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CION v2.0: a better way to T1 enhancement with iron oxides

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Introduction and purpose

Molecular imaging and nanomedicine approaches to the diagnosis, monitoring and treatment of cardiovascular diseases, *e.g.* atherosclerosis, could have significant consequence on medical practice and outcomes. Due to the exquisite sensitivity of MR to magnetic field disturbances of iron oxides (IO), a variety of IO-based agents have been utilized. However, despite many elegant new imaging techniques, the highly-sensitive detection and visualization of IO still depends on the disruption of the local magnetic field. Contrary to typical IO agents, we have presented a novel colloidal iron oxide nanoparticle (CION) that encapsulates multiple magnetite nanocrystals suspended in oil, encased in a lipid membrane thereby reducing T2* effects such that T1 effects can be detected. The purpose of this work was to develop a CION with improved longitudinal relaxivity (r1) and the ability to carry drugs.

Methods

To evaluate the role of IO concentration within the oil core, CION were created with [IO] of 7.5%, 15% and 45% (w/v) Fe_3O_4, both with and without cross-linking the outer lipid membrane. To compare the effect of iron phase, CION was made with mixed-phase maghemite (Fe_2O_3-Fe_3O_4) at 7.5% (w/v). CION were characterized using dynamic light scattering, vibrating sample magnetometer, atomic force microscopy (AFM) and transmission electron microscopy (TEM). The r1 was calculated at 1.5 T using the Look-Locker technique to measure T1 of serial dilutions of CION. To demonstrate drug-carrying capability, fumagillin was incorporated into the outer surfactant. A dissolution study was performed over 3 d.

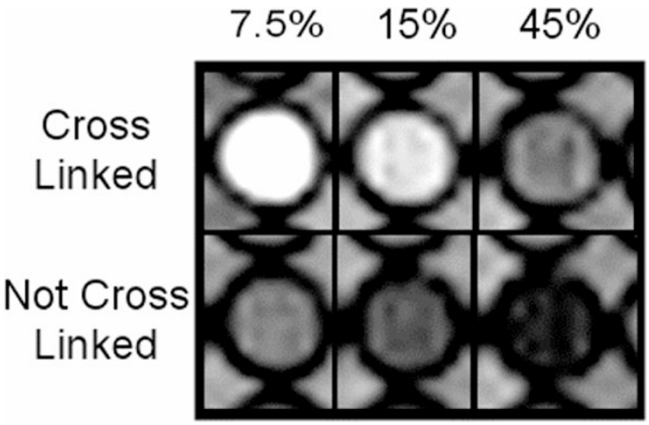

Figure 1
T1w images of various CION formulations. Cross-linking (top row) the outer lipid membrane dearly increases the T1 effects compared to without cross-linking (bottom row) as soes reducing the overall IO concentraion within the oily core of the CION (columns). At the highest iron concentration within the CION (45% w/v), the T2* effects overwhelm the T1 effects (bottom right).

Results

Hydrodynamic diameter and zeta potential of the CIONs ranged from 110-300 nm and 23 to 40 mV, respectively, depending on composition. AFM revealed an asymmetric (deformable) particle size of 114 ± 22 nm (height) by 228 ± 69 nm (diameter). TEM confirmed that the iron nanocrystals were retained in the oil core. In all cases, r1 ([Fe]mMs^{-1}) of the cross-linked CION was 2-3× greater than the non-cross-linked version. Decreasing magnetite loading (45%, 15%, 7.5%) increased r1 from 1.8, 4.5, to 7.7, respectively. Comparing CION comprising magnetite vs. mixed-phased maghemite nanocrystals gave an r1 of 7.7 vs. 1.3, respectively, the lower susceptibility pure phase performing better. T1-weighted imaging confirmed r1 relationships (see Figure 1). For loading fumagillin into CION, 98% efficiency was achieved with less than 1% released over 3 d.

Conclusion

Targeted CION is a positive-contrast T1 agent wherein pure magnetite, low Fe concentration, and cross-linking each augment overall r1 relaxivity. Additionally, CION offers a good potential platform for targeted drug delivery exhibiting excellent drug retention in dissolution.

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