Surface modification of magnetic nanoparticles (MNPs) using zwitterionic dopamine sulfonate (ZDS) for elongated blood circulation to detect tumor cells via MRI

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ABSTRACT

Magnetic nanoparticles (MNP) have enormous potential to be used as contrast agents on MRI, because the magnetisms they possess are proportional to contrast effects. However, when applied, myriads of serum proteins rapidly adsorb to the particles and their function suffers drastic changes. The phenomenon is called 'bio-corona effect'. Due to the effect, nanoparticles are rapidly removed from blood. The effect renders the particles to sufficient size for mononuclear phagocytic cells to engulf. One of the prevailing methods to overcome this challenge is to coat the particles by polyethylene glycol (PEG) groups. Nonetheless, it is known that the ligands easily form polymers, which increases the size of the particles. It results in vulnerability to mononuclear phagocytic system (MPS). Therefore, we synthesized and coated zwitterionic dopamine sulfonate (ZDS) to Zn^{2+} doped nanoparticle ($Zn_{0.4}Fe_{2.6}O_4$) through ligand exchanging method. We compared the size, zeta potential, and stability of nanoparticles coated with different ligands such as PEG and silica. We expected that the smaller size and neutral charge of ZDS will prevent the elimination from the blood. Due to the enhanced permeability effect (EPR), which provides a room for the nanoparticles to penetrate and reside in tumor tissue, elongated blood circulation could efficiently convey the particles to the tumor sites. We intravenously injected these particles to cancer xenografted BALB/c nude mice and successfully observed the contrast effect on MRI images.

Introduction

Mechanisms for NP sequestration

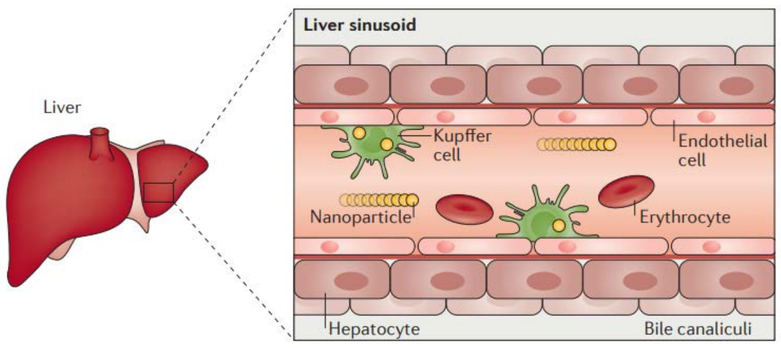


Figure 1. The liver is the primary organ for the mononuclear phagocytic system (MPS) that entraps a vast majority of the administered nanoparticle dose. Kupffer cells are aligned through the liver sinusoid. The nanoparticles are engulfed by phagocytic cells mostly according to their size.

Enhanced permeability and retention effect

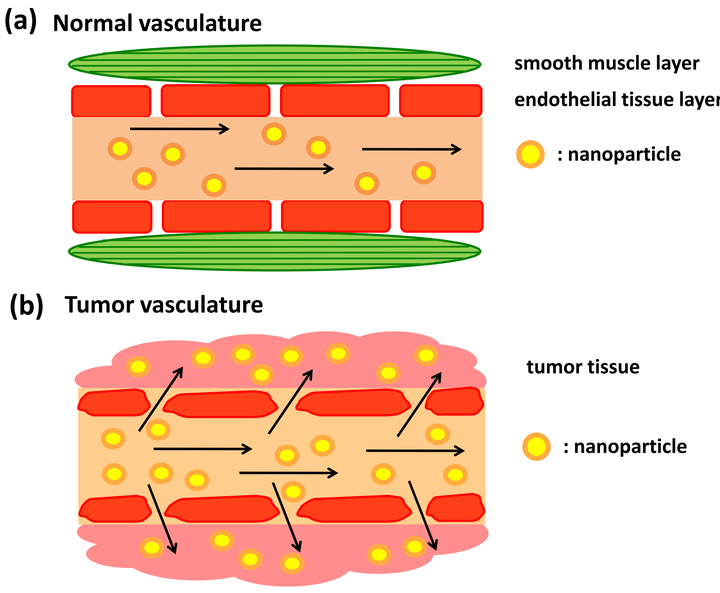


Figure 2. (a) Smooth muscle layer is surrounding the endothelial cells. It maintains the airtight pathway for nanoparticles to pass by. (b) On the other hand, the mother vessels formed by tumor angiogenesis are flaccid and provides the fenestration for nanoparticles to diffuse into the tumor tissue. This leads to the lingering movement of nanoparticles inside the tumor cells.

