Pharmacokinetics and bio-distribution of a novel silica-based multimodal nanoparticle

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Introduction

Silica is a highly potential carrier material for novel and multimodal nanoparticles that will find their use in molecular imaging. Although extensive studies report on their surface modification and inclusion of a wide variety of diagnostically active materials, *e.g.* iron oxide or quantum dots, their limited bio-applicability has still to be resolved. Here we report the first study on the pharmacokinetics and bio-distribution of silica-coated quantum dots with a biocompatible paramagnetic and pegylated lipidic coating (Q-SiPaLC) in mice. In the novel surface coating method, hydrophilic silica-coated quantum dots are first made hydrophobic, after which they are enclosed in paramagnetic and pegylated lipids to yield Q-SiPaLCs (Figure 1A). Upon intravenous administration of the Q-SiPaLCs, magnetic resonance angiography (MRA) was performed and the nanoparticle pharmacokinetics and biodistribution were studied using ICP-MS and fluorescence imaging. Fluorescence imaging and confocal scanning laser microscopy (CSLM) were employed for optical investigation of the particle biodistribution on organ and (sub)cellular level, respectively.

Material and Methods

QDs were incorporated in silica, rendered hydrophobic and coated with paramagnetic and pegylated lipids to yield the Q-SiPaLCs as schematically represented in figure 1A. The inset shows a transmission electron microscope (TEM) image of the silica-coated QDs (Si-QDs). Non-coated Si-QDs were used as a control agent. For *in vivo* MRA mice were anesthetized and an infusion line with the Q-SiPaLC contrast agent was inserted into the tail vein. Animals were placed in a 9 T MRI scanner. Three dimensional gradient echo images were generated prior to and at several time points post administration of the contrast agent. For determination of the half-life value sequential blood draws were taken post injection. Gadolinium, cadmium and silicon concentrations were determined using ICP-MS. In addition, relaxation measurements of the samples were performed using a Bruker Minispec. For half-life value determination with fluorescence imaging blood samples were taken and centrifuged after sampling to separate red blood cells from plasma. Fluorescence signal from the plasma was quantified and related to the half-life values obtained with ICP-MS. The Q-SiPaLCs and Si-QDs bio-distributions were investigated by fluorescence imaging and ICP-MS of the heart, liver, kidneys and spleen of mice sacrificed at different time points post injection. All fluorescence imaging experiments were performed on a Xenogen IVIS-200. Sections of the heart, liver, kidney and spleen were stained for endothelial cells with lectin-Alexa-488, for macrophages with CD68-Alexa-647 and for cell nuclei with DAPI and imaged on a Zeiss LSM-510 Meta CSLM.

Results and Discussion

The suitability of the monodisperse and multimodal Q-SiPaLCs (Figure 1A) for MR imaging is shown by the angiograms in Figure 1B and. Due to the high relaxivity (r_1 = 14.4 $mM^{-1}s^{-1}$) of Q-SiPaLCs the poorly visible blood vessels prior to administration (Figure 1B, left) became clearly visible post administration (Figure 1B, right). The half-life values of Q-SiPaLCs and Si-QDs were calculated from the curves presented in Figure 1C. As compared to the non-coated silica particles we observed a 10-fold increase in case the particles were coated with lipids ($t_{1/2}$ = 17 min vs. 180 min). Fluorescence imaging of the intact organs revealed that the Q-SiPaLCs were mainly cleared by the liver and spleen. No accumulation was observed in the kidneys and heart (Figure 2A). CSLM of organ sections confirmed these observations since a high uptake of Q-SiPaLCs in liver and spleen and negligible uptake in the kidneys and heart was observed. Importantly, compared to half-life values of commercially available pegylated QDs ($t_{1/2}$ = 3-4 min) our approach yields considerable higher values ($t_{1/2}$ = 180 min) (1).

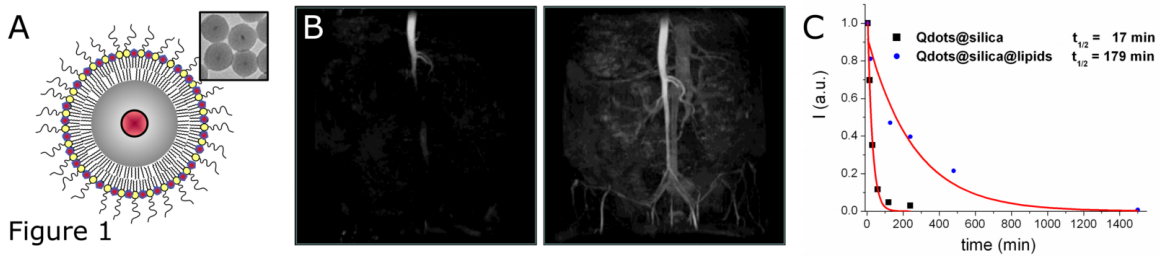

Figure 1

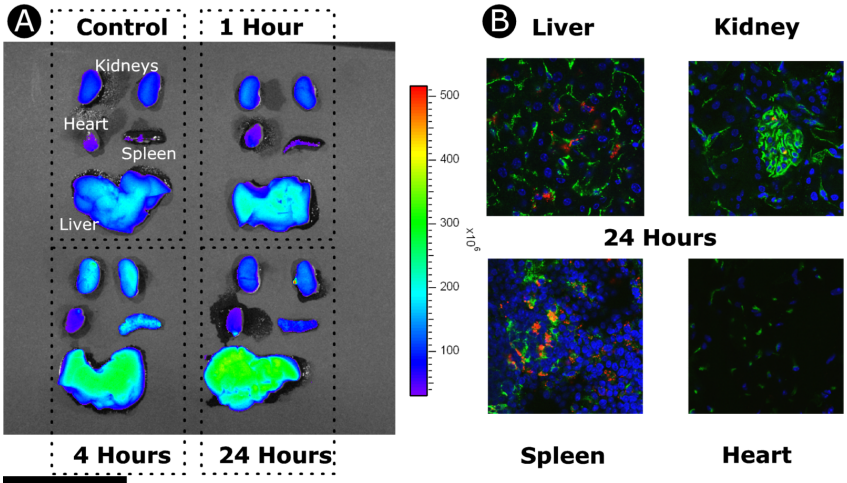

Figure 2

Conclusions

In this study we investigated the pharmacokinetics and biodistribution of silica nanoparticles with a paramagnetic and pegylated lipidic coating using a multimodality approach. The pharmacokinetics of the lipid-coated particle is improved drastically as compared to the non-coated nanoparticle. The improved properties of the Q-SiPaLCs as compared to non-coated Si-QDs and commercially available QDs shows the importance of this novel silica coating for the development of silica-based and bio-applicable multimodal nanoparticles and may therefore be generalized to improve the applicability of a wide range of different nanocrystals.

Reference

(1) Schipper *et al.* J. Nuclear Med. 2007.