T1 Relaxivity of Liposomal-Encapsulated Gadolinium Contrast Agents: Effect of Particle Size and Gadolinium Concentration

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Introduction: Long circulating PEGylated liposome-encapsulated Gadolinium nanoparticles (liposomal-Gd) have been used as MR contrast agents for several applications [1-3]. The encapsulation of Gadolinium chelates inside long circulating liposomes changes the pharmacokinetics of the contrast agent and provides the long circulation and intravascular property to these agents. Further, the shielding of Gadolinium chelates by the lipid bilayer of the liposome changes the relaxation properties of the liposomal-based Gadolinium agents. In this study, the effect of liposome size and internal Gadolinium concentration on the T1 molar relaxivity of liposomal-Gd was investigated. Liposomal-Gd formulations of different liposome size and various internal Gadolinium concentrations were synthesized. The T1 molar relaxivities of the liposomal-Gd formulations were determined on a 2 Tesla and a 7 Tesla MR scanner.

Materials and Methods: Three solutions with different Gadolinium concentrations were used for liposomal-Gd synthesis (500 mM, 350 mM and 250 mM Gadolinium). A lipid mixture consisting of 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine, Cholesterol and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(poly(ethylene glycol))-2000] (mPEG2000-DSPE) in the ratio 55:40:5 was dissolved in ethanol and then hydrated with one of the three Gadolinium solutions and stirred for 2 hr at 60°C. Depending on the final liposome size, the solution was sequentially extruded with ten passes through 400 nm, ten passes through 200 nm, ten passes through 100 nm and ten passes through 50 nm Nuclepore membrane. The solutions were then exhaustively dialyzed against 150 mM sodium chloride solution. The size of the resultant liposomal formulations was determined by dynamic light scattering (DLS). The concentration of Gadolinium in the liposomal-Gd formulations was determined using inductively coupled plasma atomic emission spectroscopy (ICP-AES). T1 measurements were performed on 2 T and 7 T MR scanner. A 7-cm birdcage RF body coil was used for transmit and receive for experiments on the 2 T scanner. A 3-cm birdcage RF body coil was used for transmit and receive for experiments on the 7 T scanner. The temperature in the MR scanner was maintained at 37±0.5°C throughout the experiment. The T1 relaxation times of the samples were determined using a multi spin multi-echo (MSME) sequence. The following imaging parameters were used for experiments performed on 2 T and 7 T scanner: echo time (TE) = 8 ms, repetition time (TR) was varied from 30 – 14000 ms, Slice thickness = 4 mm, bandwidth = 31.25 KHz, image matrix = 256 x 128, number of excitations (NEX) = 1.

Nuclepore size (nm)	Initial Gd concentration (mM)		
	200	**350**	**500**
50	75.3	70.5	72.6
100	100.7	94.1	94.5
200	154.1	153.4	160.8
400	253.5	310.3	274.2

Table 1. DLS determined diameter (nm) of liposomal-Gd formulations.

Results and Discussion: The resultant size of various liposomal-Gd formulations synthesized is shown in Table 1. A plot of T1 molar relaxivity as a function of liposome size for various liposomal-Gd formulations, at 2 Tesla, is shown in Figure 1A. The T1 relaxivity decreases with an increase in the liposome size. The drop in T1 relaxivity is attributed to the decreased surface area to volume ratio which increases with liposome size. As the surface area to volume ratio decreases, the number of bulk protons (outside the liposome) that can interact with the Gadolinium atoms, encapsulated within the liposome, deceases. The largest change in T1 relaxivity was observed between liposomes that were extruded through 50 nm and 100 nm membranes. The T1 molar relaxivities of various liposomal-Gd formulations at 7 Tesla are shown in Figure 1B. Similar to the behavior at 2 T, the T1 relaxivity decreased with an increase in the liposome size. At both field strengths, the variation in the internal Gadolinium concentration did not have any major effect on the T1 relaxivity of the liposomal-Gd for the same liposome size. This indicates that the movement of protons through the lipid bilayer is the dominant factor in determining the T1 relaxivity of the liposomal-Gd.

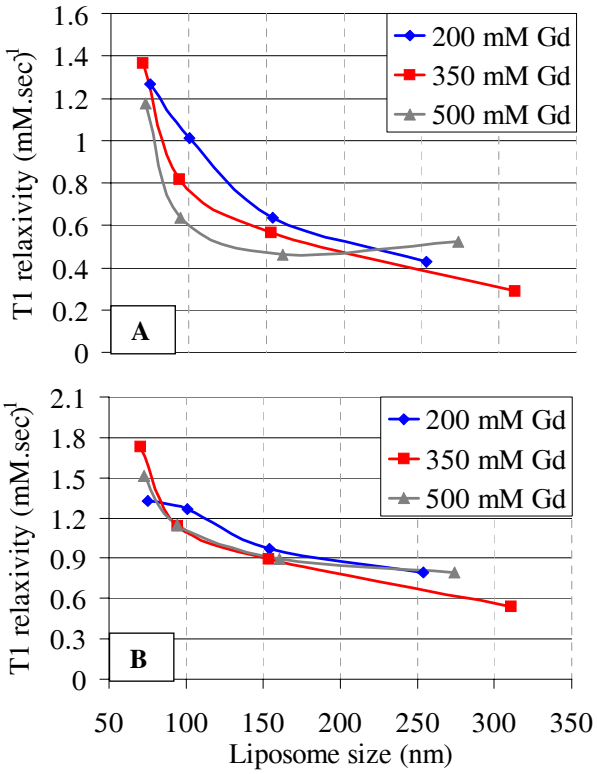

Figure 1. T1 molar relaxivity of liposomal-Gd formulations at 2 Tesla (A) and 7 Tesla (B).

Conclusion: The following study demonstrates that the liposome size plays a critical role on the T1 relaxivity of liposomal-Gd formulations with the maximum T1 relaxivity observed for the smallest liposome size. Further, the internal Gadolinium concentration does not have a major effect on the T1 relaxivity. More importantly, the long circulating liposomal-Gd formulations that are routinely utilized (50-100 nm) provide good imaging properties for use as intravascular T1-based MR contrast agents.

References:

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