

Mesoporous Silica Nanoparticles (MSNs) as MRI/PET Dual-Modality Imaging Probes
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INTRODUCTION: Gadolinium-based nanoparticles have been developed as ‘positive- T_1 ’ contrast agents for magnetic resonance imaging (MRI) procedures. Paramagnetic elements, such as gadolinium, decrease the relaxation time of ^1H protons in biological tissues, inducing signal enhancement in MRI. The main advantage of MRI over other biomedical imaging modalities, is the possibility to perform whole-body anatomical resolution imaging, and the achievement of high contrast effects in low density tissues. However, high Gd concentrations are needed in order to reach MRI cell tracking detection thresholds, about a factor of 1000 compared with radioisotope concentrations needed to perform nuclear imaging scans (e.g. with positron emission tomography, PET). Mesoporous silica nanoparticles (MSNs) are promising materials currently being developed as cell labels and for drug delivery applications [1]. Labeling MSNs with paramagnetic chelates and radioactive isotopes would enable the detection with both MRI and PET, of small amounts of labeled cells and particles delivered for therapeutic use. This would provide an efficient way to quantify the local amount of MSN delivered *in vivo*, a very important biological data in the perspective of establishing quantitative diagnostic and/or therapy with drug eluting MSNs. The development of such particles require an adequate labeling with Gd and ^{64}Cu , followed by a rapid purification step to get rid of unreacted metal salts that could be potentially toxic to cells and to biological tissues.

MATERIALS AND METHODS: In this work, MSNs were functionalized with DTPA, a chelator of both Gd and ^{64}Cu that is efficiently excreted by the kidneys upon detachment from nanoparticles. Dialysis, the most common method for purifying magnetic nanoparticles, is long and therefore not suited in the case of fast radioactive decays. It also produces large amounts of radioactive aqueous waste. Because the half-life of ^{64}Cu is very short (12.7 h), size exclusion chromatography (SEC) [2] was used as a rapid purification method to clear-off excess of Gd and Cu. One (1mL) samples of labeled MSNs were chromatographed on a G-25 Sephadex-filled column. The total elution volume was 200 ml and fractions of 500 μl were collected and analyzed by ^1H -NMR (Figure 1). ^1H -NMR (Bruker minispec 60mq) is commonly used for measuring the longitudinal and transversal (T_1 , T_2) relaxation times of MRI contrast agents, which is a direct indication of Gd concentration (high Gd concentrations results in short T_2 in Figure 1). Finally, purified particles were imaged with transmission emission microscopy (TEM) and their hydrodynamic size measured with dynamic light scattering (DLS). MRI was also used in order to quantify the contrast enhancement properties of the purified colloidal suspensions.

RESULTS: MSNs were successfully and efficiently eluted in 35 minutes by SEC (Figure 1). The eluted particles extracted from the Gd:MSNs elution peak (Figure 1, left in the graph) and visualised in TEM, had a mean diameter in the range (150-200 nm; Figure 2 a,b). The hydrodynamic diameter of the colloids was 230 nm \pm 83 (Figure 2.c). Relaxivities (r_1 and r_2) were extracted from T_1 and T_2 values, and provided a r_2/r_1 ratio corresponding to 2.14. This value, as well as T_1 -weighted MRI images of the solutions (Figure 1.b), confirmed the behavior of these particles as “positive” contrast agents. As expected from the theory of signal enhancement in spin echo MRI sequences, the most concentrated suspensions demonstrated signal inflexion. This is a satisfactory indication in the perspective of using these particles only in dilute concentrations.

CONCLUSION: Gd-DTPA-labeled MSNs are efficient “positive” MRI contrast agents. They can be rapidly and efficiently purified by SEC, which is crucial for the labeling of MSNs with short-lived radioactive metals (e.g ^{64}Cu) used in PET/MRI procedures for molecular and cellular imaging.

References

- [1] Guillet-Nicolas, R.; Bridot, J.-L.; Seo, Y.; Fortin, M.-A.; Kleitz, F. *Advanced Functional Materials*, **21** (2011) 4653-4662.
 [2] Hagel, L. *Protein Purification: Principles, High Resolution Methods, and Applications*, John Wiley and Sons, Inc., Hoboken, (2011) 51-91.

