Docetaxel Liposomes – A Formulations Screening Study

Iselin Karlsen, Natasa Skalko-Basnet, Ann Mari Holsæter
Department of Pharmacy, University of Tromsø The Arctic University of Tromsø

Introduction

Docetaxel (DOC) is a potent anticancer drug with several limitations, including poor solubility and the reported serious side effects, attributed to either the drug itself or the solvent used. Thus, it is interesting to entrap the drug into liposomes in order to solubilize the drug and improve the therapeutic outcome.

Aim

The fist aim of this study was to establish a small-scale screening method for preparing and characterizing DOC-liposomes. Secondly, the established methods were applied to investigate the effect of lipid composition on the liposomal drug entrapment.

Methods

DOC-liposomes were made by the thin-film hydration method and size reduced by probe sonication. Centrifugation was used to remove crystallized DOC from the liposome dispersion. The amount of DOC was quantified by HPLC both in the total sample before centrifugation and in the supernatant containing the liposome dispersion after centrifugation. Liposome size and the zeta potential were determined using the Malvern Zetasizer Nanoseries ZS, and lipid recovery in the supernatant was determined by a phosphatidylcholine assay.

Results

When establishing the liposome preparation method, two formulations contained Soy phospholipids (SPC) and a combination of SPC and cholesterol (80:20 w/w) and a DOC:lipid ratio of 1:10 (w/w), were selected. The results obtained clearly demonstrated the reproducibility of the method and the negative effect of cholesterol on the DOC-entrapment (Table 1)

Table 1. Docetaxel-liposome characteristics for the plain SPC and the SPC-Cholesterol liposomes (n=3)

Liposome formulation	Liposome diameter (nm ± SD)	Poly disp. Index (AU ± SD)	Zeta Potential (mV ± SD)	DOC- entrapment (% ± SD)*	Lipid recovery (% ± SD)
SPC-DOC	83.7 ± 4.1	0.27 ± 0.02	-0.19 ± 0.14	103.3 ± 3.3	89.5 ± 2.2
SPC-CHOL-DOC	59.8 ± 3.3	0.21 ± 0.01	-2.14 ± 0.37	25.2 ± 3.0	94.7 ± 1.0

** Values adjustment for the lipid recovery in the supernatant after centrifugation using the Equation:* $DOC\ entrapment\ (\%) = \frac{Recovery\ of\ DOC\ (\%)}{Recovery\ of\ PC\ (\%)}\ x\ 100$

The formulation screening study involved 14 different liposomal formulations where the DOC entrapment varied between 20.2 and 114.6 %. The formulation containing 20% (w/w) positively charge DOTAP was the most promising with the highest drug entrapment, a diameter of 78.0 nm and a zeta potential of 76.3 mV. Thus, the SPC:DOTAP formulation was further investigated varying the concentration of DOTAP and DOC, and the results showed that a DOTAP concentration down to 10% (w/w) DOTAP gave the superior DOC-entrapment, and that the 1:10 (w/w) DOC:lipid ratio was the optimal with regard to obtaining high drug entrapment.

Conclusion

A small-scale probe sonication method for preparing DOC-liposomes was successfully established. Liposomes comprising the cationic lipid DOTAP showed best entrapment when screening different liposome formulations.