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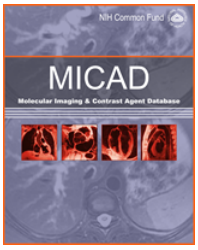

PEGylated paramagnetic lipid-coated silica nanoparticles with a fluorescent quantum dot core

Q-SiPaLCs

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Chemical name:	PEGylated paramagnetic lipid-coated silica nanoparticles with a fluorescent quantum dot core	
Abbreviated name:	Q-SiPaLCs	
Synonym:		
Agent Category:	Nanoparticles	
Target:	Non-targeted	
Target Category:		
Method of detection:	Multimodal imaging (magnetic resonance imaging and optical imaging)	
Source of signal / contrast:	Gd and quantum dot (QD)	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is available.

Background

[PubMed]

The PEGylated paramagnetic lipid-coated silica nanoparticle with a fluorescent quantum dot (QD) core, abbreviated as Q-SiPaLCs, is a bimodal imaging agent that has been developed by Koole et al. and van Schooneveld et al. for combined magnetic resonance imaging (MRI) and optical imaging (1-3).

The idea of using multiple modalities in a single imaging session comes from the fact that imaging modalities with high sensitivity have relatively poor resolution, while those with high resolution have relatively poor sensitivity (4, 5). Integration of multiple modalities in imaging would combine the advantages of each modality and allow better characterization of diseases and disease processes (6). Development of hybrid imaging technology has also triggered great effort in the development of multimodal imaging agents to boost the benefits of hybrid instrument technology (7, 8).

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In principle, the synthesis of multimodal agents is similar to that of single-mode agents (8). A large molecule is usually necessary for efficient labeling and delivery of multiple reporters. Intensively investigated large molecules include liposomes, dendrimers, polymers, and endogenous nanoparticles (8, 9). In the case of liposomes, reporters are either encapsulated in the aqueous interior space or incorporated into the lipid bilayer (1, 2). The latter approach usually results in an improved ionic relaxivity of the MRI metals. In the development of multimodal agents, questions arise from the multistep conjugations that often lead to a low chemical yield. The presence of different molecules on the same nanoparticle surface may interfere with the targeting capabilities and the subsequent intracellular uptake of the agents. The optimization of multimodal imaging agents is more challenging in terms of immunogenicity, toxicity, specificity, interference with biological processes, and accumulation in target organs (7, 8).

Koole et al. and van Schooneveld et al. synthesized a series of multimodal imaging agents by coating silica particles with a dense monolayer of PEGylated paramagnetic lipids without the use of coupling agents (1-3). The presence of a dense lipid layer around the inorganic particle core renders these particles stable in aqueous dispersion and bioapplicable. The lipid coating also allows for conjugation of target-specific molecules at the surface. These agents include Q-SiPaLCs, RGD-conjugated Q-SiPaLCs, and Au-SiFluPaLCs. Of these agents, Q-SiPaLCs were synthesized as a bimodal contrast agent for combined MRI and optical imaging (2, 3). This bimodal agent is composed of a silica-coated QD core with a PEGylated paramagnetic lipid coating (1). The QD core enables its detection with optical imaging, while the paramagnetic lipids generate the MRI signal. This agent has been characterized *in vitro* and in mice (2, 3). This chapter summarizes the data obtained with Q-SiPaLCs. Another chapter in MICAD summarizes the data obtained with Au-SiFluPaLCs.

Related Resource Links:

Multimodal imaging agents in MICAD

Synthesis

[PubMed]

Koole et al. described the synthesis of Q-SiPaLCs and characterized the particles in detail (2). CdSe QDs (3.4 nm in diameter) were synthesized *via* the conventional organometallic synthesis route. The QDs were coated with seven monolayers of inorganic shells (2 × CdSe, 3 × $Cd_{0.5}Zn_{0.5}Se$, 2 × ZnSe). The resulting core-shell-shell QDs (CSS-QDs) increased to 7.7 ± 0.9 nm in diameter with a quantum yield (QY) of 60% and were photostable in air for months. The CSS-QDs were incorporated in silica spheres by a reverse microemulsion method. The silica-coated QDs were subsequently capped with hydrophobic octadecanol (ODOH), at which point the ODOH-coated silica nanoparticles were dispersed in chloroform/methanol and further coated with PEGylated paramagnetic lipids. The PEGylated paramagnetic lipids were prepared with 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(poly(ethylene glycol))-2000] (PEG-DSPE), 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[maleimide-(poly(ethylene glycol))2000] (Mal-PEG-DSPE), and gadolinium diethylenetriamine pentaacetic acid-di(stearylamide) (Gd-DTPA-DSA) in a molar ratio of 0.4/0.1/0.5.

