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Thiolated Albumin Polymer for Improved Intranasal Delivery of Levodopa Methyl Ester

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Background: Intranasal delivery bypasses the blood-brain barrier but is limited by rapid mucociliary clearance. To overcome this, thiolated polymers are used to enhance mucosal retention via covalent disulfide bonding with mucus glycoproteins.

Aim: This study aimed to develop and characterize a novel mucoadhesive drug delivery system for the intranasal administration of Levodopa Methyl Ester (LDME) utilizing cysteine-modified Bovine Serum Albumin (BSA-Cys) as a nanocarrier.

Methods: BSA-Cys was synthesized by conjugating L-cysteine to BSA at three distinct molar ratios (1:1, 55:1, and 100:1) using EDC/NHS coupling chemistry, and characterized using FT-IR, DSC, TGA, and XRPD. Performance was evaluated through drug release studies, texture-based mucoadhesion testing, and PAMPA permeability assays.

Results: Comprehensive solid-state characterization (FT-IR, DSC, TGA, and XRPD) confirmed the successful removal of free cysteine and the preservation of an amorphous protein matrix, which is ideal for rapid drug dissolution. Ellman's assay validated the presence of accessible thiol groups across all formulations. Thiolated BSA derivatives exhibited significantly superior mucoadhesive properties compared to native BSA; Notably, the 100:1 conjugate achieved the highest total adhesive work (58.1 Nm mm), indicating strong resistance to mechanical clearance. *In vitro* release studies demonstrated that the modification sustained drug release in PBS and SNES. Furthermore, the BSA-Cys formulation demonstrated an increase in drug flux in the PAMPA model compared to the control, attributed to the "thiol effect" on membrane permeability.

Conclusion: This thiolated albumin platform successfully enhances the mucosal residence and permeability of LDME. Future research will focus on structural confirmation via NMR/CD, alongside cytotoxicity and stability testing for neurological applications.