Optimization of blood circulating times of magnetic nanoparticles based on the effect of PEG molecular weight coating and nanoparticle size followed by Magnetic Resonance Imaging.

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Abstract

Magnetic Resonance based Molecular Imaging has emerged as a very promising technique for early detection and treatment monitoring of a wide variety of diseases, among them, cancer, neurodegenerative disorders, stroke, etc. The limited sensitivity and specificity of conventional MRI are being overcome by the development of novel contrast agents, most of them based on nanotechnology approaches, with improved magnetic and biological properties. In this work, we report a facile and robust ligand-exchange method to synthesize magnetic nanoparticles based on iron oxide and manganese ferrite nanoparticles as MRI contrast agents with long circulation times. The selection of the right molecular weight PEG coating on the nanoparticles and the nanoparticle size are crucial points in the design that will determine the fate of the magnetic nanoparticles. Therefore, PEGylated small magnetic nanoparticles (PEG-MNPs), using PEG MWs ranging from 600 to 8000, were synthesized, resulting in highly stable and water-soluble nanoparticles. Semi-quantitative and quantitative MRI studies allowed us to track the pharmacokinetics and biodistribution of intravenously injected PEG-MNPs (HD < 50 nm) in vivo up to one week. Results show that high MW PEGs (6000-8000) lead to nanoparticle aggregation and low MW PEGs (≤1500) are not able to stabilize the 6 nm iron oxide nanoparticles in physiological medium or confer stealth properties, thus leading to rapid recognition by the RES. In contrast, PEG3000-MNPs show excellent in vivo behavior, they do not aggregate and exhibit better stealth properties, giving rise to slower liver uptake and longer circulation times. Moreover, we synthesize manganese ferrite nanoparticles between 6 and 14 nm covered by a 3kDa polyethylene glycol (PEG) shell that leads to a great stability and confer the best stealth properties. These PEGylated MNPs have shown different relaxivities r_1 and r_2 depending on their nanoparticle core size, for instance the 6 nm PEGylated MNP has a r_1 value of 13.3 $mM^{-1}s^{-1}$ and a r_2 value of 65 $mM^{-1}s^{-1}$ with a low ratio r_2/r_1 of 4.9, resulting in a good dual T_1 and T_2 contrast agent at clinical magnetic field. On the other hand, the 14 nm PEGylated MNP is an excellent T_2 contrast agent at high magnetic field, with a r_2 value of 335.6 $mM^{-1}s^{-1}$. The polymer core shell of the PEGylated MNPs minimizes their cytotoxicity, and permits long blood circulation times (24 h). This combination of cellular compatibility, excellent T_2 and T_1 values at low fields, together with long circulation times and moderate liver uptake, make these nanomaterials very promising contrast agents for molecular imaging.

References

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[2] Pernia Leal, M., Rivera-Fernandez, S., Franco, J. M., Pozo, D., de La Fuente, J. M. and Garcia-Martin, M. L. Long-circulating PEGylated manganese ferrite nanoparticles for MRI-based molecular imaging. ***Nanoscale*** 2015, **7**, 2050-2059