Figures

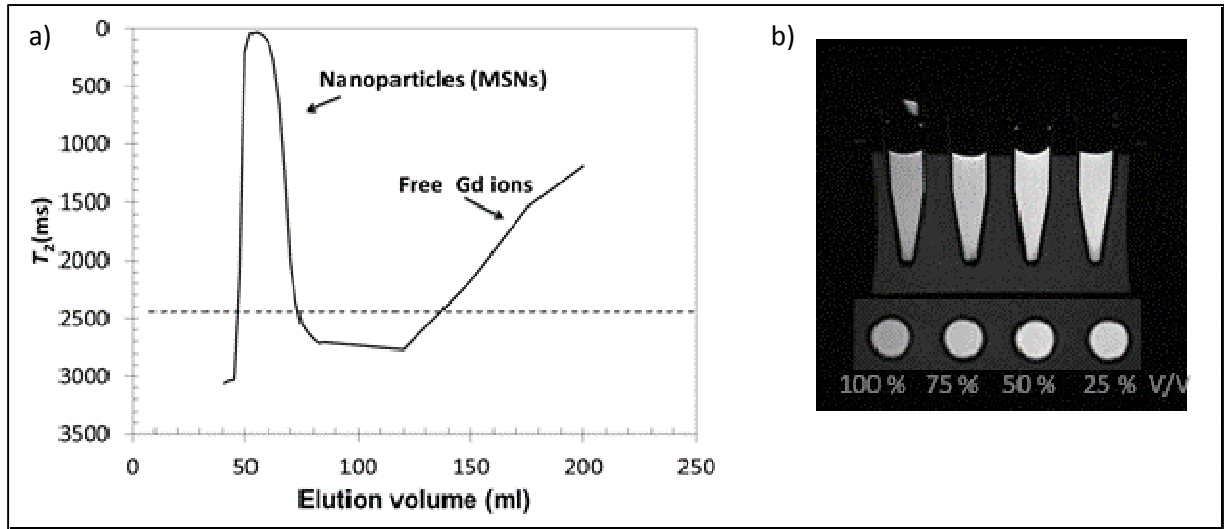


Figure 1: a) SEC profile: transverse relaxation times (T_2) measured on 500 μl -fractions of eluted Gd-labeled MSNs nanoparticle suspensions used in MRI studies. Short T_2 s reflect the strong presence of Gd in the collected fractions. The first peak correspond to Gd-labeled MSNs shown in Figure 2, and the right part of the graph, to residual Gd^{3+} ions. b) T_1 -weighted MR images of MSNs, measured with a 1 T small-animal MRI system (M2M, Aspect Imaging; matrix: 256x256; repetition time 600 ms ; echo time:11.6 ms; dwell time:16 ; slice thickness:1.9 mm; interslice: 0.1 mm; field of view: 70 mm; 3 excitations; $T = 25^\circ\text{C}$).

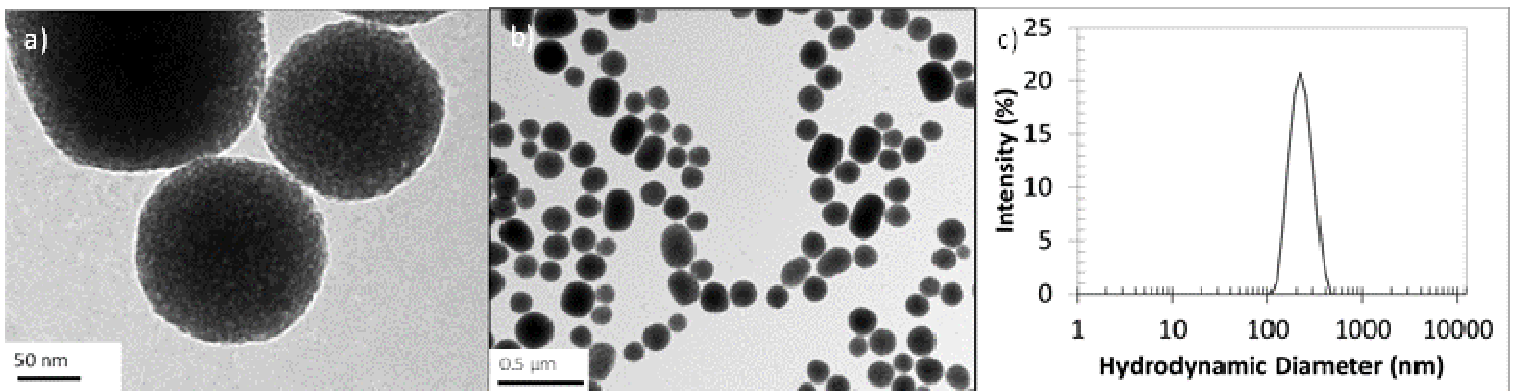


Figure 2: a,b) TEM images of purified MSNs and c) DLS b) 40 kX and c) DLS profiles for the same material, in 150 mM NaCl nanopure water.