Multifunctional Magnetic Nanoparticles for Imaging and Drug Delivery

Technology Fields: Diagnostics; Therapeutics
Technology ID: 59

Summary
One of the limitations in the drug delivery field is the inability to specifically target therapeutic or imaging agents to certain tissues, organs or tumors. Magnetic nanoparticles have emerged as effective drug delivery systems, which can be directed by externally applied magnetic fields and specifically tailoring their functional properties. Unfortunately, available magnetic nanoparticles with therapeutic and imaging agents have several limitations: creation involves a complex multi-step process, they have a limited agent loading capacity, experience rapid bound agent dissociation, and go through rapid loss of magnetization ability. Researchers at the University of Nebraska Medical Center have developed a novel magnetic nanoparticle technology with a high drug-loading capacity, adjustable release profile, high aqueous dispersion stability, biocompatibility with tissue and cells, and prolonged stable retention of magnetic properties.

Market Value
This technology can be used to increase the efficacy, lower toxicity, and eliminating side effects of existing and novel therapeutical agents. An alternative market is the medical imaging sector, which will be able to achieve more precise and rapid methods for imaging diseases and conditions. The main competitive advantages of the novel magnetic nanoparticles include simple and inexpensive production, ability to effectively incorporate and release in controlled manner wide variety of therapeutical or imaging agents, and stable magnetic properties of complexed nanoparticles.

Features and Benefits
• Effective drug delivery system
• Specifically target tumors and other pathological conditions
• High drug loading capacity
• A desirable release profile

Publications
• Vasir JK, Labhasetwar V. Biodegradable nanoparticles for
Magnetic nanoparticles for MRI imaging and combinational anti-cancer therapies
Modern MRI techniques that can differentiate diseased tissue, tumors, inflammation, and microscopic blood vessels depend on contrast agents to enhance their appearance [1]. Conventional contrast agents include paramagnetic transition metal ions (such as Mn$^{2+}$ and Fe$^{3+}$) or rare-earth chelates (such as Gd$^{3+}$) [1]. There are drawbacks to using these metals. First, free manganese causes cardio-vascular, central nervous system, lung, liver, reproductive and fetal toxicity [2], while gadolinium chelates causes serious kidney damage [3]. Second, body circulation of those agents is very time limited, making complete MRI analysis very difficult [4]. Third, conventional contrast agents cannot fully address MRI's potential for early detection of inflammation, atherosclerosis, tumor detection, cancer metastasis and monitor therapy efficacy [5]. Finally, conventional agents are limited only to imaging and provide no additional ability to carry therapeutical agents [5].

Magnetic nanoparticles (MNP) developed by UNMC researchers for MRI imaging have a very low toxicity and have longer circulating time in the body. MNPs can fully explore MRI’s potential by drastically increasing tissue contrast and serve the dual purpose of contrast agent and drug delivery system.

**Advantages of MNP for MRI**
- Low toxicity
- Prolonged body circulation time
- Increases imaging contrast
- Ability to carry multiple agents

**Why enhance MRI images?**
- Early detection of atherosclerosis, inflammation, thrombosis
- Tracking metastasis and progression of tumor
- Track the distribution of cells in the body
- Detect solid tumors
- Personalized treatment
- Monitor the treatment effectiveness

Executive summary
Low toxicity of MNPs

Toxicity of the MNP’s (MNP’s) can be associated with the iron oxide core of nanoparticles. Since the iron dose of the MNPs is many times lower than body iron levels, injected iron would be easily metabolized and regulated by the body’s normal physiological iron homeostatic mechanisms. Importantly, studies show that the injected iron does not cause long-term changes in liver enzyme levels or oxidative stress, and most of the changes are only transient. Biodistribution, elimination, and oxidative stress studies have shown that MNP’s have a very low toxicity, and minimal effect on the body normal homeostasis.

Figure 1. Changes in lipid hydroperoxide levels as a measure of oxidative stress in different tissues following injection of MNPs in rats [6].