Figures

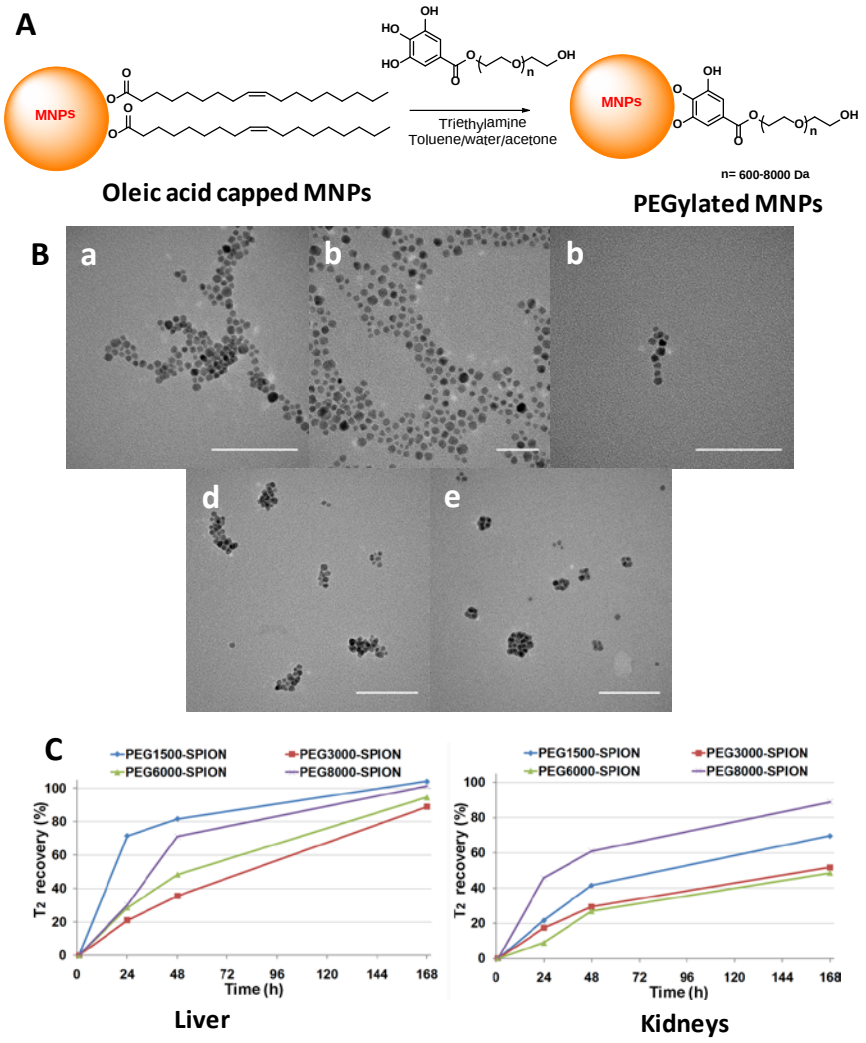

Figure 1. A) Scheme of ligand exchange procedure.; B) Representative TEM images of water soluble molecular weight PEGylated iron oxide nanoparticles: a) PEG600-SPIONs; b) PEG1500-SPIONs; c) PEG3000-SPION; d) PEG6000-SPIONs and e) PEG8000-SPIONs. Scale bar corresponds to 50 nm. And C) T_2 recovery of the liver and kidneys after PEG-MNPs injections.

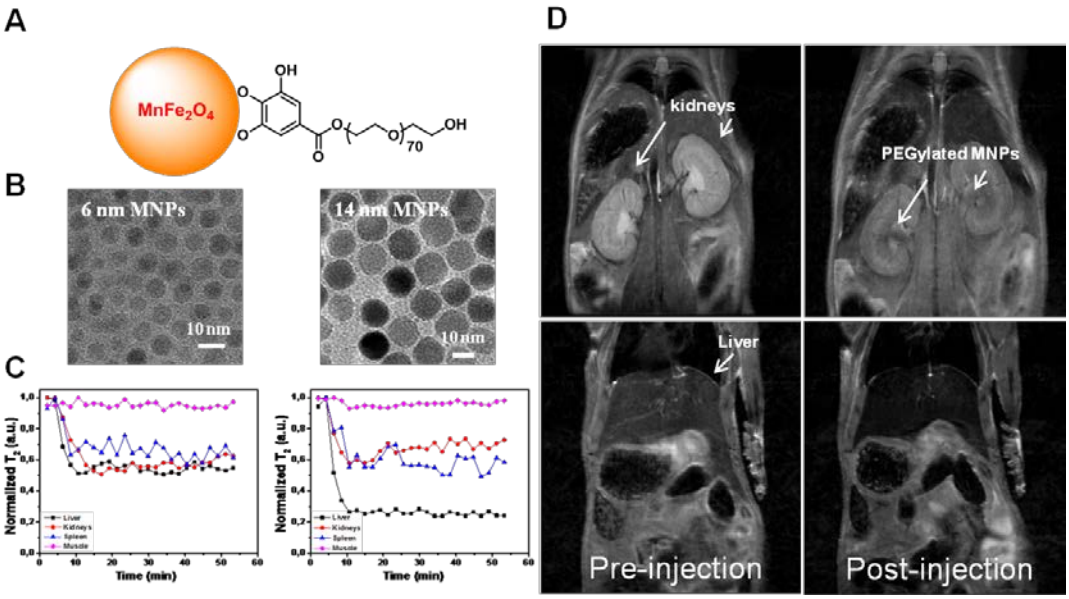

Figure 2. A) Scheme of PEGylated MNPs; B) TEM images of PEGylated MNPs of 6 and 14 nm; C) In vivo kinetic studies of T_2 with 6 nm MNP-GA-PEG-OH and 14 nm MNP-GA-PEG-OH; D) Distribution of MNP-GA-PEG-OH. Before injection of the MNPs (left) and after injection (right).