Bio-corona effect

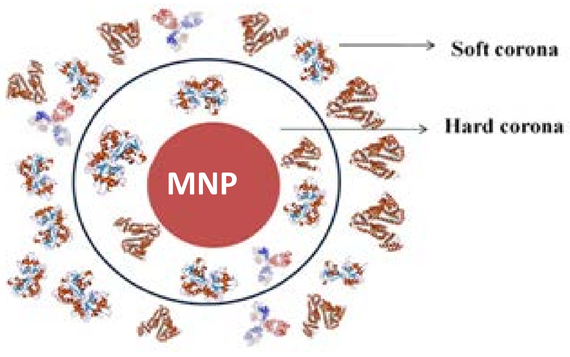


Figure 3. When nanoparticles are applied to a biological system, their surface is surrounded by biomolecules such as serum proteins. This drastically changes the feature of nanoparticles, rendering new 'biological character' of those molecules. Bio-corona effect contributes to the increment of the nanoparticle diameter, and it facilitates MPS to devour the particles.

Zwitterionic Dopamine Sulfonate coating

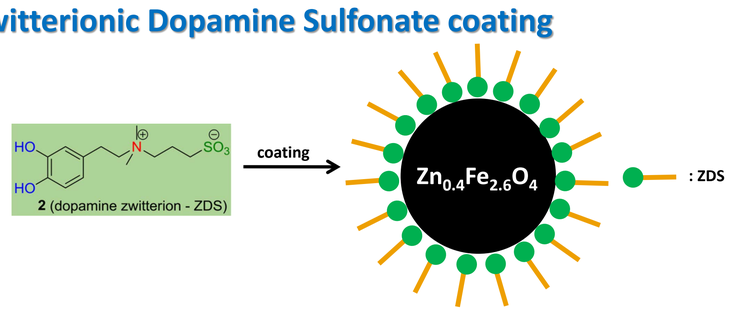
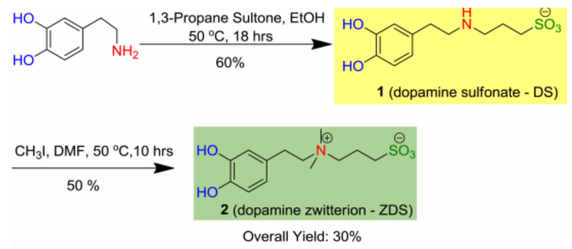


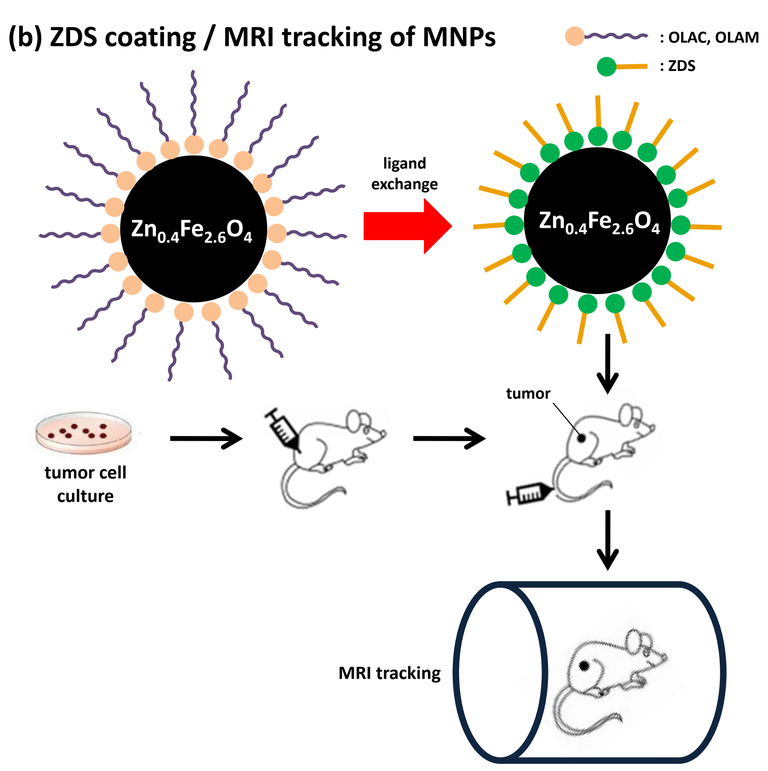
Figure 4. By using zwitterionic dopamine sulfonate (ZDS) as a ligand to conjugate on the MNP surface, bio-corona effect is alleviated due to its neutral charge. Furthermore, thin coating it provides help MNPs to circumvent the MPS processes.

