Temperature sensitive liposomes for drug delivery with MRI-HIFU

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Introduction

Temperature-triggered drug delivery is one of the treatment options in oncology that allows to deliver a high concentration of a chemotherapeutic compound to a tumor. Heating of the tumor slightly above body temperature can be accomplished using high intensity focused ultrasound (HIFU) under MR image guidance[1], while temperature sensitive liposomes (TSLs) can serve as drug carriers that efficiently release their payload upon heating. The combined encapsulation of a drug with MRI contrast agents may provide the ability of monitoring the drug delivery process in vivo using MRI[2,3]. In the work presented here, TSLs incorporating both a chemotherapeutic drug, *i.e.* doxorubicin, and a clinically approved MRI contrast agent, [Gd(HPDO3A)(H_2O)] (ProHance®) were prepared and evaluated for MR image guided drug delivery. Three different liposomal compositions were investigated for their temperature sensitive release properties.

Materials and methods

The three different liposomal formulations were prepared by lipid film hydration; low temperature-sensitive liposomes (LTSL, T_m= 38.8 ^{0}C), traditional temperature-sensitive liposomes (TTSL, T_m= 40.9 ^{0}C) and non-temperature sensitive liposomes (NTSL, T_m> 60 ^{0}C), all containing doxorubicin and [Gd(HPDO3A)(H_2O)]. The release of doxorubicin from the liposomes was determined by measuring the intensity of fluorescence (λ_{em} = 485 nm and λ_{ex} = 590 nm) as a function of the temperature. The release of [Gd(HPDO3A)(H_2O)] was studied by measuring the longitudinal relaxation time (T_1) as a function of the temperature at 300 MHz (Bruker Avance 300). For MRI-HIFU experiments, a gel phantom was prepared (agar 2% (*w/w*), silica 2% (*w/w*)), containing spots of agarose gel mixed with 10% (*v/v*) liposomes. Before and after heating for 2 min. at 42 ^{0}C with HIFU (Philips), a T_1 map was obtained with a Look-Locker EPI-sequence on a 3T clinical scanner (Achieva, Philips Healthcare, The Netherlands).

Results

The LTSL and TTSL showed a rapid release of encapsulated doxorubicin and [Gd(HPDO3A)(H_2O)] at $T \geq T_m$ (Figure 1). Within the measured temperature range the NTSL did not show any leakage of neither doxorubicin nor the MRI contrast agent. The spots containing LTSL and TTSL showed a significant decrease of the T_1 after the HIFU exposure, while the control spots containing NTSL or no liposomes did not show any changes (Figure 2).

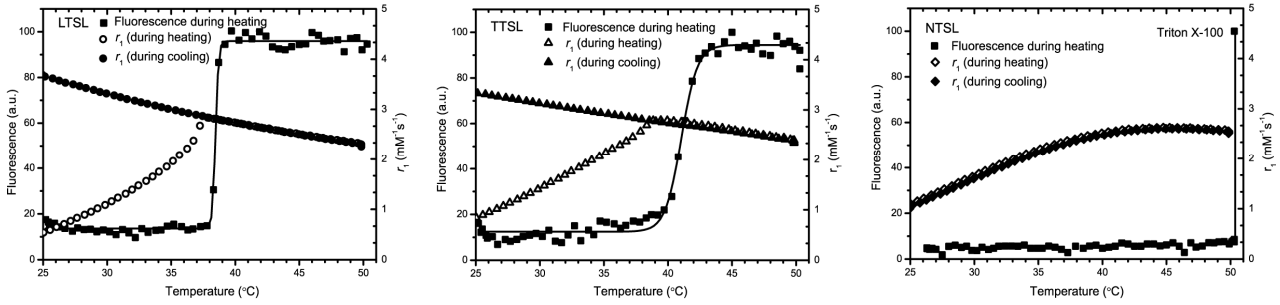

Figure 1. Fluorescence and T_1 relaxivity of liposomes (LTSL, TTSL and NTSL) during a linear temperature increase (0.5 K/min) from 25 ^{0}C to 50 ^{0}C.

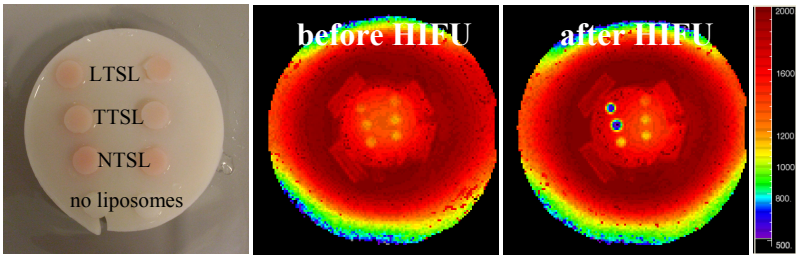

Figure 2. Gel phantom (left), T_1 map before HIFU (middle), T_1 map after HIFU (right). Only the left agarose spots were exposed to HIFU, the right spots served as a control.

Discussion and conclusion

Three different liposomal formulations containing both doxorubicin and [Gd(HPDO3A)(H_2O)] were successfully synthesized and investigated for their temperature sensitive release properties. The *in vitro* data presented here show that the LTSL and TTSL systems encapsulating both doxorubicin and [Gd(HPDO3A)(H_2O)] present promising formulations for *in vivo* use. In future work, these systems will be investigated *in vivo* for temperature induced drug delivery under MR image guidance using high intensity focused ultrasound to locally heat the target tissue.

References: 1) Dromi *et al*., Clin.Canc.Res. 2007 ; 2) Salomir *et al*., JMRI 2005 ; 3) de Smet *et al.* JCR (submitted)