Preparation of MRI contrast agents through dispersion of nanoparticles produced by laser pyrolisis

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Introduction

The commercial method of preparing superparamagnetic contrast agents is the co-precipitation of iron salts in solution in the presence of a polymeric coating (mainly dextran). Generally speaking, iron oxide particles prepared by this method have a broad particle size distribution, which requires a secondary size selection process to obtain the final commercial product. This increases the preparation time and the cost of the material. It should be emphasized that particle size is limited by toxicity (smaller than 200 nm) and tissular diffusion (smaller than 20 nm). Recently, laser-induced pyrolysis of iron pentacarbonyl vapors has been reported to produce pure maghemite nanoparticles with sizes smaller than 10 nm and narrow particle size distribution [1]. This continuous process yields pure non-aggregated particles and avoids the need for size-selection process. In addition, the particle size and the crystallinity of the resulting powder can be varied by adjusting experimental conditions such as the oxidation conditions and the laser power. In this work, biocompatible dispersions have been prepared for the first time by dispersion of laser pyrolysis products in the presence of dextran. The relevant physical properties of the powders and dispersions and the blood clearance of the particles in rats are reported to evaluate its possible use as superparamagnetic iron oxide contrasts (SPIO).

Material and Methods

Superparamagnetic nanoparticles of iron oxide were synthesized by laser-induced pyrolysis of iron pentacarbonyl vapors, following the method described in [2]. A suspension of 200 mg of maghemite in 2.5 ml of 0.5 M NaOH was prepared by sonication for five minutes. A solution of 200 mg of 6 kD dextran in 2.5 ml of 0.5 M NaOH, used as dispersant plus coating media, was added under sonication (kept 24 hr at 30 ^{o}C). The dark brown dispersion obtained was dialyzed in 5 L of distilled water during 24 hr using a 12,000-14,000 nominal molecular weight cut off membrane. The dispersion was made 1 mM in tri-sodium citrate dihydrate and 5 wt. % in L-mannitol to make it suitable for parenteral administration. X-ray diffraction (XRD) patterns were recorded between 10 and 100^{o} (2θ) at 0.5 °/min. ^{57}Fe Mössbauer absorption spectroscopy was used to characterise the iron oxide particles. Hydrodynamic diameter of the aggregates, considering the magnetic cores and the coating, was calculated by Photon Correlation Spectroscopy (PCS). TEM was employed to measure the number averaged diameter of the magnetic core of the aggregates. RARE (T_R 3000 ms, T_E 60 ms) coronal T2-weighted images were collected at 4.7 Tesla using both 12 cm and 26 cm birdcage coils with a FOV of 8 and 15 cm respectively. The slice thickness was 2 mm, 256x192 acquisition matrix size, and 2 excitations. The animals were imaged before and 10 min after contrast injection.

Results and discussion

XRD showed that the particles obtained by laser pyrolysis have an inverse spinel structure with a unit cell parameter a = 8.34 Å, similar to maghemite. A mean crystallite size of 4.8±0.9 nm was obtained. Analysis of the TEM pictures gives a mean particle size of 4 ± 2 nm. The distribution was adjusted to a log-normal distribution function with parameters μ = 1.23 and σ = 0.559 (Figure 1).The average diameter for the aggregates was 28 ± 22 nm. The powders were dispersed in a 0.5 M NaOH aqueous solution of dextrane by intensive sonication, yielding colloids of dextran coated particles in a single step. These superparamagnetic colloids, called USMP1, have a mean particle-aggregate diameter of 46 nm measured by PCS. The R_1 and R_2 relaxivities are 1 and 314 s^{-1}/mM Fe respectively at 4.7T and 25 ^{o}C. USMP1 shows a monoexponential blood clearance in rats with a blood half-life of 7 ± 1min. Using as magnetic resonance imaging agent, in vivo MR imaging showed an increased contrast of the T2 MRI image 10 min after the USMP1 administration in the liver and spleen and in less extent in the brain (Figure 2).

Conclusion

Laser pyrolysis, a useful technique to tailor the preparation of a wide variety of nanosized magnetic powders with narrow size distributions, controlled physical properties and different chemical compositions, can be employed for the preparation of superparamagnetic contrast agents for MRI.

References

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