Negative stain transmission electron microscopy (TEM) revealed a hydrophobic layer of 3.9 ± 0.5 nm around individual particles, confirming the presence of ODOH coating around the silica (~2 nm) and the stearyl chains of the lipids (~2 nm) around the particles (2). The hydrodynamic diameter was estimated to be 50 nm for ODOH-coated particles, which increased to 58 nm after lipid coating, as determined with dynamic light scattering. The absorption spectrum of the nanoparticles displayed multiple absorption features as a result of discrete excitonic transitions in the CSS-QDs, which can be observed due to the high quality and monodispersity of QDs. The initial QY of the CSS-QDs decreased from 65% to 25% after the silica coating, however the QY was difficult to be measured because of the scattering of the silica particles in ethanol. The QY increased to 35% after capping with ODOH, which could be accurately determined because of the scattering-free dispersion of the

hydrophobic particles in chloroform. The silica coating and further coating steps did not change the shape of absorption or emission spectra of the QDs. The emission maximum of the CSS-QDs was ~630 nm.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The longitudinal relaxivity r_1 of the Q-SiPaLCs was calculated to be 14.4 $mM^{-1}s^{-1}$, which is three to four times higher than that of the free Gd-chelate molecules (2). This difference is ascribed to the lower tumbling rate of the Gd-lipids in the micelle compared to free Gd-DTPA-DSA. The r_2/r_1 ratio was 1.6, indicating that Q-SiPaLCs can be used as an effective T1 agent. The r_2/r_1 ratio is often used to determine whether a contrast agent is more suitable for T1-weighted or for T2-weighted MRI.

Inductively coupled plasma mass spectrometry (ICP-MS) showed that the number of Gd-lipids was 2,500 per silica particle, and it was estimated that half of the lipids carried Gd-DTPA-DSA (2).

Cell viability was determined with murine J744A.1 macrophages after incubation with different concentrations of Q-SiPaLCs or bare silica particles (3). After incubation with Q-SiPaLCs for 1 d and 3 d, the number of surviving cells was found to be considerably higher than the number of surviving cells after incubation with bare silica particles. The investigators observed no significant difference in cell survival between Q-SiPaLCs and bare silica particles after incubation for 2 h.

Animal Studies

Rodents

[PubMed]

van Schooneveld et al. determined the half-life of Q-SiPaLCs with C57bl6 mice (n = 2/time point) (3). The cadmium (Cd) half-lives in plasma were 14 ± 2 min and 162 ± 34 min for the bare and lipid-coated silica nanoparticles, respectively, as determined with ICP-MS. These values closely resembled the half-lives as determined with fluorescence imaging, which were 18 ± 3 min for bare nanoparticles and 165 ± 28 min for lipid-coated nanoparticles. The molar Gd/Cd ratio in blood had a constant average value of 2.95 ± 0.34 at all time points after injection of the Q-SiPaLCs, which was identical to that of the Q-SiPaLCs before injection. These results indicated that the paramagnetic lipids did not dissociate from the nanoparticles in the blood.

Dynamic MRI of the aorta was performed at 9.4 T (n = 3 mice) and showed clear enhancement of the vasculature for at least 2 h after intravenous administration of the Q-SiPaLCs (45 µmol Gd/kg) compared to the prescan (3).

Optical imaging was performed for liver, spleen, kidney, and heart from mice euthanized at 1, 4, and 24 h after injection of the nanoparticles (n = 2 mice/time point) (3). The fluorescence signal in the liver of mice injected with Q-SiPaLCs increased gradually with time, while a negligible fluorescence signal was obtained from the spleen, heart, and kidney. The fluorescence intensity in the liver did not reach its maximum value until 4 h after injection. In the case of the bare silica particles, the fluorescence signal from the liver increased greatly, whereas the signals from the spleen, heart, and kidney were negligible. Contrary to the Q-SiPaLCs, maximum fluorescence signal in the liver was observed as early as 1 h after injection.

Organ distribution of the particles was determined with ICP-MS by determining the Cd content in organs (n = 1 mouse/time point and particle) (3). Fourteen nmol/kg particles of either lipid-coated or bare silica nanoparticles were administered intravenously into C57bl6 mice, which resulted in calculated 1.1 µmol Gd per mice (or 45 µmol/kg). Cd determinations allowed for comparison between the Q-SiPaLCs and bare silica particles because

both types of particles contain equal amounts of this element. Similar to the optical imaging results, ICP-MS showed that the Q-SiPaLCs accumulated gradually in the liver, whereas negligible amounts of Cd were found in the kidney, lung, and heart. In contrast to the optical imaging results, a gradual uptake of the Q-SiPaLCs was also observed in the spleen. This discrepancy was also observed for the bare silica particles and was attributed to the high absorbance of the QD emission by the spleen. Bare silica particles accumulated within 1 h in the liver, lung, and spleen to a greater extent than that observed with Q-SiPaLCs, leading to breathing problems and liver necrosis. Three of 11 mice died after bare silica particles were administered, whereas no acute adverse effects were observed after the administration of Q-SiPaLCs.

The distribution of Q-SiPaLCs at the cellular level was investigated with confocal scanning laser microscopy and TEM (3). Mice were euthanized 24 h after particle injection, and organ sections were taken from the liver, spleen, kidney, lung, and heart. The Q-SiPaLCs and bare silica particles were observed in the liver and spleen, and bare silica particles were also observed in the lung. The macrophage stain revealed a high degree of colocalization between both types of particles and macrophages. The Q-SiPaLCs were localized in the lysosomal parts of macrophages and remained well dispersed in the organs; bare silica particles aggregated to a much larger extent, and the aggregates were mostly found in or adjacent to blood vessels. In the lung, aggregates were also found to block the capillaries.

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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