Hydrophobic ion pair complexes of a GLP-1 peptide receptor agonist analogue designed to increase peptide permeability across the buccal epithelium

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Introduction

GLP-1 peptide analogues are faced with permeation obstacles in crossing intestinal epithelial membranes due to hydrophilicity, large molecular weight, and high polar surface area. While fluxes can be boosted 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 receptor agonist (RA) peptide analogue with close similarity in structure to semaglutide, with an aim of producing a formulation that may be suitable for buccal administration. This was achieved via non-covalent lipidation. The reversible ionic interactions should dissociate during the absorption step, restoring the original peptide structure and leaving the receptor affinity of peptide unaffected [2]. Lipidation of peptides was out via synthesis of hydrophobic ion paired (HIP) complexes of the peptide with counter-ions, ultimately designed to be incorporated into a lipid-based self-nanoemulsion, SNEDDS [3].

Aims

- Design HIPs of a GLP-1 peptide analogue with anionic and cationic counterions.
- Effect of HIPs on structural and physical properties of the selected GLP-1 analogue
- Use of FTIR and PXRD to provide structural information on the HIP-peptide product formed with counter-ions
- Microscopic (TEM) structural analysis of the GLP-RA and HIPs.

Method

1. Process of HIPs development via ionic interaction of counter ions

Various molar ratios of the GLP-RA and DODAB were mixed and vortexed to see the formation of precipitates; the precipitates were centrifuged and lyophilized.

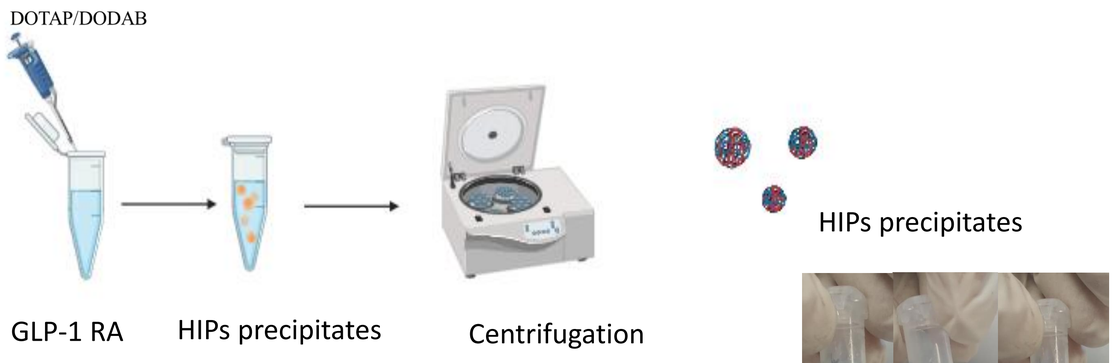


Figure 1: Process flow diagram of HIPs development

2. *Water/octanol partition coefficients*

To assess the lipophilicity of HIPs, the water/octanol partition coefficient was measured. 30 mg of HIPs were dissolved in octanol and then mixed with equal volume of water. Quantity of GLP-RA partitioned in each phase is measured via HPLC.

