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### Formulation and optimization of lamotrigine-loaded bovine serum albumin nanoparticles by using full factorial design

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Lamotrigine (LAM) as a BCS II class anti-epileptic drug with poor water solubility, is applied alone or in combination with other drugs to control seizures and to prevent the extreme mood swings of bipolar disorder in adults. The application of albumin nanoparticles means a promising approach for nose-to-brain delivery of LAM and to improve its bioavailability.

In this study, our aim to develop and optimize was LAM-loaded bovine serum albumin (BSA) nanoparticles (LAM-NPs) for nose-to-brain delivery via quality by design (QbD) approach. The main objective was the optimization of particle size (<250 nm) and encapsulation efficiency (>50%) of LAM-NPs using 3<sup>3</sup> factorial design. Then, the effect of different types of crosslinking agents (glutaraldehyde, glucose and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC)) was studied on the selected formulations.

The optimized formulations were characterized regarding to particle size, PDI, zeta potential (before and after freeze-drying), encapsulation efficiency (EE%), *in vitro* blood-brain barrier permeability (BBB-PAMPA) and rapid equilibrium dialysis (RED) as well as *in vitro* drug release. The optimized LAM-NPs showed  $168.9 \pm 2.15$  nm particle size with a zeta potential of  $-45.4 \pm 0.43$  mV and  $0.078 \pm 0.007$  of PDI before freeze-drying, whereas  $171.9 \pm 0.3$  nm particle size,  $-41.8 \pm 0.7$  mV zeta potential and  $0.118 \pm 0.007$  of PDI after freeze-drying. The EE% was 81.94%. PAMPA result showed an increase in the permeability of LAM through the BBB. In addition, LAM-NPs showed higher drug both at nasal (pH=5.6) and at cerebrospinal fluid condition (pH = 7.4) in comparison to initial LAM.

The optimized formulation could be a promising for enhancing bioavailability of LAM through nose-to-brain delivery and to ensure sustained drug release.

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