ENHANCED DOXORUBICIN RELEASE AND PERMEABILITY OF THERMOSENSITIVE LIPOSOMES THROUGH AN IN VITRO BLOOD-BRAIN BARRIER MODEL

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Among several intriguing nanocarriers, liposomes have been intensively investigated based on their biocompatibility and their ability to be multi-functionalized for specific targeting and long-circulating times. In this study, an in vitro blood-brain barrier (BBB) model was developed by co-culturing murine brain endothelial cells (bEnd.3) with astrocytes (C8-D1A). By measuring the permeability of FITC-Dextran and trans-endothelial electrical resistance (TEER) [1], we confirmed that the BBB model was successfully established. After such confirmation, the permeability and Doxorubicin (DOX) drug release efficiency from several antibody-functionalized, PEGylated, thermosensitive and non-thermosensitive liposomes (Ab-Liposomes) were tested against the BBB model in an effort to increase BBB passage and deliver anti-tumor drugs for glioblastoma multiforme effectively while diminishing cytotoxicity.

An anti-glioma antibody was first conjugated onto mal-DSPE-mPEG2000 by a standard click chemistry reaction [2]. Ab-Liposomes were synthesized according to a well-established rehydration method [3]. Briefly, DPPC:DSPC:DSPE-mPEG2000-Ab (traditional thermosensitive liposome, TTSL), DPPC:MPPC:DSPE-mPEG2000-Ab (lyso-thermosensitive liposome, LTSL) and DOPC:DSPE-mPEG2000-Ab (non-thermosensitive liposome, NTSL) were dissolved in an organic solvent and vacuum-dried overnight. Then, thin lipid films were rehydrated with an ammonium sulfate solution (PH=5.5) and extruded through 100nm filters to determine their diameters. The liposome solution was then gel-filtered with a HEPES buffer (PH=7.4) and DOX was loaded into the liposomes during an overnight incubation due to the pH gradient effect.

Results showed that all the PEGylated Ab-liposomes had great permeability using the in vitro BBB model. However, compared to NTSL, TTSL and LTSL had significantly higher drug release efficiency towards tumor cells. In addition, during the drug release rate test, LSTL showed higher DOX release rates at its transition temperature (43°C) than TTSL, suggesting that LSTL could be a good candidate for brain tumor drug delivery.

Keywords: blood-brain barrier, liposome, drug delivery

References:


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