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Measurement of the magnetite nanoparticles' relaxivity during encapsulation into polylactide carriers

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ABSTRACT

Polylactide (PLA)-based carriers are currently widely employed in biomedical applications, where imaging modalities are in high demand; however, information regarding the contrast properties of the PLA-based magnetic carriers in MRI applications is lacking. Therefore, we measured the MRI parameters of the magnetite nanoparticles with different encapsulation rates in PLA spheres. The MRI measurements were performed at the 4.7 T and 0.178 T systems, where the relative contrast, transversal relaxation time (T_2), and transversal relaxivity (r_2) were evaluated and compared. The results reveal that these parameters can be used in order to determine the magnetic nanoparticles' encapsulation into PLA carriers, as well as in the quantification of the particles' loading rate. Such an approach can be utilised in biomedical applications to determine the rate of drugs' encapsulation into the PLA carrier system, for example, as well as for drug release tracking from the carriers.

1. Introduction

Polymer-based magnetic carriers attract significant interest in biomedical applications, including Magnetic Resonance Imaging (MRI), hyperthermia, molecules' separation, and drug targeting [1]. A broad range of polymers have been used to synthesise these carriers; however, only polylactide (PLA)-based polymers are currently being widely used in biomedical applications, particularly in tissue engineering [2]. This is primarily due to their excellent biocompatible and biodegradable properties, and low toxicity [2]. PLA is a thermoplastic, aliphatic polyester that is derived from renewable resources such as corn starch, tapioca roots, or sugarcane. It represents one of the highest consumption by volume of all the bioplastics produced globally, with products such as mulch films and tea bags being manufactured from PLA. While the magnetic behaviour, as well as the general properties of PLA-based magnetic carriers have been quite well described [3], what is missing is information related to the contrast properties of such carriers in MRI applications, in regard to the encapsulation rate of the magnetic nanoparticles. The existing publications provide only information about imaging possibility with MRI, but do not show the contrast changes related to different loading factor of magnetic nanoparticles into the carriers [e.g. 3–5]. Therefore, we explored the relative contrast, transverse relaxation time (T_2), and transverse relaxivity (r_2) changes induced by different loading factors of magnetite nanoparticles (MGNPs) in PLA carriers. Such data can be useful, for example, in the non-invasive determination of drug encapsulation efficiency in PLA-based carriers, or drug release tracking from the carriers.

2. Material and methods

PLA-magnetite carriers were prepared by a modified nanoprecipitation method, as described in [6]. Briefly, 100 mg of PLA was dissolved in 10 ml of acetone to prepare the organic phase, before an aqueous colloid was prepared by mixing a solution of Pluronic F68 as a stabilising agent (25.6 mg in 5 ml) and 0.8 ml magnetic fluid (45 mg Fe_3O_4/ml). Then, the organic phase was added dropwise into the aqueous colloid and stirred vigorously for several hours to allow for the complete evaporation of the organic solvent at room temperature. A turbid nanoparticles suspension was formed. Non-loaded PLA nanospheres were prepared in the same

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manner, but without the magnetic nanoparticles. Subsequently, the Dynamic Light Scattering (DLS) method (Zetasizer, Malvern Instruments) was used to determine the hydrodynamic diameter (D_{hydro}) of those loaded, as well as non-loaded PLA carriers.

Prior to the MRI measurements, the PLA samples were divided into three groups:

(i) PLA-based carriers without magnetite nanoparticles;
(ii) PLA with non-encapsulated magnetite nanoparticles, where the particles are anchored onto the surface of the carriers;
(iii) PLA with encapsulated magnetite nanoparticles, where the particles are encapsulated inside the PLA carriers. Moreover, these were prepared with differing magnetite nanoparticles' input concentrations (2 mg/ml, 5 mg/ml, 7 mg/ml, 17 mg/ml, 30 mg/ml), resulting in the diverse loading factors of the particles inside the PLA carriers.

Relaxivity and relative contrast measurements were performed at the 4.7 T system (VARIAN). The images were acquired with T_2-weighted Multi Echo Multi Slice (MEMS) sequence, with a repetition time of TR = 81 ms, and an echo time of TE = 8 ms. The transverse relaxation time T_2 was obtained spectroscopically through the Car-Purcell-Meiboom-Gill (CPMG) echo pulse sequence. For comparison, relative contrast measurements were also performed at the clinical low-field 0.2 T system (ESAOTE), where images were acquired with the standard T_2 weighted Gradient Echo protocol (TR = 3500 ms, TE = 22 ms). For all the acquired samples, the relative contrast, transverse relaxation time T_2, and transverse relaxivity r_2 values were evaluated and compared.

The relative contrast is defined as follows:

$$RC = (I - I_0)/I_0 \quad (1)$$

where I_0 is the signal intensity without magnetite nanoparticles (reference), and I represents the signal intensity with magnetite nanoparticles.

