Gadolinium-incorporated mesoporous silica nanoparticles

$Gd_2O_3@SiO_2$

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Created: July 11, 2011; Updated: August 10, 2011.

Chemical name:	Gadolinium-incorporated mesoporous silica nanoparticles	
Abbreviated name:	$Gd_2O_3@SiO_2$	
Synonym:		
Agent Category:	Nanoparticles	
Target:	Non-targeted	
Target Category:	Non-targeted	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal / contrast:	Gadolinium (Gd)	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is available.

Background

[PubMed]

The gadolinium (Gd^{3+})-incorporated mesoporous silica nanoparticle (NP), abbreviated as $Gd_2O_3@SiO_2$, is a non-targeted contrast agent developed by Shao et al. for magnetic resonance imaging (MRI) of tumors (1).

The application of NPs in molecular imaging and drug delivery is currently undergoing a tremendous expansion because of the unique features of NPs, including high stability, high carrier capacity, incorporation feasibility of both hydrophilic and hydrophobic substances, controlled release of drug payloads, and biocompatibility (2-5). The design of

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NLM Citation: Shan L. Gadolinium-incorporated mesoporous silica nanoparticles. 2011 Jul 11 [Updated 2011 Aug 10]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

NP-based paramagnetic contrast agents must meet certain criteria, which are different from the criteria for the development and use of NPs in drug delivery. For example, paramagnetic metals incorporated into the NPs should be easily accessed by a large number of labile water molecules (6, 7). NP agents must also be stable and safe when used in clinic, and must exhibit isotropic and slow tumbling motion when used *in vivo*. Silica inorganic NPs are well qualified for use in contrast agent development because they have a mesoporous structure, their sizes can be tuned from 1.5 nm to 30 nm, and they offer large surface areas (>1,000 m^2/g) for ligand conjugation (5, 6).

Functionalization of the internal surface of silica NPs *via* the use of alkoxysilanes allows the surface properties to be tailored for various purposes. In general, Gd^{3+}-labeled silica NPs are designed either by incorporating Gd^{3+} into silica or by grafting Gd^{3+}-chelates onto the NP surface (6, 7). Incorporating Gd^{3+} into silica results in contrast agents with a high relaxivity because of the high payload of Gd^{3+} and the slow tumbling motion of the NPs. Grafting Gd^{3+}-chelates onto the NP surface may limit the Gd^{3+} loading because of the reduced number of available anchoring sites on the NP surface. MRI studies have confirmed the usefulness of silica NP-based contrast agents in animal models of human disease. However, numerous questions remain to be addressed for their application in humans. Because the synthetic methods and the nanomaterials for synthesis are highly versatile, it is difficult to determine the relationship between the chemical physical properties of NPs and their *in vivo* behaviors. The ultimate fate and toxicity of NPs themselves and their metabolites are still poorly understood (7, 8).

As discussed in detail by Fadeel and Garcia-Bennett, silica NPs are commonly prepared by the sol-gel process, which generates silica NPs through the hydrolysis and polycondensation of silicon alkoxide (7). The sol-gel technique is also popular for the synthesis of other types of NPs because the NP properties, such as particle size, pore size, amount of incorporated metals, and surface functional groups, can be easily controlled (4, 7). Synthesis of NPs with the sol-gel technique is also cost-effective on the laboratory scale. Shao et al. reported a one-step synthesis of Gd^{3+}-incorporated silica NPs ($Gd_2O_3@SiO_2$) with a mesoporous structure and high surface area (1). The NPs possess desirable MRI contrast enhancement properties, making them suitable for potential application as target-specific contrast agents for molecular MRI. This chapter summarizes data regarding $Gd_2O_3@SiO_2$ (1).

Synthesis

[PubMed]

Shao et al. described the one-step synthetic process for producing $Gd_2O_3@SiO_2$ NPs, which was optimized with a systematic orthogonal test approach (1). Briefly, surfactant pluronic P-123 was first dissolved in distilled water. Reagents HCl, tetraethoxysilane, $GdCl_3{\cdot}6H_2O$, and an ammonium hydroxide solution were then added sequentially and allowed to react for several minutes to several hours after addition of each reagent. The

generated Gd_2O_3@SiO_2 NPs were centrifuged, washed, and dried in air for 12 h at 60°C, and the NPs were then calcined for 6 h at 500°C.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Shao et al. characterized Gd_2O_3@SiO_2 NPs with different techniques (1). Under transmission electron microscopy, Gd_2O_3@SiO_2 NPs presented an intragranular network morphology. The mean diameter of the NPs was 29.18 nm. Dark and bright spots could be observed in the network with energy dispersive x-ray spectroscopy. The dark spots were determined to be Gd-rich areas with an atomic fraction of 3.42% Gd, and the bright spots were Gd-depleted areas primarily composed of SiO_2. The overall Gd concentration was measured with inductively coupled plasma-atomic emission spectrometry to be 1.547 (atom.%). N_2 adsorption–desorption isotherms of NPs before and after incorporation of Gd^{3+} exhibited a typical type IV curve with a clear hysteresis loop. The starting relative pressure for the loop shifted from 0.5 to 0.7, the pore size increased from 7.0 nm to 12.6 nm, and the surface area decreased from 644.9 m^2/g to 236.9 m^2/g with the introduction of Gd^{3+}. The increase in pore size and the decrease in surface area may be caused by the partial destruction of the mesoporous structure when Gd_2O_3 clusters precipitate in the mesoporous silica. No free Gd ions were detected after the Gd_2O_3@SiO_2 NPs were dissolved in phosphate-buffered saline at a concentration of 157.25 mg Gd/L and stored for 48 h at 37.5°C. These results indicate that Gd^{3+} is incorporated into the silica framework, that the structure of the Gd_2O_3@SiO_2 NPs is mesoporous, and that the NPs are stable *in vitro* (1).

In vitro T1-weighted phantom images at 1.5 T showed that Gd_2O_3@SiO_2 NPs generated a higher signal intensity and had a larger T1 relaxivity than commercial Gd-labeled diethylene triaminepentaacetic acid (Gd-DTPA) (1).

Animal Studies

Rodents

[PubMed]

MRI with Gd_2O_3@SiO_2 NPs was performed in mice bearing subcutaneous xenografts of CNE-2 tumor cells (nasopharyngeal carcinoma cells) (1). T1-Weighted images were obtained at different times after administration of 100 µl of 100 mg/ml NPs or saline *via* the tail vein. Significant signal enhancement was observed in the livers from mice treated with Gd_2O_3@SiO_2 NPs from 15 min after injection, and the enhancement lasted for >24 h. The tumor xenografts exhibited increased signal intensity starting at 30 min after injection. Detailed data for the *in vivo* studies, especially for the dynamic enhancement of tumors, were not provided.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

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