NON-INJECTED GLP-1 ANALOGUE ADMINISTRATION: SELF-NANOEMULSIFICATION WITH HYDROPHOBIC IONPAIRING

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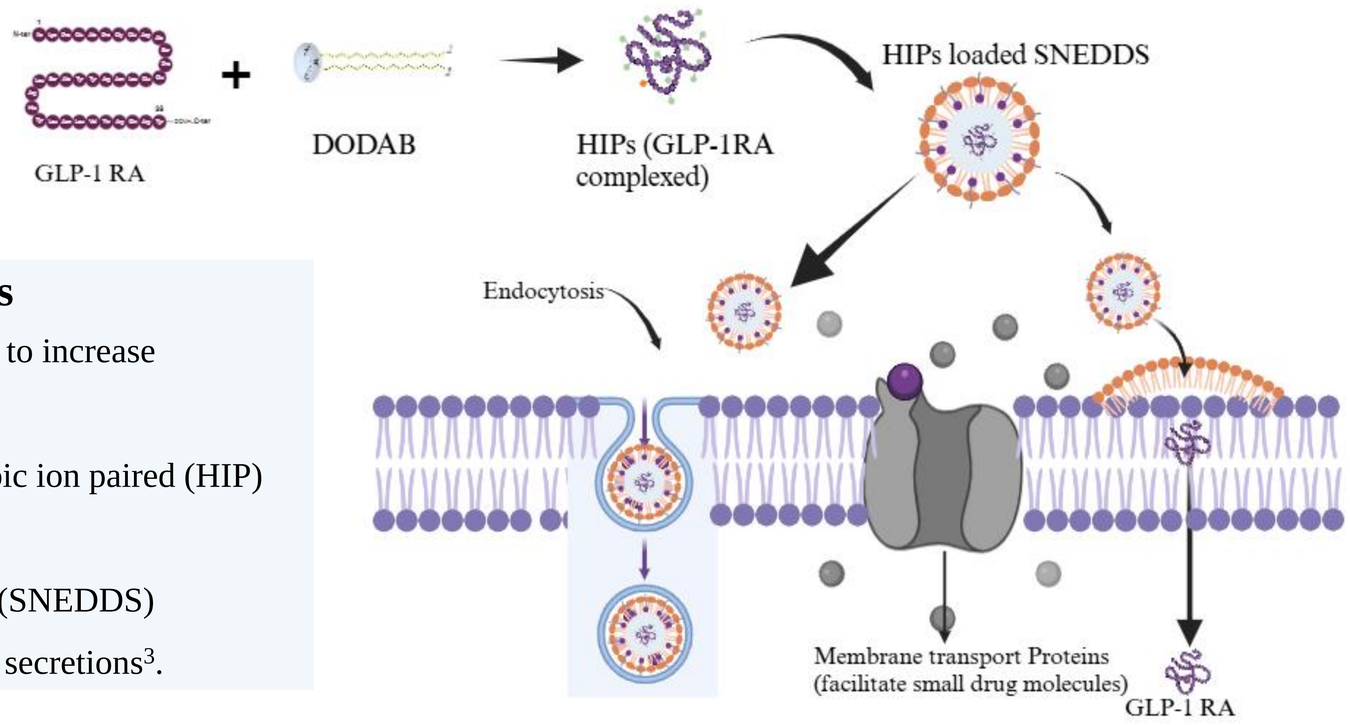
Introduction

Challenges to oral bioavailability of GLP-1 RA

- Low epithelial permeation
- Enzymatic degradation
- Hydrophilic nature
- High molecule polar surface areas



Strategies to improve permeation through buccal mucosal layers

- Non-covalent lipidation via ionic complexation of cationic lipids with GLP-1RA to increase lipophilicity of hydrophilic peptide [1]
- Non-covalent lipidation of peptides can be carried out via synthesis of hydrophobic ion paired (HIP) complexes [2]
- HIP complexes designed to be incorporated into lipid-based self-nano emulsions (SNEDDS)
- SNEDDS are lipid-based premixtures which are emulsified when mixed with gut secretions[3].