Scheme

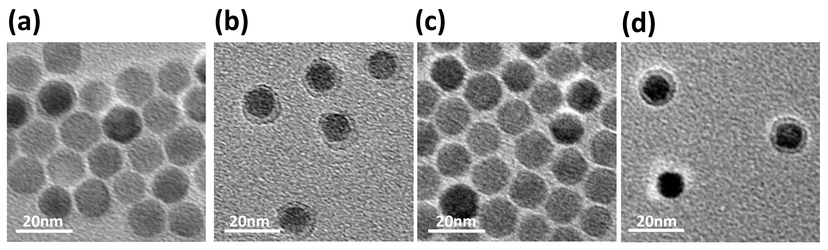
(a) ZDS synthesis

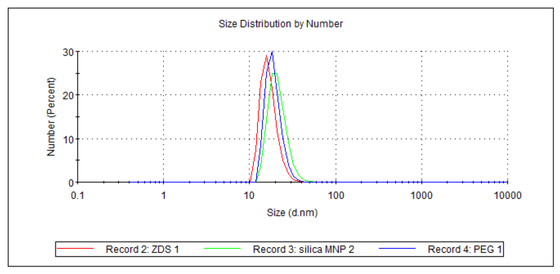


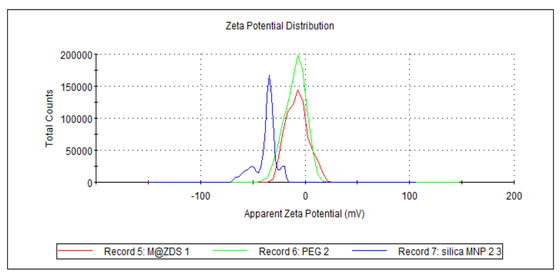
(b) ZDS coating / MRI tracking of MNPs



Results







(g)

	MNP(core)	ZDS	PEG	Silica
HD (nm)	14.81	16.33	19.55	22.33
Zeta potential (mV)		-7.64	-9.63	-37.4

Figure 5. TEM image of 13nm $Zn_{0.4}Fe_{2.6}O_4$ nanoparticles (core) attached to different ligands. (a) Core coated with oleic acid/oleic amine (OA), (b) core coated with ZDS, (c) core coated with PEG, (d) and core coated with silica. (e) The graph shows the size distribution of each particles. ZDS, silica, PEG coated particles are depicted in color of red, green, blue respectively. (f) The graph shows the zeta potential of each particles.

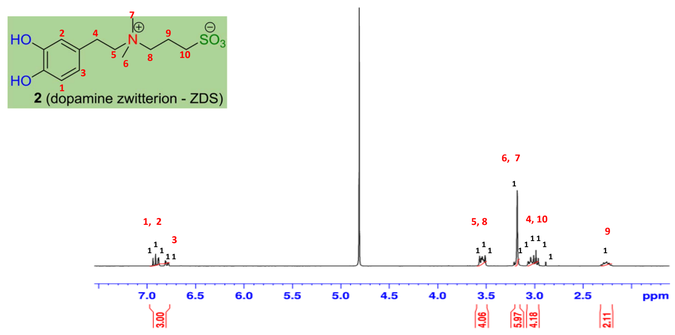
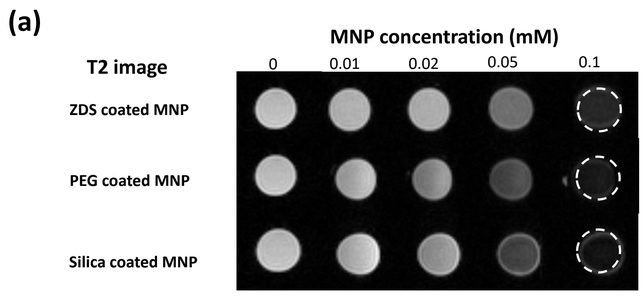
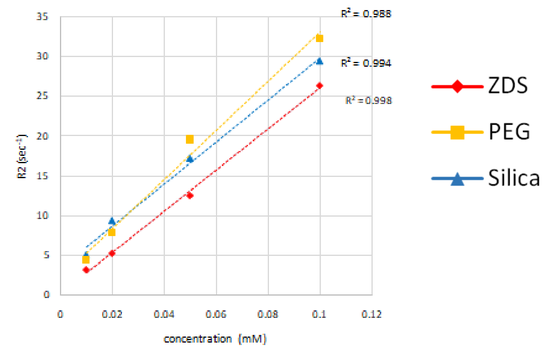


Figure 6. After the synthesis and purification of ZDS, it was characterized by NMR. NMR spectrum of zwitterionic dopamine sulfonate (ZDS) demonstrated that the molecule synthesized was pure ZDS.

