

TEMPERATURE DEPENDENCE OF T_1 RELAXATION TIME OF NEW LONG-CIRCULATING THERMOSENSITIVE LIPOSOMES WITH ENCAPSULATED GADODIAMIDE

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Introduction

The use of thermosensitive liposomes (TSL) with either encapsulated gadolinium or manganese ions for MR thermometry and drug release has been proposed, exploiting the fact that paramagnetic gadolinium or manganese ions are released at the phase transition temperature of TSL from gel to liquid and act as T_1 -shortening MR contrast agent [1,2]. Recently, a novel formulation for long-circulating thermosensitive liposomes (LTSL) with encapsulated gadodiamide has been successfully developed and showed the phase transition temperature of 42°C which is consistent with the therapeutic temperature for the tumor treatment using the combined chemotherapy and hyperthermia [3,4]. The purpose of this work is to characterize the temperature dependence of T_1 relaxation time of these LTSL.

Methods

A sample of LTSL with encapsulated gadodiamide (OMNISCAN™, Amersham, USA) consists of three lipids in the ratio of DPPC/DSPC/DPPGOG 5:2:3 (m/m) and was prepared by successive hydration, extrusion and dialysis [3]. For comparison, an additional sample of LTSL with 2.5 mmol/l of non-encapsulated gadodiamide was prepared. All T_1 measurements were performed on a 0.47 T-NMR-Analyzer (Minispec, Bruker, Germany). The temperature of the samples was varied between 30°C and 50°C in step of 2°C. For each sample, T_1 was acquired three times at each temperature and averaged. In order to assess the phase transition temperature, the differential scanning calorimetry (DSC) of the sample of LTSL with encapsulated gadodiamide was performed.

Results

Fig. 1 depicts the measured T_1 values of the sample of the LTSL with encapsulated gadodiamide, while heated from 30°C up to 50°C and subsequently cooled down to 30°C. During the heating from 30°C to 37°C, the encapsulated gadodiamide was not released from the LTSL and the sample showed the typical, approximately linear temperature dependence of T_1 with a correlation coefficient $R = 0.62$ and a slope of 0.6 ± 0.4 ms/°C using linear regression. From 37°C to 50 °C, the encapsulated gadodiamide was gradually released from the LTSL due to the phase transition at about 42 °C from gel to liquid, consistent with the results from the DSC of the LTSL in Fig. 2. The released gadodiamide resulted in the drastic T_1 shortening. During the cooling from 50°C down to 30°C, the sample showed again an approximately linear temperature dependence of T_1 with $R = 0.98$ and a slope of 1.5 ± 0.2 ms/°C, since the encapsulated gadodiamide was fully released from the LTSL. For comparison, the measured T_1 values of another sample of the LTSL with 2.5 mmol/l of non-encapsulated gadodiamide was also plotted in Fig. 1, while heated from 30°C to 50°C. This sample showed nearly the same tem-

perature dependence of T_1 with $R = 0.99$ and a slope of $1.1 \pm 0.1 \text{ ms}/^\circ\text{C}$ as the sample of the LTSL with encapsulated gadodiamide during the cooling.

Conclusions

The temperature dependence of T_1 of the new LTSL with encapsulated gadodiamide has been studied at working temperatures for the combined chemotherapy and hyperthermia between 30°C and 50°C . During the phase transition, T_1 of the LTSL with encapsulated gadodiamide strongly decreased due to gadodiamide release if the temperature increased. The phase transition temperature of about 42°C is therefore relevant for cytostatic drug release. Otherwise, the LTSL with encapsulated or non-encapsulated gadodiamide showed the typical, approximately linear temperature dependence of T_1 . Moreover, the temperature both in heating and cooling process during the tumor treatment using the combined therapy could be derived from the measured T_1 according to Fig. 1. The future work will concentrate on in vivo experiments.

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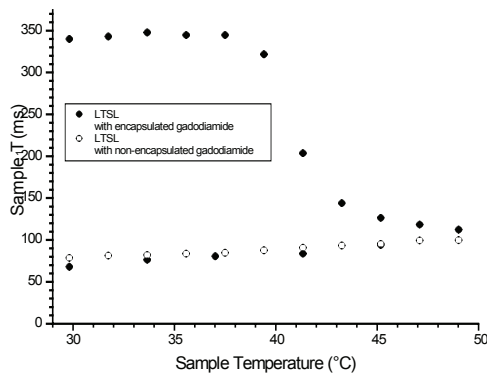


Fig. 1: Temperature dependence of T_1 of two samples at 0.47 T. The sample of LTSL with encapsulated gadodiamide was firstly heated and subsequently cooled down. The sample of LTSL with non-encapsulated gadodiamide was merely heated.

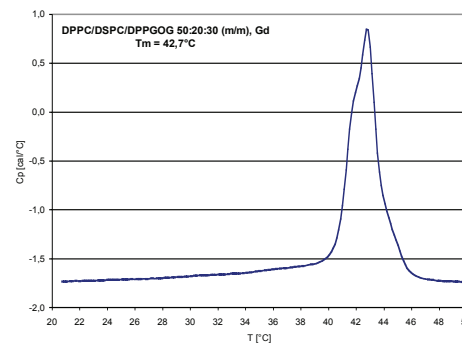


Fig. 2: Differential scanning calorimetry (DSC) of the LTSL with the phase transition temperature of 42.7°C