Methods/Results

Development of Hydrophobic ionic complexes and characterization

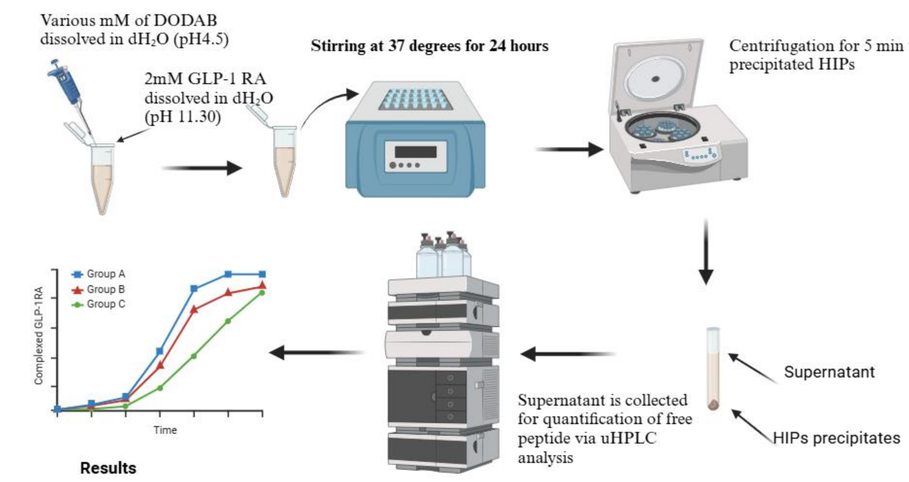


Table 1: Effect of molar ratios on yields of GLP-1 RA HIPs.

Prototype	Ratio (GLP-1 RA: DODAB)	GLP-1 RA in supernatant (mg)	% GLP-1 RA complexed
HIP-1	1:3	1.04	73
HIP-2	1:4	0.564	86
HIP-3	1:6	0.37	90
HIP-4	1:8	0.306	92

FTIR spectra of HIPs, GLP-1RA and DODAB

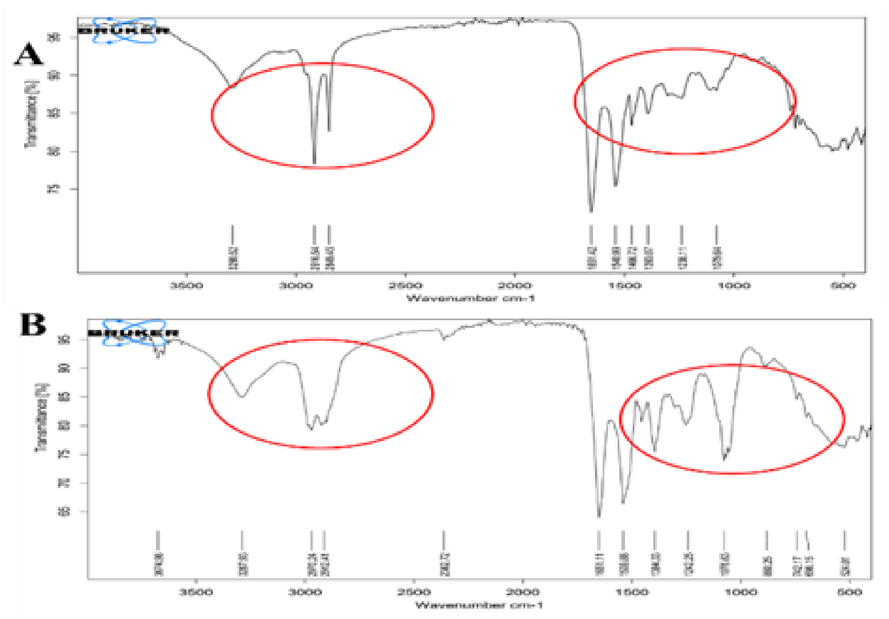


Figure 1: FTIR spectra of A) GLP-1 RA and B) HIPs

FTIR spectra as shown in **Figure 1**, demonstrate differentiating projections and peaks, which confirm the formation of complexes via ionic interactions between DODAB and GLP-1 RA.