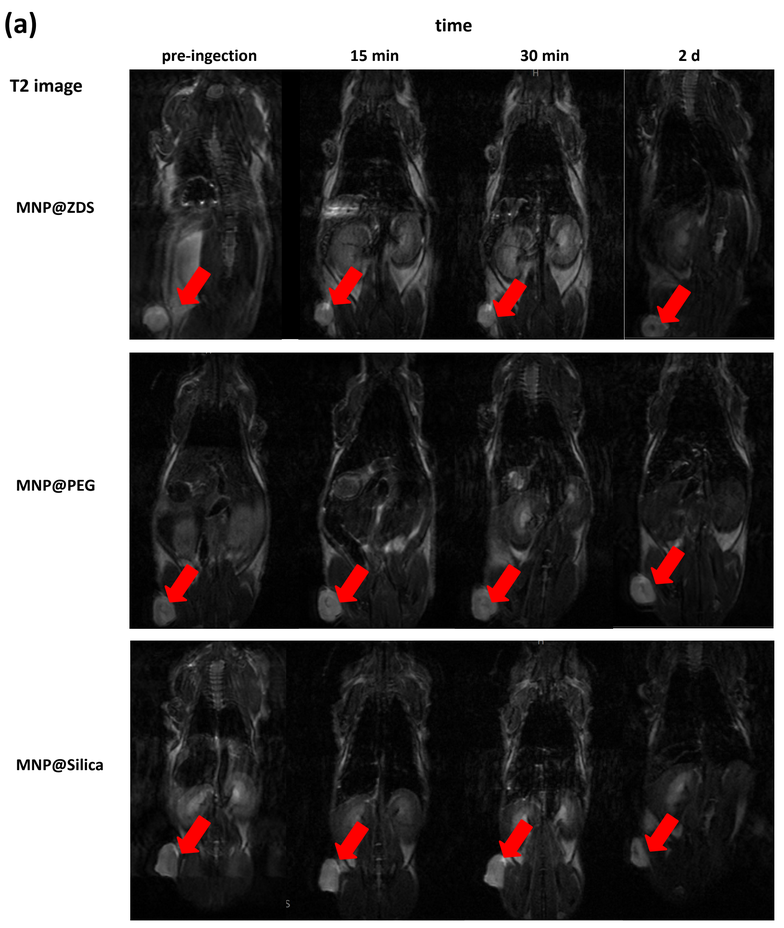




(c)

	ZDS	PEG	Silica
r2 ($mM^{-1}sec^{-1}$)	258.9	309.5	262.9

Figure 7. (a) T_2-weighted MR images of ZDS, PEG, silica coated MNPs were measured via MRI. (b) Graph of R2 values by concentration of ZDS, PEG, silica coated MNPs. Each particles are drawn in red, yellow, blue respectively. (c) The slope of the graphs implies the r2 value of each particles.



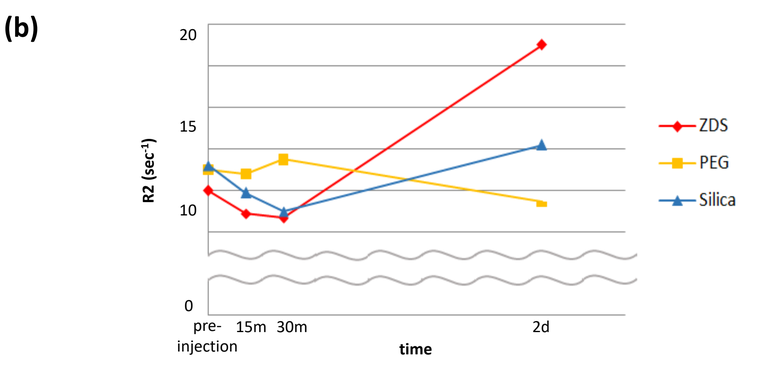


Figure 8. (a) T_2-weighted MR images of a mouse injected with ZDS-coated, PEG-coated, and Silica-coated $Zn_{0.4}Fe_{2.6}O_4$ nanoparticles, (b) Graphs of R2 values of ZDS-coated, PEG-coated, and silica-coated $Zn_{0.4}Fe_{2.6}O_4$ nanoparticles by time.

Conclusion

We synthesized and coated zwitterionic dopamine sulfonate (ZDS) to Zn^{2+} doped superparamagnetic nanoparticles ($Zn_{0.4}Fe_{2.6}O_4$). The particles were small sized, neutral, and stable enough to circumvent bio-corona effect, which results in the mononuclear phagocytic system (MPS) that sequesters nanoparticles through out the body.

2 days post-injection demonstrated the prolonged blood circulation of the nanoparticles. The resulted R2 values in tumor site of mice injected with the ZDS coated particle outweighed that of PEG, silica coated controls. The *in vivo* study using BALB/c nude mice exhibited relatively darker T2 contrast images due to higher MNP concentrations. This result elucidated the fact that attaching zwitterionic ligands to MNPs will bestow the opportunity to use intravenous injection of nanoparticles to track cancer residing in unknown regions.

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