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Abstract

Brain targeting: optimisation and biocompatibility of valproic acid-loaded nanostructured lipid carriers (VPA-NLC) for nose-to-brain delivery†

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Abstract: The nose-to-brain route is one of the most promising alternative to promote drug delivery to the brain in the treatment of neurological diseases. Nasally administered drugs can be directly transported through the olfactory and trigeminal nerves, but enzymatic activity and the mucociliary clearance limit this process. Encapsulation of drugs in lipid nanoparticles, such as nanostructured lipid carriers (NLC), protects molecules against enzymatic activity, while promotes direct nose-to-brain transport.

In this work, a valproic acid-loaded NLC (VPA-NLC) formulation was optimised using the quality-by-design (QbD) approach. A mixture design and a central composite design were used to optimise the critical material attributes (CMAs) and the critical process parameters (CPPs), respectively. The *in vitro* drug release profile and VPA-NLC morphology were investigated. The biocompatibility was assessed in human neuronal and nasal epithelial cells. VPA-NLC showed a particle size of 75 ± 1.05 nm, a polydispersity index (PDI) of 0.179 ± 0.006, an encapsulation efficiency (EE) of 85.7 % and a zeta potential (ZP) of 27.4 ± 0.351 mV. Transmission electron microscopy (TEM) images showed spherical nanoparticles smaller than 100 nm. Drug release studies showed about 50% of drug release after 6 hours and 100% after 24h. The VPA-NLC revealed safety up to 75 μg/mL in both cell lines. The optimised VPA-NLC formulation met the criteria of small particle size and PDI, and high EE and absolute ZP, which are required to follow the direct nose-to-brain transport. Additional experiments are being carried out to predict the *in vivo* safety and effectiveness of this formulation.

Keywords: Design of experiment; intranasal; nanostructured lipid carriers; nose-to-brain; quality by design; valproic acid.

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