The transverse relaxivity r_2 is calculated as follows:

$$R_2 = r_2 C + R_2^0 \quad (2)$$

where R_2^0 is the transverse relaxation rate in the absence of nanoparticles, R_2 represents the transverse relaxation rate in the presence of nanoparticles, and C is the nanoparticles' concentration.

3. Results and discussion

Initially, we were interested in whether the PLA itself would have any influence on the MRI signal, such as affecting the relaxation properties of the medium, or the contrast properties of the magnetite nanoparticles. Fig. 1 represents the comparison of the relative contrast with regard to the PLA concentration for those samples with pure PLA (dotted line[1]), PLA with non-encapsulated magnetite nanoparticles (solid line), and PLA with encapsulated magnetite nanoparticles (dashed line), measured at 4.7 T. It can be seen that the concentration of magnetite nanoparticles increases with raised PLA concentration, with that represented by the relative contrast parameter increasing in those samples with magnetite nanoparticles (solid and dashed lines). The same situation but rather for the transversal relaxation time T_2 is presented in Fig. 2, where it is evident that the relative contrast, as well as relaxation time T_2, are not affected by the PLA. The conclusion thus being that PLA has a negligible influence on the MRI signal.

The relative contrast of encapsulated ("in"), and non-encapsulated ("out") magnetic nanoparticles in PLA carriers measured with the 4.7 T MRI system is shown in Fig. 3. The encapsulated carriers are prepared with different loading factors of magnetite nanoparticles, represented by their differing input con-

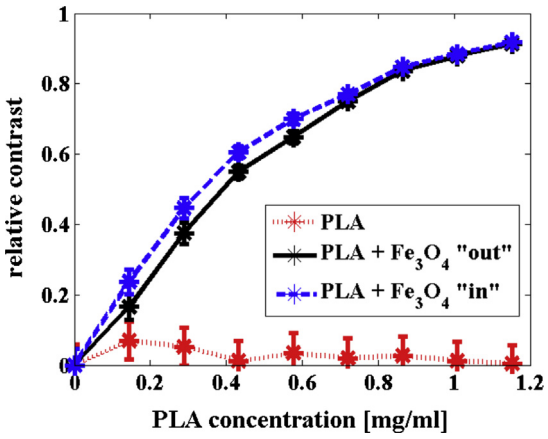

Fig. 1. Comparison of relative contrast values of pure PLA carriers and PLA carriers with loaded ("in") and non-loaded ("out") magnetite nanoparticles in concentration ranges of 0.01–0.08 mg/ml. Measured at 4.7 T.

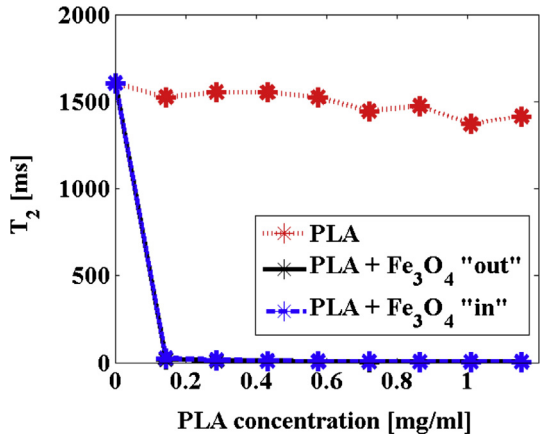

Fig. 2. Comparison of T_2 relaxation time values of pure PLA carriers and PLA carriers with loaded ("in") and non-loaded ("out") magnetite nanoparticles in concentration ranges of 0.01–0.08 mg/ml. Measured at 4.7 T.

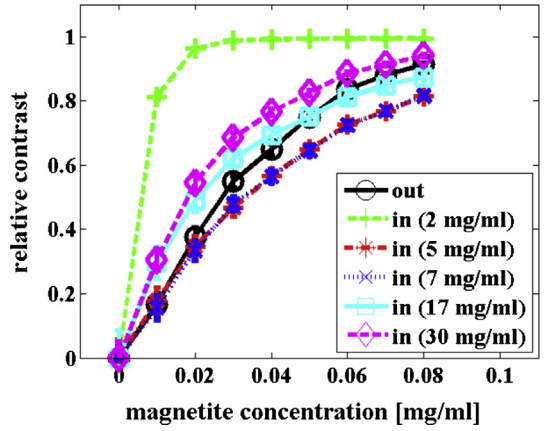

Fig. 3. Relative contrast of encapsulated ("in"), and non-encapsulated ("out") magnetite nanoparticles in PLA-based carriers. The encapsulated carriers are prepared with different loading factors of magnetite nanoparticles, represented by their differing input concentrations during sample preparation (2 mg/ml, 5 mg/ml, 7 mg/ml, 17 mg/ml, 30 mg/ml). Measured at 4.7 T.

[1] For interpretation of colors in figures, the reader is referred to the web version of this article.