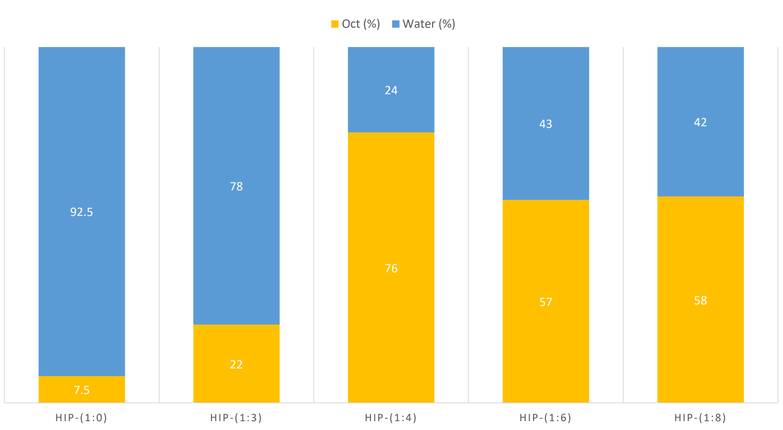
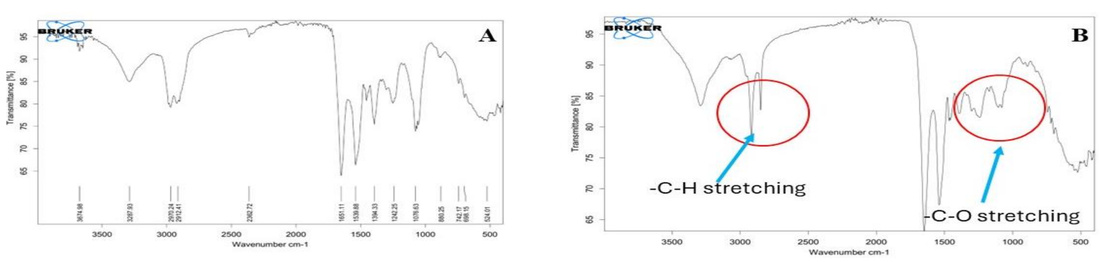


Figure 2: Partition coefficients of HIPs formulated with molar ratios of GLP-RA and DODAB

3. FTIR spectra of HIPs



GLP-RA HIPs of GLP-RA with DODAB

Figure 3: FTIR spectra of GLP-RA and HIPs formulated at 1:4 ratio of GLP-RA and DODAB, -C-H and –C-O stretching in HIPs confirm the formation of ionic interactions.

