Design of a Bilayer Film for Buccal Administration of a GLP-1 Receptor Agonist Peptide for the Treatment of Type 2 Diabetes Mellitus

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Background: The buccal route has attracted renewed interest in peptide delivery due to its rich vascularization, low enzymatic degradation, and greater patient acceptability. This route offers a promising alternative to injections and oral delivery. It also eliminates the inconvenience of painful injections, while it offers advantages over oral by avoiding the liver first pass effect and complex oral dosing regimens to avoid food interference. In this study, we aim to overcome the buccal mucosa barrier, by co-administering a permeation enhancer, the bile salt, sodium glycodeoxycholate (GDC), with a lipidated long half-life Glucagon-Peptide-1 receptor peptide-analogue (GLP-1 RA) in multilayer buccal films. The next generational buccal films will be designed to enhance bioavailability of GLP-1 RAs by the buccal route. Challenges addressed include sufficient loading of the peptide and enhancer, mucoadhesiveness of the film, and proof that GDC can enhance flux of the peptide across isolated porcine buccal mucosae.

Methods: We fabricated GLP-1 RA and GDC-loaded bilayer films using semi-automated solvent casting and performed physicochemical characterizations such as loading efficiency, *in vitro* disintegration/dissolution study, rheology, and mucoadhesion tests. We also tested the mechanical strength of films, drug-excipient compatibility (FTIR), stability testing over 1 month using HPLC and circular dichroism, and drug-excipients distribution in film (Raman microscopy). Then, we conducted GDC cytotoxicity study with human TR-146 buccal epithelial cells followed by the *ex vivo* permeability study of the GLP-1 RA across porcine buccal mucosae. Initially, we used Hilltop chambers (HTC), a device for administering solution mixtures buccally, to investigate the most potent ratios of GLP-1 RA to GDC for improved GLP-1 RA flux. Subsequently, the same amount of GLP-1 RA and GDC was loaded into bilayer films for *ex-vivo* flux evaluation. For histological assessment of tissue, Haematoxylin and Eosin (H&E) was used.

Results: Among the six formulations evaluated, we identified a prototype film based on their favorable physico-chemical properties. Another finding suggested that GDC at a concentration of 1 mM or lower, was not cytotoxic. On the other hand, the *ex vivo* permeability study across porcine buccal mucosae demonstrated that GLP-1 RA flux was the highest in a 1:2 ratio of GLP-1 RA (50mg/ml) and GDC (94.4mg/ml) applied in 0.2ml in Hilltop chambers (HTC), where ~6% of GLP-1 RA permeated the tissue in 3 hours. An equivalent amount of GLP-1 RA and GDC was loaded in the mucoadhesive layer wrapped around a backing layer made from a Eudragit polymer in bilayer film format. In *ex-vivo* flux studies, these bilayer films achieved ~2% flux of the GLP-1 RA across the porcine buccal mucosa in 3h. Tissue damage severity increased proportionally with higher concentrations of GDC.

Conclusions: Based on excellent physicochemical properties, a buccal bilayer film formulation using water-soluble biodegradable natural polymer and anionic water-soluble synthetic polymer was selected as prototype film for the next phase. The *ex-vivo* flux results clearly indicated that the combination of the GLP-1 RA and GDC in the ratio of 1:2, whether delivered *via* HTC or fabricated into a bilayer-film, is an effective approach for peptide delivery *via* the buccal route. The combination of GDC and a GLP-1 RA in a bilayer film construct is a promising platform for buccal peptide administration.