraction of 9-nm FCC FePt MNPs, homogenous distribution of SAR cannot raise the temperature of tumor cells above 42.5°C, and the LBM can give precise prediction of the temperature distribution and is efficient for dealing with space and time [94].

We readily admit that there are many problems remaining to be solved, such as ligand-mediated targeting, and tissue distribution monitoring prior to the control of \textit{in vivo} temperature evolution. A promising use of magnetic nanoparticles as mediators for magnetic fluid hyperthermia should include inserting them within the tumor mass in a homogenous way and overheating the tumor cells selectively and locally.

4. CONCLUSIONS

Nano-composite materials have been increasingly applied. Some researchers have applied two or more types of nanoparticles to form nanocomposite materials with multiple functions which may meet the requirements in detection, diagnosis, and targeted therapy. Applications of magnetic nanoparticles [MNPs] have been widely spread throughout biotechnology, biomedical, materials science, engineering, and environmental areas. Much attention has been paid to the synthesis of different kinds of MNPs. Improving imaging contrast, biocompatibility, and specific targeting capability remains the mainstay of MNP development for medicine. To improve MRI signal-to-background ratios, MNP cores with high magnetic moments, such as doped iron oxide nanocrystals, metallic/ alloy nanoparticles, and nanocomposites, have been developed. To improve biocompatibility, surface coatings, such as gold, silica and a number of biocompatible polymers have been investigated. The use of gold or silica as shell materials allows for potential application of toxic materials as nanoparticle cores with strong magnetic properties. By incorporating advances in nanoscale engineering, molecular imaging, and novel therapeutics, MNP platforms have the potential to enable physicians to diagnose and treat diseases, such as cancer and cardiovascular disease, with greater effectiveness than ever before.

The pharmacokinetics of magnetic nanomaterials is different from that of traditional drugs. The main differences are that most nanoparticles can be rapidly cleared from the blood and thus have a short half-life. However, this does not reflect nanoparticle excretion from the body. These nanoparticles are taken up by macrophages in the liver and spleen. Thus, the content of nanoparticles is relatively high in the liver and spleen. The pharmacokinetic model of nanoparticles is similar to the two- or three-compartment model. Although numerous studies have been conducted to investigate magnetic nanoparticles, the findings are still inconsistent, and definite conclusions have not been drawn.

Magnetic nanoparticles have significant prospective biomedical uses in drug delivery, clinical diagnosis, magnetic resonance imaging, and hyperthermia cancer therapy. Magnetic nanoparticles will be of higher and higher value in nanomaterials. However, it remains to be seen if results in human patients will be as promising as those achieved in animal studies. Undoubtedly, the public will raise concerns regarding the relationship between nanotechnology and medical therapy and biological research. More and more research efforts are promoting the development of magnetic nanoparticles.

CONFLICT OF INTEREST

The authors certify that this article content has no conflicts of interest.

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REFERENCES

[17] Chen, B.A.; Cheng, J.; Wu, Y.N.; Gao, F.; Xu, W.; Shen, H.; Ding, J.; Gao, C.; Sun, Q.; Sun, X.; Cheng, H.; Li, G.; Chen, W.; Chen, N.; Liu, L.; Li, X.; Wang, X. Magnetic nanoparticle of Fe3O4 and 5-bromotetrandrine interact synergistically to induce...