Result

4. XRD spectra of HIPs

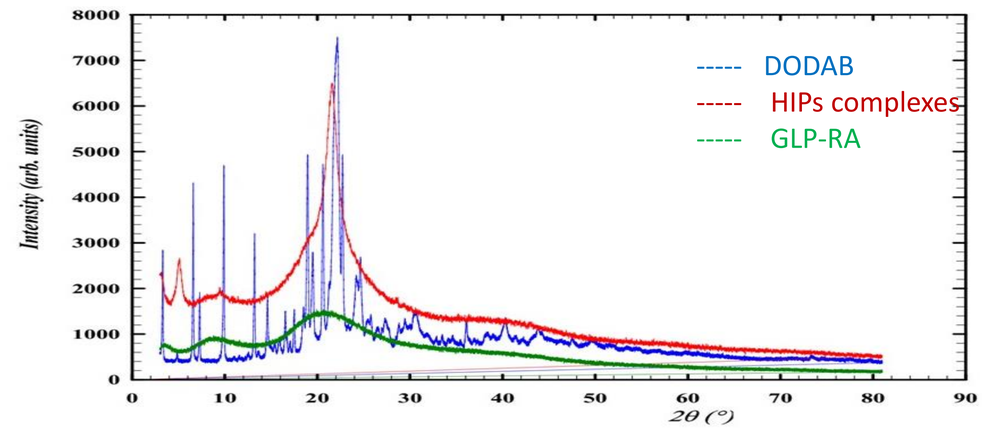
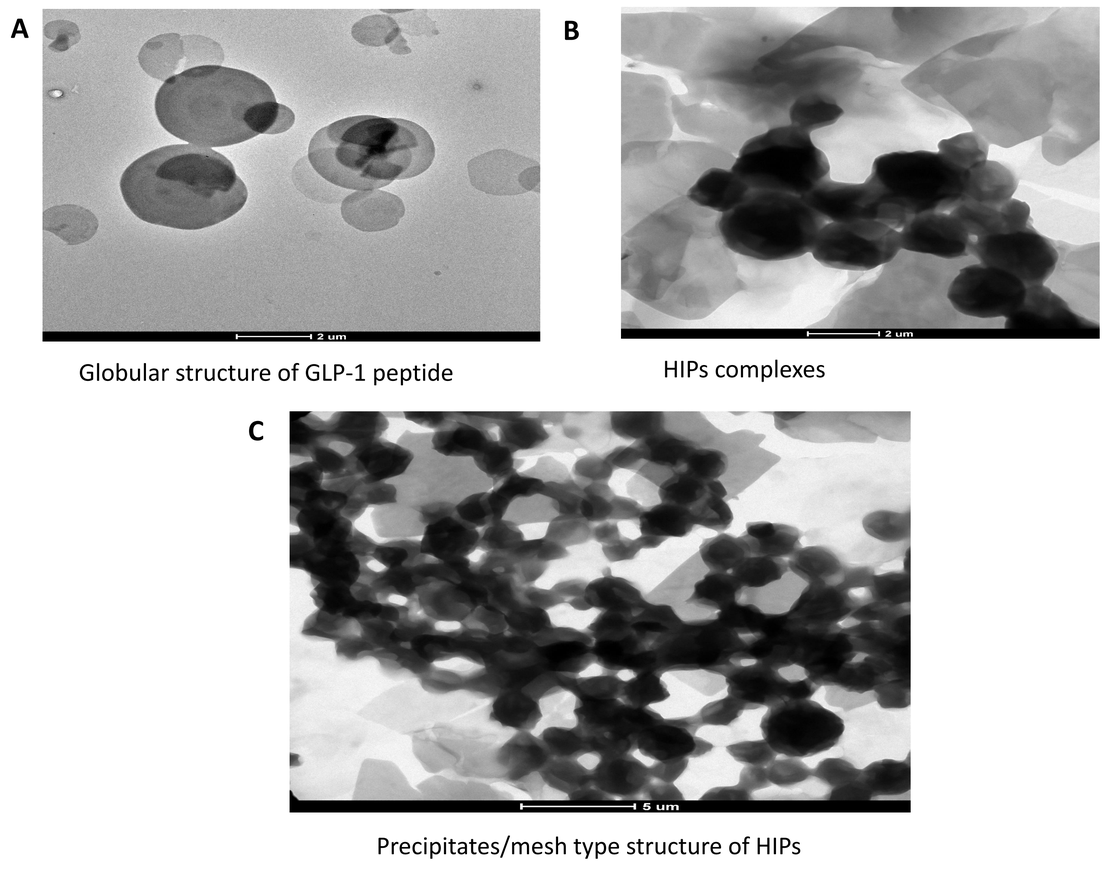


Figure 4: XRD spectra of GLP-RA, DODAB and HIPs formulated at 1:4 ratio of GLP-RA and DODAB. The changes in diffraction peaks in HIPs confirm formation of new lipidic structures in the crystalline structure of peptides.

5. TEM images of HIPs complexes with the GLP-1 RA



Globular structure of GLP-1 peptide HIPs complexes

Precipitates/mesh type structure of HIPs

Figure 5: TEM microscopic images of GLP-RA, HIPs complexes of GLP-RA and DODAB, (A) globular structure of GLP-RA, (B) precipitates of HIPs and (C) mesh type structure of HIPs developed by cross linking of DODAB and GLP-RA.

Conclusions

This work supports the potential of non-covalent lipidation in the form of HIPs as a strategy ultimately to improve buccal epithelial permeation of GLP-RA peptides. Screening counter-ions revealed DODAB as a lead candidate for HIP formation. Water/Octanol partition coefficient confirm the increased lipophilic nature of GLP-RA, furthermore FTIR and XRD analysis confirm the non-covalent interactions of GLP-RA and DODAB. TEM images show the development of mesh structures which is indication of cross linking and precipitation of GLP-RA with DODAB.

Reference

1. Maher, S., R.J. Mrsny, and D.J. Brayden, Intestinal permeation enhancers for oral peptide delivery. Adv. Drug Deliv. Rev, 2016. 106: p. 277-319.

2. Noh, G., et al., Recent progress in hydrophobic ion-pairing and lipid-based drug delivery systems for enhanced oral delivery of biopharmaceuticals. J. Pharmaceutical Invest, 2022: (52): p. 1-19.

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