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

Faramarzi AR¹, Barzin J*¹ and Mobedi H²

¹Department of Biomaterials, Iran Polymer and Petrochemical Institute, Iran
²Department of Novel Drug Delivery Systems, Iran Polymer & Petrochemical Institute, Iran

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*Corresponding author: Barzin J, Department of Biomaterials, Iran Polymer and Petrochemical Institute, Iran, Tel: +98 21 44787026; Email: j.barzin@ipp.i.ac.ir

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 r₁ and r₂* 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 r₂* 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 electrospraying [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 (Fe₃O₄) content (43.3 wt % for PLGA and 69.6 wt % for cellulose) and high magnetization cores (72.1 emu/g). While PLGA and cellulose NPs have shown maximum r₂* values per millimole of iron (399 sec⁻¹ mm⁻¹ for cellulose and 505 sec⁻¹ mm⁻¹ for PLGA), micron-sized PLGA particles have displayed a much higher r₂* 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 r₂* molar relaxivity, while magnetic cellulose particles have remained intact, preserving over 85% of their initial r₂* molar relaxivity [11]. Influence of iron oxide size ranging from 10 nm to 180 nm 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 885.6 nm 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 Polyisorbate 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 use in the detection of thrombi and in targeted thrombolysis using MRI monitoring. Based on their results, there has been a significant difference in the transverse relaxation rate (R₂*) or in the values of signal-to-noise ratio (SNR) between the magnetite based NPs and a magnetite solution with the same concentration of Fe₃O₄ [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 0.4-3μm sized composite particles. Compared to alone iron oxide NPs, produced MPIOs have shown enhanced parameters consist of 5-fold the r₂ relaxivity, 3-fold residence time inside the cells and 2-fold R₂ 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.

References
1. Nasonkïda N, Boy E, Ren J, AiH, Khemtong C, et al. (2006) Multifunctional Polymeric Micelles as Cancer-Targeted, MRI-Ultrasonic Drug Delivery Systems. Nano Lett 6(11): 2427-2430.
2. Xu C, Miranda-ND, Ankrum JA, Matthiesen ME, Phillips JA, et al. (2012) Tracking mesenchymal stem cells with iron oxide nanoparticle loaded poly (lactide-co-glycolide) nanoparticles. Nano Lett 8(12): 4131-4139.
3. Shapiro EM (2015) Biodegradable, polymer encapsulated, metal oxide particles for MRI-based cell tracking. Magn Reson Med 73(1): 376-389.
4. Scherer C, Neto AMF (2005) Ferrofluids: Properties and Applications. Braz J Phys 35(3): 718-727.
5. Otsuka H, Nogasaki Y, Kataoka K (2003) PLGylated nanoparticles for biological and pharmaceutical applications. Adv Drug Deliv Rev 55(3): 403-419.
6. Shuai X, Ai H, Nasonkïda N, Kim S, Gao J (2004) Micellar carriers based on block copolymers of poly (ε-caprolactone) and poly (ethylene glycol) for doxorubicin delivery. J Control Release 98(3): 415-426.
7. Faramarzi AR, Barzin J, Mobedi H (2017) Producing PLGA fine particles containing high magnetite nanoparticles by using the electrospray technique. J Polym Res 24:13.
8. Faramarzi AR, Barzin J, Mobedi H (2016) Effect of solution and apparatus parameters on the morphology and size of electrosprayed PLGA microparticles. Fibers Polym 17(11): 1806-1819.
9. Faramarzi AR, Barzin J, Mobedi H, Gorji M (2017) Polymeric Pharmaceutical Nanoparticles Developed by Electrospray, In Nanostructures for Novel Therapy: Synthesis, Characterization and Applications. In: Fical D & Grumesezcu AM (Eds.), Elsevier, USA, pp. 137-160.
10. Zhou J, Guo D, Zhang Y, Wu W, Ran H, et al. (2014) Construction and Evaluation of Fe3O4-Based PLGA Nanoparticles Carrying rtPA Used in the Detection of Thrombosis and in Targeted Thrombolysis. ACS Appl Mater Interfaces 6(8): 5566-5576.
11. Nkansah MK, Thakral D, Shapiro EM (2011) Magnetic poly (lactide-co-glycolide) and cellulose nanoparticles for MRI-Based cell tracking. Magn Reson Med 65(6): 1776-1785.
12. Leea SJ, Jeonga JR, Shinac SC, Kimb JC, Chang, et al. (2004) Nanoparticles of magnetic ferric oxides encapsulated with poly (D, L lactic acid-glycolide) and their applications to magnetic resonance imaging contrast agent. J Magn Mater 243-2433.
13. Sun Y, Zheng Y, Ran H, Zhou Y, Shen H, et al. (2012) Superparamagnetic PLGA-iron oxide microcapsules for dual-modality US/MR imaging and high intensity focused US breast cancer ablation. Biomaterials 33(24): 5854-5864.
14. Ling W, Wei K, Zou F, Zhong S (2012) Temozolomide loaded PLGA-based superparamagnetic nano particles for magnetic resonance imaging and treatment of malignant glioma. Int J Pharm 430(1-2): 266-275.
15. Niu C, Wang Z, Lu G, Krupka TM, Sun Y, et al. (2013) Doxorubicin loaded super paramagnetic PLGA-iron oxide multifunctional microbubbles for dual-mode US/MR imaging and therapy of metastasis in lymph nodes. Biomaterials 34(9): 2307-2317.