Gold nanoparticles for MRI

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Introduction

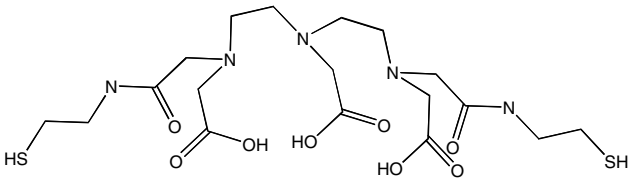
The improvement of the sensitivity of magnetic resonance imaging (MRI), a non-invasive and powerful medical imaging technique, requires the development of original contrast agents with a higher efficiency than gadolinium chelates (DTPA:Gd), widely used for diagnosis. To achieve this goal, the strategy that we explored consists in the use of gold nanoparticles as a carrier for gadolinium chelates.

Material and methods

T_1 measurements and MR imaging were performed at 7T using an inversion recovery FLASH (IR-FLASH) imaging sequence with varying IR time. T_1-weighted contrast enhancement was controlled running a standard Spin-Echo (SE) sequence with 500 ms TR and 12 ms TE. The morphology and the structure of the gold nanoparticles was determined by transmission electron microscopy (TEM, a JEOL 2010 microscope operating at 200 kV) and X ray diffraction (XRD) using a D5000 Siemens diffractometer with the Cu-K□1 and Cu-K□2 X-rays (□=0.15406 nm and □=0.15444 nm). Atomic composition analyses of the surface were performed by X ray photoelectron spectroscopy (XPS). The immobilization of Gd^{3+} ions on the nanoparticles surface was monitored by colorimetric titration with xylenol orange.

Results and discussion

The immobilization of Gd^{3+} ions onto gold nanoparticles requires the use of molecules which are able both to chelate Gd^{3+} ions and to anchor on gold surface. To achieve this goal, gold particles were synthesized by reducing gold salt in presence of dithiolated derivative of diethylenetriaminepentaacetic acid (DTDTPA, Scheme 1). The characterization by TEM, XRD showed that the size of the nanoparticles is about 2.4 nm with a narrow size distribution. As the presence of DTDTPA grafted to gold nanoparticles which is confirmed by TGA and XPS analyses confers a negative zeta-potential, a great colloidal stability is ensured by electrostatic repulsion in aqueous solution from pH 2 to 14. Moreover these characterization techniques combined to infrared spectrophotometry demonstrated that the organic shell adsorbed on gold nanoparticles thanks to the interaction between gold and sulfur atoms is composed of several layer of DTDTPA bound to each other because of the formation of inter and intralayer disulfide bonds between ungrafted thiols of neighbouring ligands. After addition of gadolinium chloride, TGA, colorimetric titration and XPS revealed the presence of about 150 Gd3+ ions entrapped in the multilayered shell. These particles exhibit therefore a high relaxivity (r_1=585 $mM^{-1}.s^{-1}$ versus 3.0 $mM^{-1}.s^{-1}$ for DTPA:Gd) rendering them very attractive as contrast agents for MRI.



Scheme 1. DTDTPA

Conclusion

We demonstrated that gold nanoparticles with a size of 2-2.5 nm can be synthesized according to the Brust protocol by using an original dithiolated ligand (DTDTPA). If this capping molecule is not anchored on gold particles by both sulphur atoms, they allow however the formation of a robust multilayered shell with inter and intralayer disulfide bonds. The presence of gadolinium chelates on gold nanoparticles makes them very attractive as contrast agents for MRI since the immobilization of a large number of DTDTPA:Gd on each particle generates a more pronounced enhancement than in the case of single DTPA:Gd which is widely used in clinical diagnosis. The biocompatibility of gold allows envisaging their use in living organisms for diagnostic (MRI) and/or therapy (hyperthermia).