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The Impact of Liposomal Formulations on the Release and Brain Delivery of Methotrexate: A *In Vivo* Microdialysis Study

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Abstract

The impact of liposomal formulations on the *in vivo* release and brain delivery of methotrexate (MTX) was quantitatively assessed in rats. Two PEGylated liposomal MTX formulations based on hydrogenated soy phosphatidylcholine (HSPC) or egg-yolk phosphatidylcholine (EYPC) were prepared. The drug release and uptake into the brain after intravenous administration of both formulations were compared with unformulated MTX by determining the released, unbound MTX in brain and plasma using microdialysis. Total MTX concentrations in plasma were determined using regular blood sampling. The administration of both high- and low-dose EYPC liposomes resulted in 10 times higher extent of MTX release in plasma compared to that obtained from HSPC liposomes ($p < 0.05$). MTX itself possessed limited brain uptake with steady-state unbound brain-to-plasma concentration ratio ($K_{p,uu}$) of 0.10 ± 0.06. Encapsulation in HSPC liposomes did not affect MTX brain uptake ($K_{p,uu}$ 0.11 ± 0.05). In contrast, EYPC liposomes significantly improved MTX brain delivery with a 3-fold increase of $K_{p,uu}$, (0.28 ± 0.14 and 0.32 ± 0.13 for high- and low-dose EYPC liposomal MTX, respectively, $p < 0.05$). These results provide unique quantitative evidence that liposomal formulations based on different phospholipids can result in very different brain delivery of MTX.

Keywords: Liposome, Nanocarrier, Blood-brain barrier, Brain delivery, *In vivo* release, Microdialysis, Methotrexate

Abbeviation used: CNS, Central nervous system; BBB, Blood-brain barrier; MTX, Methotrexate; HSPC, Hydrogenated soy phosphatidylcholine; EYPC, Egg-yolk phosphatidylcholine; PEG, Polyethylene glycol; $K_{p,uu}$, Unbound brain-to-plasma concentration ratio at steady state; ISF, Interstitial fluid; ACN, Acetonitrile; FA, Formic acid; PDI, Polydispersity index.

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