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Intranasal Delivery of Rivastigmine to Brain: In Silico Designed Nano Drug-Polymer Complexes

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Extended Abstract

Drug delivery through the intranasal route via the olfactory region overcomes multifaceted challenges vested in a variety of physiological, metabolic, and biochemical convolutions associated with the blood-brain barrier that obstruct the delivery of biomolecules to the brain. However, mucociliary clearance, enzyme degradation, and low permeability of the nasal epithelium are significant impediments to achieving therapeutic drug levels in the brain through this route. Though seemingly trivial, these challenges necessitate conferring enhanced residence time, enhanced permeability, and reduced enzymatic drug degradation in the intranasal drug delivery systems. In light of these considerations, systematic selection of polymer-drug complexes exhibiting high nasal mucin affinity and adherence and conspicuous drug release profile become inevitable. In silico optimization of these attributes is envisaged to aid in selecting drug-polymer pairs with high accuracy and performance [1]. The present investigation involved the selection of polymers for enhanced affinity with rivastigmine tartrate (RT), an anti-Alzheimer drug for brain targeting. In addition, the interaction of these complexes with nasal mucin (PDB ID: 5AJN) was optimized using in silico tools. Molecular docking (Cresset software; Flare module) [2] and dynamic simulations (Material Studio 2022; Forcite module) [3] were employed to analyze the binding affinity as well as the loading/release of RT from these complexes. Sodium hyaluronate, sodium alginate, Eudragit RL (EDRL), HPMC, and starch were shortlisted on the basis of their binding affinity with nasal mucin and RT [4]. The Hildebrand solubility parameters and Florry-huggins interaction parameters were calculated to predict the solubility/ miscibility of the drug in different monomers [5]. The Radius of gyration (Rg) and Radial Distribution Function (RDF) evaluated the molecular dynamic simulation analysis [6]. The results revealed the shortest Rg value and H-bond distance coupled with the highest H-bond strength of EDRL with RT and mucin. This suggested maximum RT encapsulation and adherence with nasal mucin for a prolonged period accompanied by sustained release in the nasal milieu from the nano-particulate delivery system.

The present work demonstrates that Molecular modeling techniques can be useful tools for assessing the function of intermolecular interaction for a particular system. These computational methods bring local structures into account and are not restricted to short-range interactions. This method would be helpful during the formulation development process to screen lead excipient (polymer) and other solvents desired for the study based on the solubility and interaction parameters; with which excessive wet-lab work can be reduced to a much extent.

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