Nanoparticle CEST MRI for better visualization

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INTRODUCTION:

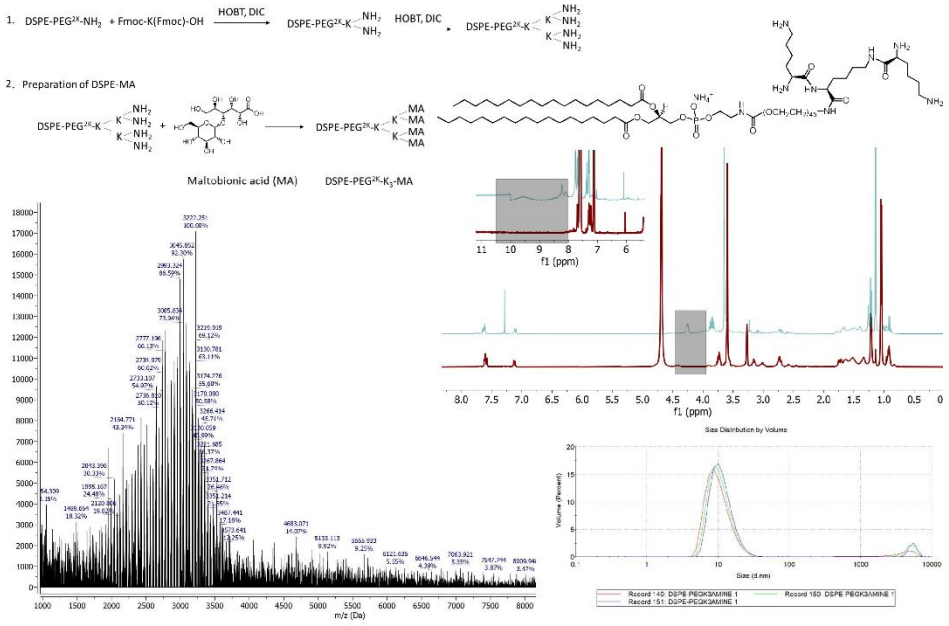
Amphiphilic diamagnetic CEST agents can be formulated into micellar and liposomal nanoparticles to increase the exchange rates of protons/ water molecules per particle compared to small molecules alone. Modified nanoparticle CEST agents may target tumors and provide an alternative MR imaging technique.

METHODS:

Micellar and liposomal nanoparticles were made by mixing an amphiphilic lipid (a diamagnetic CEST agent) with other lipids (DPPC, Cholesterol) or alone. One DSPE-PEG^{2K}-NH_2 amine was coupled with lysine (K) amino acid molecules to make the amphiphilic CEST agent with exchangeable amine and amide protons in its polar head. Liposomes are made by hydrating thin lipid film and extruding it to a size of around 100 nm. MALDI-TOF-MS (Matrix-assisted laser desorption/ionization coupled to time-of-flight mass spectrometry) was done to confirm the molecular weight of the lipid. ^{1}H NMR was acquired with a 400 MHz Bruker NMR to visualize the exchangeable amine and amide protons in different solvents. A DLS (Dynamic Light Scattering) instrument was used to measure the nanoparticles' size, distribution, and zeta potential. The addition of maltobionic acid (MA) to the polar head of amphiphilic lipid will provide better tumor targeting of the liposomes by improving the localization of the agent in the tumor site. CEST is observed using a Bruker BioSpec 7T MRI with a horizontal bore system.

RESULTS:

Our study has led to some intriguing findings. The synthesized amphiphilic lipid was characterized using MALDI-TOF MS and ^{1}H NMR, revealing exchangeable amide proton peaks in the ^{1}H NMR that were visible in DMSO-d_6/ $CDCl_3$ and disappeared upon the addition of methanol-d_4. The expected CEST peak positions for the exchangeable amide protons at 3.5 and 4.8 ppm offsets relative to the bulk water proton peak were observed. Interestingly, a 17 nm-sized micelle was found to form when the amphiphilic lipid was sonicated in DI water alone. We are currently in the process of acquiring MRI data to further explore these findings.



DISCUSSION:

The Z-spectra's asymmetry and multipool Lorentzian fitting will help elucidate the CEST peak position and intensity. Comparing the CEST with existing diamagnetic and paramagnetic lipoCEST examples[1] would position itself as a class. Due to multiple exchange sites, liposomal nanoparticles are expected to produce intense localized CEST during MRI acquisition. Adding MA to the polar head of amphiphilic lipid will provide the Warburg effect for better tumor targeting of the liposomes and localization of the liposomes therein.

CONCLUSION:

Nanoparticle CEST could help overcome the current primary challenge of CEST MRI acquisitions—the high detection limit of the CEST agents. This amphiphilic lipid is expected to have lower toxicity to viable cells and similar pharmacokinetics to liposomes made of natural/semisynthetic lipids.

REFERENCES:

1. Morrow, J. R., *et al.* Encyclopedia of Inorganic and Bioinorganic Chemistry 2020, pp 1-19.