

Study of Gd-based MR contrast agents encapsulated in the phosphatidylglyceroglycerol-based thermosensitive liposomes for improved MR-guided chemothermotherapy

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Introduction: Recently, a new formulation based on phosphatidylglyceroglycerol (DPPGOG) of thermosensitive liposomes (TSL) with encapsulated ¹H MR T₁ contrast agent (CA) gadodiamide has been designed [1] and characterized in vitro and in vivo [2,3] for noninvasive MR temperature monitoring during chemotherapy combined with hyperthermia in patients with soft tissue sarcomas. The encapsulated gadodiamide is released around the gel-to-liquid crystalline phase transition temperature of phospholipid membrane and leads to the MR signal intensity change due to T₁ shortening. In this work, four representative Gd-based T₁ CAs with diverse chemical structures were separately encapsulated in the DPPGOG-TSL and studied by measuring the dependence of their T₁ on temperature while heated from 30 to 50 °C to explore their potential for the optimal T₁ enhancement effect.

Materials and Methods: Linear nonionic Gd-DTPA-BMA (Omniscan™, GE, USA), linear ionic Gd-DTPA (Magnevist®, Bayer, Germany), macrocyclic nonionic Gd-BT-DO3A (Gadovist®, Bayer, Germany), and macrocyclic ionic Gd-DOTA (Dotarem®, Guerbet, France) were previously diluted to 323 mOs kg⁻¹ with water from the stock solutions and yielded a final concentration of 250, 81, 202, and 115 mM, respectively, under consideration of their different osmolalities [4]. The DPPGOG-TSL with these CAs were then prepared separately by successive lipid film hydration, extrusion, and dialysis [2]. A sample of the DPPGOG-TSL with each CA was incubated for 10 minutes at the desired temperature in order to reach the thermal equilibrium while heated from 30 to 46 °C in steps of 2 °C and the T₁ ± standard deviation was acquired once. All T₁ measurements were performed on a 0.47 T-NMR-Analyzer (Minispec NMS120, Bruker, Germany) and by using the inversion recovery technique in combination with a water bath and a thermostat.

Results: In Figure 1, from 30 to 38 °C, water exchange between the DPPGOG-TSL interior and exterior increased with the exception of negligible CA release from the DPPGOG-TSL, resulting in the slight T₁ decreases. The release began at approximately 37.6 °C and ended at 43.4 °C, resulting in the drastic T₁ decreases. Above 43 °C, all encapsulated CAs were completely released and T₁ changes were not more obvious. Table 1 summarized T₁ values at 37.6 °C and 43.4 °C as well as the corresponding percent T₁ decreases (ΔT₁%). The DPPGOG-TSL with encapsulated macrocyclic nonionic Gadovist® and linear nonionic Omniscan™ showed strong ΔT₁% of -67% and -64%, respectively. In comparison, those with encapsulated macrocyclic ionic Dotarem® and linear ionic Magnevist® showed weak ΔT₁% of -40% and -14%, respectively.

Conclusions: These preliminary results showed that Gd-based CAs with nonionic chemical structure seem to be more suitable than that with ionic structure and additionally one with macrocyclic structure is better than that with linear structure for the optimal application of DPPGOG-TSL to noninvasive MR thermometry during tumor treatment using chemotherapy combined with hyperthermia.

References: [1] Lindner LH, et al. Clin Cancer Res 2004;10:2168–2178. [2] Wang T, et al. Contrast Media Mol Imaging 2008;3:19–26. [3] Peller M, et al. Invest Radiol 2008;43:877–892. [4] Laurent S, et al. Contrast Media Mol Imaging 2006;1:128–137.

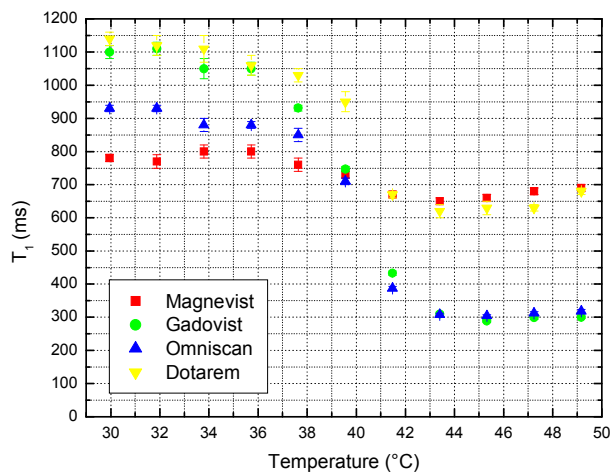


Figure 1: Temperature dependence of the T₁ of DPPGOG-TSL with diverse encapsulated Gd-based CAs while heated from 30 to 50 °C.

CA trade name	Chemical structure	T _{1,37.6°C} (ms)	T _{1,43.4°C} (ms)	ΔT ₁ %
Magnevist®	linear ionic	760 ± 20	650 ± 10	-14%
Gadovist®	macrocyclic nonionic	931 ± 9	310 ± 5	-67%
Omniscan™	linear nonionic	850 ± 20	308 ± 4	-64%
Dotarem®	macrocyclic ionic	1030 ± 20	620 ± 20	-40%

Table 1: The T₁ of DPPGOG-TSL with diverse encapsulated Gd-based CAs at 37.6 (T_{1,37.6°C}) and 43.4 °C (T_{1,43.4°C}) as well as the corresponding percent T₁ decreases ΔT₁% = (T_{1,43.4°C} - T_{1,37.6°C}) / T_{1,37.6°C}. These T₁ values are also found in Figure 1.