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Comparative In Vitro Evaluation of Oppositely Charged Donepezil-Loaded Liposomes for Intranasal Drug Delivery

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Background: Intranasal administration provides a direct and non-invasive route for central nervous system (CNS) drug delivery; however, many therapeutic agents still exhibit limited permeability across the nasal mucosa. This study aimed to develop and compare the physicochemical and functional characteristics of oppositely charged liposomes loaded with donepezil hydrochloride (DPZ), using dicetyl phosphate (DCP) and stearylamine (SA) as charge-modifying excipients.

Methods: Liposomes were prepared using a phosphatidylcholine/cholesterol molar ratio of 7:2 through the thin-film hydration technique, followed by probe sonication to obtain nanosized vesicles. The formulations were characterized in terms of vesicle size, zeta potential, and encapsulation efficiency using dynamic light scattering and UV-visible spectrophotometry. The influence of DCP and SA (0.5–2 molar ratios) on vesicle size, surface charge, drug-release kinetics, permeability across a synthetic nasal membrane, and mucoadhesion was systematically evaluated.

Results: Incorporation of DCP led to decreased vesicle size and accelerated drug release, whereas SA increased vesicle size and enhanced mucoadhesion. Both charge inducers significantly improved DPZ encapsulation efficiency (60–80%) due to modification of the lipid bilayer structure. DCP-containing liposomes exhibited superior *in vitro* nasal permeability compared with the plain DPZ solution, while SA-modified vesicles demonstrated stronger mucoadhesive properties.

Conclusion: Both negatively and positively charged liposomal formulations improved the intranasal delivery potential of donepezil. Higher DCP concentrations (PC:CH:DCP 7:2:2) favored permeability, whereas lower SA levels (PC:CH:SA 7:2:0.5) enhanced mucoadhesion. These findings highlight surface-charge modulation as a promising strategy for optimizing liposomal carriers for CNS-targeted intranasal therapy. This work forms part of a broader research program in which dopamine-loaded and vinpocetine-loaded intranasal liposomal formulations are concurrently being developed to further advance nanocarrier-based nose-to-brain drug-delivery systems.