Quantification of release of thermosensitive liposome-encapsulated gadodiamide

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Introduction: Thermosensitive liposomes (TSL) were designed for enhanced local release of drugs by hyperthermia, exploiting the fact that TSL-encapsulated drugs are released at the gel-to-liquid-crystalline phase transition of TSL [1]. Recently, a novel formulation of TSL has been successfully developed [2]. In previous work, the temperature dependence of T_1 of these TSL with the encapsulated T_1 MR contrast agent, gadodiamide, has been studied and showed potential in monitoring the therapeutic temperature at 42 °C during tumor treatment using combined chemotherapy and hyperthermia [3]. In this work, the concentration of released gadodiamide was evaluated.

Theory: In general, the concentration C of the T_1 contrast agent delivered to the tissue can be expressed as Equation 1: $C = (1/T_1(C)-1/T_1(0))/r_1$ where $T_1(0)$ is the intrinsic T_1 of the tissue, $T_1(C)$ is its shortened value, and r_1 is the T_1 relaxivity with units of 1/(mM*s) [4]. To estimate the concentration of released gadodiamide, it was assumed that $T_1(0)$ is the T_1 of the gadodiamide-containing TSL at the beginning of the release, $T_1(C)$ is the T_1 at the end of the release, and r_1 is the T_1 relaxivity of the gadodiamide.

Materials and Methods: Gadodiamide-containing TSL consist of three lipids in the ratio of DPPC/DSPC/DPPGOG 5:2:3 (m/m) and enclose 250 mM gadodiamide (OMNISCAN™, Amersham, USA). These were prepared by successive hydration, extrusion, and dialysis [2]. In order to measure the total amount of gadodiamide present, the TSL were disrupted by adding Triton. For comparison, "empty" TSL with 0.85 mM and 0.90 mM non-encapsulated gadodiamide were prepared respectively. In addition, samples of pure water with diverse gadodiamide concentrations (0, 0.2, 0.4, 0.8, 1.6, 3.1, 6.3, 12.5, 25, 50, and 100 mM) were prepared for the evaluation of the T_1 relaxivity of gadodiamide. The temperature of all samples was varied between 30 °C and 50 °C and the corresponding T_1 was acquired at each temperature. All T_1 measurements were performed on a 0.47 T-NMR-Analyzer (Minispec, Bruker, Germany).

Results: Fig. 1 depicts the measured T_1 of gadodiamide-containing TSL while heated from 36.5 °C to 45.2 °C. The encapsulated gadodiamide was gradually released and resulted in the "sigmoid" T_1 shortening. The release began approximately at 38.5 °C with $T_1(0)$ = 1210 ms and ended at 43.3 °C with $T_1(C)$ = 257 ms. Fig. 2 shows the T_1 measurement of pure water with diverse gadodiamide concentrations at 43.3 °C. A linear relationship between the measured $1/T_1$ and gadodiamide concentration was presented with a high correlation coefficient R = 1.00 using linear regression. According to Equation 1, the resulting slope of this line, r_1 = 3.58 1/(mM*s), is the T_1 relaxivity of the gadodiamide at 43.3 °C. Combining the measured $T_1(0)$, $T_1(C)$, and r_1 values with Equation 1, the concentration of released gadodiamide is calculated as C = 0.86 mM. For comparison, the measured temperature dependence of T_1 of disrupted TSL, empty TSL with 0.85 mM as well as 0.90 mM non-encapsulated gadodiamide were plotted in Fig. 3. All samples show a typical, linear relationship between the measured T_1 and temperature with the same R = 0.99 and slopes of approximately 3.0 ms/°C. However, the fact that the intercept of the disrupted TSL is between those of the empty TSL verifies that the concentration of gadodiamide released from disrupted TSL ranges from 0.85 mM to 0.90 mM, consistent with our estimated value 0.86 mM.

Conclusions: The concentration of gadodiamide released from gadodiamide-containing TSL has been exactly estimated using MR T_1 measurement. This quantification helps us to better understand the mechanism of gadodiamide release, and thus to better characterize the gadodiamide-containing TSL, and further to optimize their application to MR online temperature monitoring during tumor treatment using combined chemotherapy and hyperthermia. The approach may additionally provide a novel noninvasive tool for drug dosimetry if the cytostatic drug can be loaded to gadodiamide.

References: [1] Yatvin MB, et al. Science 1978;202:1290-1293. [2] Lindner LH, et al. Clin Cancer Res 2004;10:2168-2178. [3] Wang T, et al. ISMRM 2006. p 1828. [4] Haacke EM, et al. Magnetic resonance imaging: physical principles and sequence design. p 367.

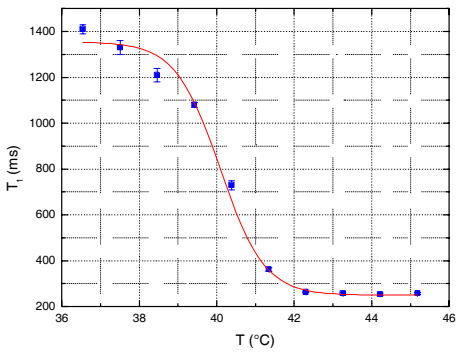

Fig. 1: Temperature dependence of T_1 of gadodiamide-containing TSL.

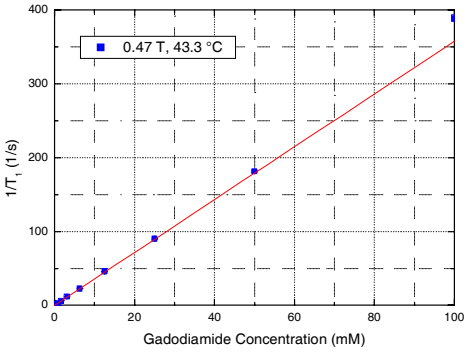

Fig. 2: T_1 measurement of pure water with diverse gadodiamide concentrations at 43.3 °C.

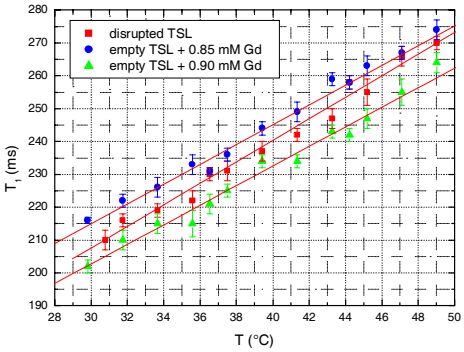

Fig. 3: Temperature dependence of T_1 of disrupted TSL, empty TSL with 0.85 mM and 0.90 mM non-encapsulated gadodiamide.