Contribution ID : **36** Type : **Poster**

Optimizing Lipid Cubosomes for Alzheimer's Drug Delivery: Impact of Lipid Composition and Stabilizers

Monday, 4 November 2024 19:55 (20)

The increasing prevalence of age-related central nervous system disorders, including Alzheimer's disease (AD) which is the most common form of dementia, is not effectively addressed by existing treatments, which fail to significantly alter the neurodegenerative progression of AD. Lipid nanoparticles, including cubosomes, are a promising approach to enhance the delivery of bioactives to the brain through improved drug bioavailability and specific targeted drug delivery while minimizing adverse effects [1–4].
In this study, monoolein-based cubosome formulations were assessed as delivery vehicles for therapeutics used to treat AD. A polytherapy approach was used, including the clinically used AD drugs galantamine and memantine in combination with neuroprotective polyphenols. The drug and polyphenolic compounds were loaded in cubosomes of various lipid compositions to form biomimetic cubic phases. Cubosomes were characterized using small angle X-ray scattering (BioSAXS beamline), cryo-TEM, dynamic light scattering and encapsulation efficiency. Small angle neutron scattering combined with selective contrast matching was further used to assess the location of the therapeutics within the cubic nanostructure.
The addition of the AD drug galantamine and memantine preserved the internal cubic phase nanostructure, while the polyphenols induced a concentration dependent phase transition or phase separation. Stabilization of the cubosomes was successfully achieved using a range of different stabilizers enhancing brain delivery while minimizing cytotoxicity. Neutron scattering studies of memantine suggested homogeneous encapsulation of the three-dimensional structure in the lipid bicontinuous cubic phase. Overall, the high-throughput studies successfully achieved biomimetic cubic phases, suggesting their potential to deliver AD drugs and neuroprotective compounds to the brain.

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2 Azhari, H. et al. Int J Pharm 600, (2021)
3 Mohammad, Y. et al. J Colloid Interface Sci 605, 146–154 (2022)
4 Cai, X. et al. Advanced Functional Materials (2024)

Topics

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Session Classification : Posters