H-NMR spectra of HIPS, GLP-1RA and DODAB

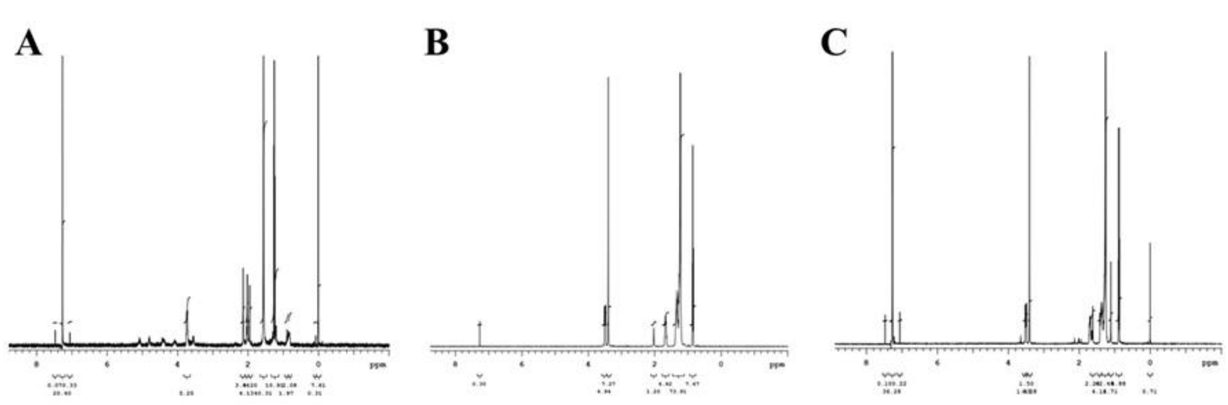


Figure 2: H-NMR spectra showing the peaks of A) GLP-1 RA, B) DODAB, and C) HIPs

H-NMR spectra also confirm the development of structural changes, which are reflected in the spectral changes in NMR peaks as shown in **Figure 2**.

Flux of HIPs entrapped within SNEDDS through Caco-2 monolayers

HIPs of GLP-1 RA produced with higher molar ratios of GLP-1 RA/DODAB yielded higher complexation as shown in **Table 1**. HIP-entrapped SNEDDS demonstrated significantly improved fluxes of GLP-1 RA through Caco-2 monolayers as shown in **Figure 3**. Likewise, cells treated with HIPs and SNEDDS-entrapped with HIPs at concentrations of 0.1-0.5 % w/w for 180 min demonstrated no significant cytotoxic effects on Caco-2 cells (data not shown).

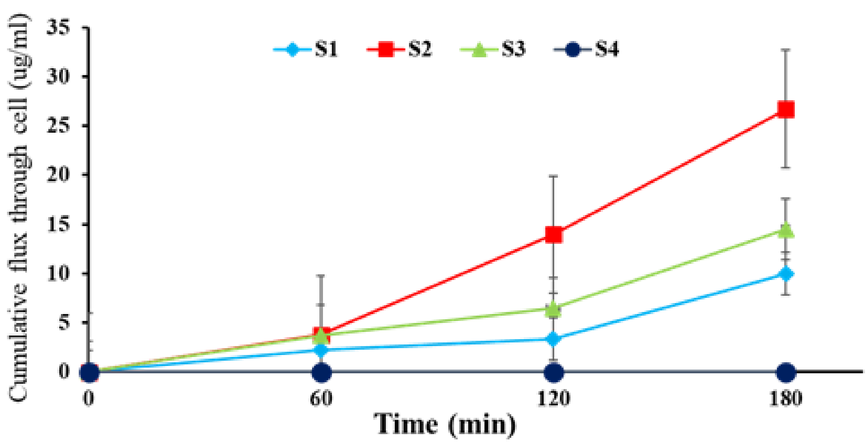


Figure 3: Cumulative flux of GLP-1 RA through Caco-2 cell line, HIPS entrapped SNEDDS formulations (S1, S2, S3), free GLP-1 RA (S4).

Conclusion

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. HIPs for complexing GLP-1 RA with a lipid-based counterion, DODAB, led to improved fluxes of GLP-1 RA across Caco-2 monolayers with minimum effects on cell viability. The outcomes of this work emphasize the potential of non-covalent lipidation in the form of HIPs as a strategy to improve epithelial permeation of GLP-1 RA. Screening counter-ions revealed DODAB as a lead candidate for HIP formation.

Reference

1. 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: 1-19.
2. Ijaz, M., et al., Development of oral self-nano-emulsifying delivery system (s) of lanreotide with improved stability against pre-systemic thiol-disulfide exchange reactions. Exp. Opin. Drug Deliv. 2016. 13(7): 923-929.
3. Claus, V, et al. Self-emulsifying drug delivery systems (SEDDS): In vivo proof of concept for oral delivery of insulin glargine. Int. J. Pharm. 639 (2023): 122964.

Acknowledgements

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