



Iron Oxide Loaded PLGA Particles for Contrast Enhancement in Magnetic Resonance Imaging (MRI)



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Abstract

Among metallic particles super paramagnetic nanoparticles (NPs) of iron oxide have had more application in molecular and cellular magnetic resonance imaging (MRI) over the last 20 years. One promising construct for MRI-based cell tracking is polymer encapsulated iron oxide nanoparticles. Further, for magnetic nanocrystals, the clustering of multiple magnetic nanocrystals within a single polymeric particle enhances r_2 and r_2^* relaxivity.

Keywords: Iron oxide; Nanoparticles; Microparticles; PLGA; MRI

Abbreviation: MRI: Magnetic Resonance Imaging; MPIOs: Micron-Sized Iron Oxide Particles; PLGA: Poly Lactic-Co-Glycolic Acid; FDA: Food and Drug Administration; EMA: European Medicine Agency; MPs: Microparticles; SNR: Signal-To-Noise Ratio; MPMBs: Multifunctional Polymer Microbubbles

Introduction

Nanomedicine platforms in the fields of drug delivery and molecular imaging have passed many developments in the past several decades. New therapeutic systems that use theranostic agents and work based on molecular targeting have potential to be the next generation of nanomedicine technology [1]. To do new researches in the field of MRI, studying in Magnetic cell labelling is necessary. Magnetic resonance imaging (MRI) in comparison with other imaging-based cell tracking tools has some advantages; such as non-invasiveness, deep penetration, and high spatial resolution [2]. Scientists have been used a variety of metal oxides to study the role of contrast agents parameters on the cell activity. Among the various metal oxides, super paramagnetic NPs of iron oxides have found more applications in the field of MRI [3]. Moreover, it is possible to use their additional capabilities such as potential use in hyperthermia, magnetic targeting and magnetic cell separation [4].

After intravenous injection, they phagocytosed by kupffer cells of liver which are part of body reticulo endothelial system. Nowadays, a clinically approved formulation, Feridex VR with different functional coating is accessible and research to make new formulations continues. One of disadvantages of developed formulations is their low iron content per particles and because iron content is less than 0.1% by volume, to create

adequate contrast cells must endocytose millions of iron oxide nanoparticles [5].

Iron oxide loaded PLGA particles in MRI

To overcome limitations, researchers have been focused on the developing micron-sized iron oxide particles (MPIOs). In comparison with ferumoxides (dextran-coated iron oxide nanoparticles), it is possible to load higher weight percentage of iron oxide in MPIOs. Moreover, they propose higher r_2^* molar relaxivity and cell activities such as cell division don't affect the relaxivity of MPIOs. Today, fluorescence loaded polymeric MPIOs are commercially available [6]. To produce such particles biodegradable and biocompatible polymeric matrices could be a good choice. For example, using copolymer of poly lactic-co-glycolic acid (PLGA) which have approved by the U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA), make it possible to produce high iron oxide content of PLGA microparticles (MPs) with powerful magnetic responsivity [7]. Especially, it is possible to fine tune PLGA physical characteristics such as size, morphology, uniformity and size distribution of PLGA particles using flexible and advantageous method of electrospaying [8,9].

This polymer have application in the parenteral administration of a drug carrier systems, intravenous drug

delivery formulations, biomimetic materials, diagnosis and treatment of disease, medical imaging, and tissue engineering [10]. Nkansah et al. [11] have compared MR parameters of magnetic PLGA and cellulose NPs and MPs which produced by oil-in-water single emulsion technique. Particles have had smooth surface morphology and high magnetite (Fe_3O_4) content (43.3wt % for PLGA and 69.6wt % for cellulose) and high magnetization cores (72.1emu/g). While PLGA and cellulose NPs have shown maximum r_2^* values per millimole of iron ($399\text{sec}^{-1}\text{mm}^{-1}$ for cellulose and $505\text{sec}^{-1}\text{mm}^{-1}$ for PLGA), micron-sized PLGA particles have displayed a much higher r_2^* per particle than either. To study *in-vitro* condition, Particles have been incubated for a month in citrate buffer (pH 5.5). Accordingly magnetic PLGA particles have lost close to 50% of their initial r_2^* molar relaxivity, while magnetic cellulose particles have remained intact, preserving over 85% of their initial r_2^* molar relaxivity [11]. Influence of iron oxide size ranging from 10nm to 180nm on the MRI parameters has been investigated by Leea et al. [12] Iron oxide loaded PLGA particles which have been produced by using an emulsification–diffusion method, have shown suitable contrast enhancement in the animal tests.

Sun et al. [13] have synthesized 885.6nm sized dual contrast agent magnetite/PLGA microcapsules using a typical double emulsion evaporation process. Results of *in-vitro* and *in-vivo* experiment have shown that applying the composite microcapsules could efficiently enhance ultrasound imaging of cancer, and greatly enhances the high intensity focused ultrasound ablation of breast cancer in rabbits. Ling et al. [14] have fabricated Polysorbate 80 coated temozolomide-loaded PLGA-based superparamagnetic nanoparticles (P80- TMZ/SPIO-NPs). High drug loaded particles have shown suitable release performance and high drug loading. Results have shown acceptable capability as a theragnostic carrier of brain cancer. Magnetite loaded PLGA NPs carrying recombinant tissue plasminogen activator have been constructed by Zhou et al. [10] employing a double emulsion solvent evaporation method (water in oil in water (W/O/W)) for using in the detection of thrombi and in targeted thrombolysis using MRI monitoring. Based on their results there has been no significant difference in the transverse relaxation rate (R_2^*) or in the values of signal-to-noise ratio (SNR) between the magnetite based NPs and a magnetite solution with the same concentration of Fe_3O_4 [10].

Nui et al. [15] have co-encapsulated chemotherapeutic drug and Iron oxide NPs into PLGA microbubbles to form multifunctional polymer microbubbles (MPMBs) by the aim of use in both tumour lymph node imaging and therapy. Their *in-vitro* experiment results have shown that the MPMBs could increase both ultrasound and MR imaging. Moreover, *in-vivo* experiments have approved that the MPMBs enhance tumour lymph nodes signals. Xu et al. [2] have produced MPs of PLGA loaded magnetite NPs by the aim of use in cellular MRI. They have synthesized 10nm magnetite NPs and have produced 0.4-

3 μm sized composite particles. Compared to alone iron oxide NPs, produced MPIOs have shown enhanced parameters consist of 5-fold the r_2 relaxivity, 3-fold residence time inside the cells and 2-fold R_2 signal.

Conclusion

It can be concluded that, polymeric micro and nanoparticles containing superparamagnetic nanoparticles of iron oxide are good candidate for using contrast enhancement agent *in-vitro* and *in-vivo*.

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