Figure 2 Changes in serum liver enzyme levels with time following a single-dose intravenous injection of MNPs in rats [6].
Prolonged circulation of MNPs

One of the key parameters of the MNPs is the minimized uptake by circulating macrophages that prevents rapid clearance by the reticuloendothelial system (RES) when injected systemically. The special pluronic coating of MNPs prevents the rapid clearance and facilitates longer circulation in the body [6]. The MNPs exhibit superior circulation time when compared to other MRI agents. In-vivo results show that the half-life of Feridex IV (ferumoxides injectable solution used for magnetic resonance imaging) was 6.4 min whereas MNPs was 31.2 min [6].

Figure 3. Schematic of oleic acid (OA)-Pluronic-coated iron oxide MNPs. Hydrophobic drugs can be partitioned in the OA layer around the iron oxide core. Pluronic anchored onto OA provides aqueous dispersity.

Figure 4. Circulation half-life of magnetic nanoparticles in mice. Calculated relative iron-oxide concentration vs. time profiles in carotid artery for Feridex IV and MNPs. Half-life ($t_{1/2}$) of clearance of particles was read at the relative concentration = 0.5 (dashed line) [6]
Multiple agents loading by MNPs

The MNPs have an extraordinary capability to load most hydrophobic therapeutical agents including paclitaxel (PTX) and doxorubicin (DOX). Studies have shown that the drug entrapment efficiency for PTX and DOX are 95% and 82% respectively [7]. When two hydrophobic agents paclitaxel and doxorubicin were loaded, total entrapment efficiency was 85% with about 74% for doxorubicin and 96% for paclitaxel [7]. The ability to entrap several agents at the same time is very important for clinical application. One of these applications is use of MRI and MNPs loaded with anti-cancer drugs for simultaneous enhanced tumor imaging and targeted anti-tumor therapy.

Figure 5. Antiproliferative effect of drugs in solution and loaded in MNPs with (a) paclitaxel, (b) doxorubicin in MCF-7 cells. Cells were treated with drug either in solution or loaded in MNPs, medium was changed on days 2 and 4, and cell viability was measured using an MTS assay on day 5. Data as mean ± s.e.m. (n=6) [7].

Figure 6. T2-weighted image of tumor bearing mouse injected with Pluronic® F127-modified MNPs. Enhanced contrast in the tumor (denoted by arrow) is apparent 4 min after the initial injection and is more pronounced at 68 min after a second injection of the MNPs.
MNPs increase MRI imaging contrast

MNP’s have a relatively higher T2 relaxivity (r2) relative to Feridex IV, which indicates increased sensitivity as an MRI contrast agent. The increased sensitivity may be attributed to the MNP’s ability of to induce more local inhomogeneity in the magnetic field than Feridex IV, creating more contrast and greater T2 relaxivity (r2) [7]. In addition, the MNP’s have a lower T1 relaxivity than Feridex IV. The T1 relaxivity is even lower when loaded with hydrophobic agents. The T1 relaxation process requires close proximity of the hydrogen atoms to the contrast agent and it appears that the more hydrophilic dextran coating used in Feridex IV allows closer proximity of the contrast agent to water molecules. In the case of MNP’s, the less hydrophilic nature of Pluronic coating containing hydrophobic polypropylene oxide has a reduced hydration effect: causing the reduced proximity of water molecules to the iron-oxide core of MNPs [7].

Figure 7. Contrast enhancement within the whole tumor and vascular tumor periphery for mice injected with saline, Feridex IV®, F127-modified MNPs, and T908-modified MNPs. A single ROI was drawn around the tumor at each axial slice (S 02 – S 09) for the pre-injection image (0 h) and the signal intensity quantified. The same ROI was used to calculate the signal intensity at 1, 2.5, 3 and 4 h.
UNeMed offers unique opportunity

The MNP’s are novel imaging agents that provide much lower toxicity, prolonged circulation, efficient loading and improved imaging contrast. UNeMed is currently seeking outlicensing opportunities in all fields for the MNP’s. For more information please contact Joe Runge and please visit UNeMed.com for more exciting new technologies.


Dr. Labhasetwar’s research focus is on translational NanoMedicine, which involves biomaterial synthesis, formulation design and development, and evaluation of different biocompatible nanoparticle-based platform technologies for targeted drug/gene delivery and imaging agents.

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