Multiparametric monitoring of drug-loaded DMSO liposomes using CEST MRI

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INTRODUCTION:

Dimethyl sulfoxide (DMSO) and its protic and aprotic analogs were reported to generate CEST effect at negative offsets[1]. Given its role as a widely used solvent for biomedical application, we are interested in investigating the physiochemical and CEST properties of DMSO liposomes. Interestingly, we observed distinctive CEST contrast at negative offsets for DMSO liposomes, demonstrating the potential of monitoring such common drug nanocarriers using a label-free approach.

METHODS:

Barbituric acid (BA) with detectable CEST signal at 5 ppm was selected as a model drug. 100 mM of BA was dissolved in HEPES buffered saline (HBS) or 10% v/v DMSO in HBS (final pH = 7.2) and incorporated into liposome respectively. Liposome was prepared with thin film hydration method and with formulation of DSPC:Cholesterol:DSPE-PEG2000 = 50:40:10[2]. Size, polydispersity index (PDI), zeta-potential and concentration of liposome were measured and unencapsulated BA was removed using Sephadex gel column. Liposomes with different solvent systems were dialyzed against HBS at 0.25, 0.5, 1, 3, and 6 hours. Samples from each timepoint were taken for CEST and UV absorbance measurements of BA (n = 3). Acquisition and saturation parameters at Bruker BioSpec 3T were: TR = 9 s, TE = 75 ms, continuous wave irradiation with B_1 = 1.2 μT, T_{sat} = 4 s. Step size is 0.1 ppm for –1 to 1 ppm range and for ±0.4 ppm around interested offsets (5 and –2 ppm), and 0.2 ppm for other regions from –10 to 10 ppm.

RESULTS:

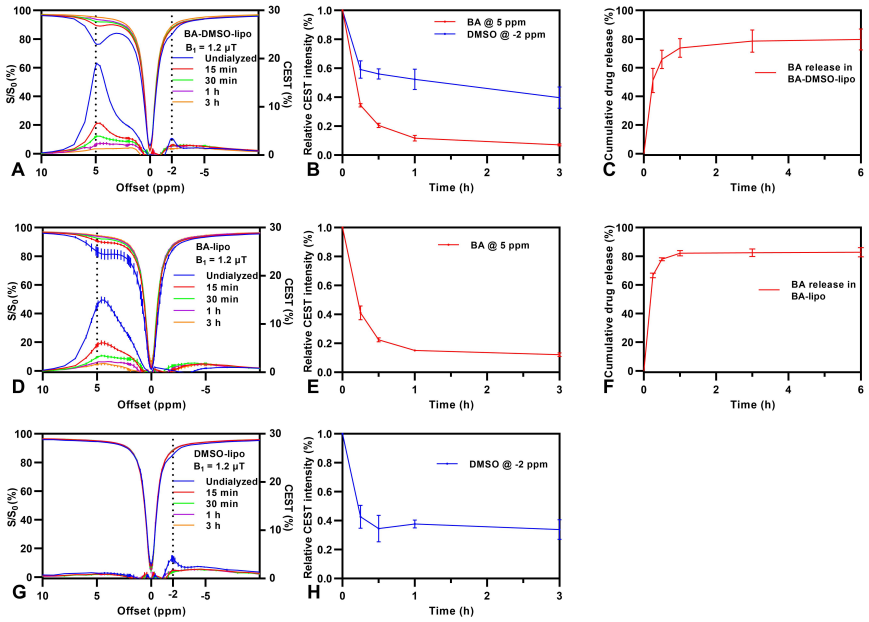

Figure 1. CEST measurement (Z-spectrum and Lorentzian analysis) and release study of BA-DMSO liposome **(A-C)**, BA-liposome **(D-F)**, and DMSO-liposome **(G, H)**

DISCUSSION:

All three groups of liposomes had size of 160- 200 nm, PDI<0.1, and zeta-potential between –1.5 and –2 mV. The loading of BA in DMSO liposome (BA-DMSO-lipo) and control liposome (BA-lipo) were around 55 mM and 53 mM. **Figure 1A** and **1D** showed that BA-DMSO-lipo had CEST peak at 5 ppm with narrower FWHM and generate ~10% higher CEST contrast when compared to BA-lipo, which could be a result of BA-DMSO interaction[3]. This could also be observed by comparing the relative change of DMSO signal at –2 ppm in BA-DMSO-lipo with DMSO-lipo (**Fig. 1B** and **1H**), where a relatively slow release and more retention of DMSO were seen in BA-DMSO-lipo. Although we observed a slightly faster release within the first hour for BA-lipo which could be due to the solvent gradient during dialysis, the overall release for both BA-DMSO-lipo and BA-lipo were comparable (**Fig. 1C** and **1F**).

CONCLUSION:

Monitoring of components of drug-DMSO-liposome system, i.e. lipid bilayer, small-molecule drug, and solvent, was demonstrated. Additionally, CEST could also probe the drug-solvent interaction and its effect on the release of the drug. With comparable physiochemical properties as DMSO-free liposome, DMSO-liposome showed potential for monitoring the delivery and solvent interaction of DMSO-formulated drugs in a label-free manner.

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