Hydrophobic Ion Pair Complexes for Enhanced Buccal Delivery of a GLP-1 Receptor Analogue

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Background: Peptide based therapeutic agents including GLP-1 analogues are faced with permeation obstacles in crossing intestinal epithelial membranes due to their hydrophilicity, large molecular weight, and high polar surface areas. While flux can be boosted to a small extent by formulation with intestinal permeation enhancers [1], other approaches include reducing hydrophilicity of the peptide through lipidic formulation. The purpose of the study was to increase the lipophilicity of a GLP-1 peptide analogue, which has similarity in structure to semaglutide. This was achieved via non-covalent lipidation. The reversible ionic interactions in non-covalent lipidation should dissociate during the absorption step, restoring the original peptide structure and leaving the receptor affinity of peptide unaffected [2]. Non-covalent lipidation of peptides was carried out via synthesis of hydrophobic ion paired (HIP) complexes of the peptide with counter-ions, designed to be incorporated into a lipid-based self-nanoemulsion, SNEDDS [3].

Methods: To develop HIP complexes with GLP-1RA, lipid-based cationic and anionic surfactants were screened at molar ratios (1:3, 1:4, 1:6, 1:8) and pH values (4-11) and temperature conditions (25 or 37◦C). Initially, screening of HIPs was based on the development of compact and non-dispersible precipitates. Later, the optimized HIPs were isolated after centrifugation at 14000rpm and quantified for GLP-1RA via HPLC. HIPs complex formation with GLP-1RA was characterized via FTIR and PXRD. Zeta potentials of the HIPs were measured via a Litesizer DIA 500 analyser.

Results: Solid, white-colored HIPs of GLP-1RA were produced at molar ratios of 1:4, 1:6, and 1:8 with DODAB as the preferred cationic surfactant. Higher molar ratios yielded higher complexation. Cationic surfactants at alkaline pH values generally produced strong precipitates. FTIR and PXRD spectrums demonstrate differentiating projections and peaks, which confirm the formation of complexes via ionic interactions between DODAB and GLP-1RA.

Conclusions: Outcomes of this work emphasize the potential of non-covalent lipidation in the form of HIPs as a strategy ultimately to improve buccal epithelial permeation of GLP-1RA. Screening counter-ions revealed DODAB as a lead candidate for HIP formation.