# Nano-thermometer with Thermo-sensitive Polymer Grafted USPIOs behaving as Positive Contrast Agents in low-field MRI

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Purpose :

This work reports the grafting of thermo-sensitive Jeffamine® M-2005 onto iron oxide nanoparticles (USPIO) and aims at deciphering the effect of a polymer corona dehydration above LCST on r_1 and r_2, while keeping the USPIOs in a dispersed state (thus a low r_2/r_1 ratio), and examining the results on the MR images with T_1-weighted and T_2*-weighted spin echo sequences
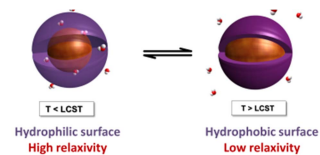
Methods:

A thermosensitive polymer characterized by a lower critical solution temperature (LCST) in water, Jeffamine® M-2005 (PEO_5-st-PPO_{37}), was grafted onto the surface of USPIO by a silanization reaction and an amide-bond coupling.

Nuclear magnetic relaxation dispersion (NMRD) profiles reporting the longitudinal relaxation rates of water protons (R_1) over a magnetic field range from 0.24 mT to 0.94 T were recorded on a Fast Field Cycling Relaxometer (Stelar, Mede, Italy). Additional longitudinal (R_1) and transverse (R_2) relaxation rates were measured at 0.47 T and 1.41 T on Minispec mq20 and mq60 relaxometers (Bruker, Karlsruhe, Germany). Low-field MR images of sample tubes were acquired on a Siemens Magnetom open magnet clinical scanner at 0.194 T (8.25 MHz). T_1-weighted images were taken with a spin-echo sequence of TR=100 ms, TE=2.8 ms, 70° flip angle. T_2*-weighted images were taken with TR=300 ms, TE=12 ms, 160×160 mm^2 field of view, 128×128 matrix, 7 mm slice thickness. The apparent transverse relaxation rates R_2*=1/T_2* at 8.25 MHz were measured for a series of six samples at increasing concentrations (0.05 to 1 mMFe) with a Carr Purcell Meiboom Gill (CPMG)-like sequence made of 16 echoes with 12 ms inter echo-time.

Results and discussion:

A ^{1}H NMR spectroscopic method was used to determine the LCST of Jeffamine M-2005® and indicated a transition temperature near 25°C. USPIO surrounded by a thermosensitive polymer exhibit a temperature-responsive behavior, their surface reversibly changing from hydrophilic below LCST to hydrophobic above it. This phenomenon was used to prove that relaxivity of iron oxide nanoparticles is influenced by the hydrophobicity of their surface [1]. Transverse relaxivity (r_2) of the USPIO@PEO_5-st-PPO_{37} core-shell nanoparticles was measured at frequencies 8.25, 20, 60, and 300 MHz and longitudinal relaxivity (r_1) was acquired between 0.01 and 300 MHz at temperatures ranging from 15 to 50°C. A decrease of these relaxivities vs. temperature with an inflection point at the LCST was observed at low field (<60MHz). The plot of longitudinal relaxativity vs. temperature showed a sigmoid shape with an inflection point near the LCST of the chains at all frequencies. For the transverse relaxavity of protons, r_2, the comparison between data of USPIOs coated by the polymer chains and of the uncoated ones led to a discrepancy between r_2 values obtained at 20 and 60 MHz on the one hand and at 8.25 and 300 MHz on the other hand: in the first case, the transverse relaxivity was identical for coated and uncoated USPIOs below the LCST, while above the LCST, r_2 decreased more rapidly than expected just by the temperature effect on viscosity (with TEPSA only).

The highest decrease of r_2 in the case of USPIOs coated by the polymer chains can be interpreted by a fully hydrated polymer shell below the LCST, totally permeable to water, so that protons can reach the iron oxide surface where the field lines of the magnetic moment are strong (Scheme 1) just as in the uncoated case. Above the LCST, the polymer shell collapsed, leading to a lower r_2 due the decrease of magnetisation caused by the dilution of iron oxide by the non magnetic layer (i.e. the same explanation as for the r_1 decrease).

To illustrate the interest of such nanoparticles for their use as smart contrast agents, MR images were realized at low field (8.25 MHz) with either T_1-or T_2-weighted spin echo sequences. USPIO@PEO_5-st-PPO_{37} shows a perfect linearity of the signal with temperature with a change of contrast from negative below the LCST to positive above it with the T_2-weighted sequence (figure).

T_2-weighted sequence (frequency = 8.5 MHz, TR = 300 ms, TE= 12 ms)
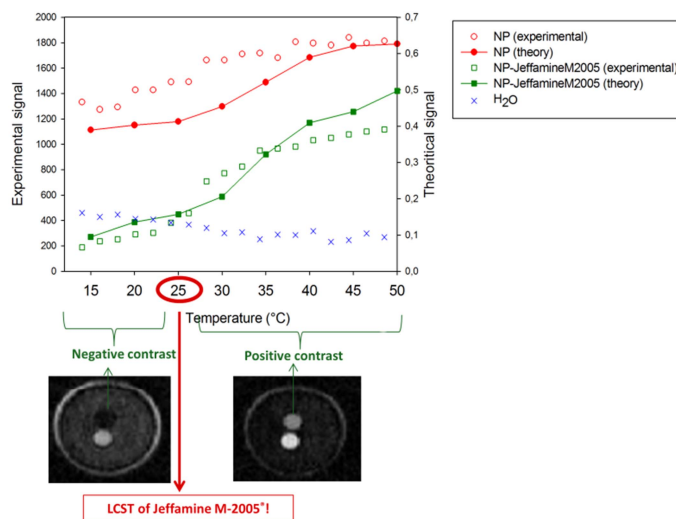
Conclusions:

The decrease of relaxivities above the LCST of the thermosensitive polymer-coated USPIO clearly shows the influence of iron oxide nanoparticles surface's hydrophobicity on relaxivity. Combining a USPIO core with a thermosensitive shell offers the possibility of modulate the MRI contrast with temperature. The perfect linearity of the signal with temperature with a T_2-weighted sequence at low field demonstrated unequivocally the interest of such nanosystems for the design of a temperature responsive contrast agent.

Reference

[1] Pinho, S. L.; Laurent, S.; Rocha, J.; Roch, A.; Delville, M. H.; Mornet, S.; Carlos, L. D.; Vander Elst, L.; Muller, R. N.; Geraldes, C. F. Relaxometric Studies of γ-Fe$_2$O$_3$@SiO$_2$ Core Shell Nanoparticles: When the Coating Matters. J. Phys. Chem. C 2012, 116, 2285-2291.

Proc. Intl. Soc. Mag. Reson. Med. 22 (2014)

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