

IN VITRO STABILITY AND DRUG RELEASE PROPERTIES OF PHOSPHATIDYLGLYCEROL CONTAINING THERMOSENSITIVE LIPOSOMES WITH ENCAPSULATED DOXORUBICIN

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Introduction: Thermosensitive liposomes (TSL) in combination with hyperthermia represent a powerful tool for tumour specific drug delivery. Lately, we reported that the novel synthetic phospholipid dipalmitoyl-sn-glycero-3-phosphoglycerol (DPPGOG) prolongs the circulation time and facilitates the content release of TSL (Clin Cancer Res. 2004). The objective of this study was to examine the in vitro characteristics of DPPGOG containing TSL with encapsulated doxorubicin (DOX).

Methods: DPPC/DSPC/DPPGOG 5:2:3 (m/m) TSL were prepared by the lipid film hydration and extrusion method. A pH gradient was used to load DOX. The size and zeta-potential was determined by Photon Correlation Spectroscopy. The lipid concentration was determined with a phosphate assay. DOX encapsulation efficiency was measured with HPLC. DOX release under certain thermal conditions was determined with fluorescence spectroscopy measurements.

Results: DOX was actively loaded to DPPGOG containing TSL with encapsulated 300 mM citrate, pH 4. The resulting drug:lipid ratio of 0.12 ± 0.01 (m/m) was confirmed independently by HPLC analysis and fluorescence spectroscopy. No signs of decomposition, e.g. hydrolysis of lipids, have been observed. At body temperature (37°C), the DOX leakage was 3.6 ± 1.1 % and 10.9 ± 4.0 % during a time period of one and three hours, respectively. Under heating conditions (41°C) almost 100 % of DOX was released within 5 minutes (74.6 ± 2.4 % during the first 60 sec). At 42 °C, 85.6 ± 1.3 % DOX was released in the first 60 sec. In the absence of serum (20 mM HEPES, 150 mM NaCl, pH 7.4), the DOX release rate constant was decreased from 263 ± 102 ($\cdot 10^4$ s⁻¹) to 55 ± 5 ($\cdot 10^4$ s⁻¹) at 42 °C.

Conclusion: DPPGOG containing DOX-TSL demonstrated promising in vitro characteristics with high stability at 37 °C and fast DOX release properties at elevated temperatures. The presented data warrant further investigation of DOX containing DPPGOG TSL for clinical application.