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

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Introduction

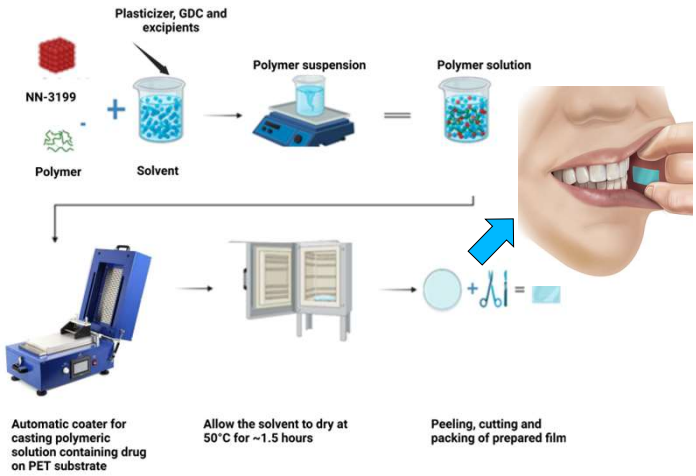
Peptides are a major class of therapeutic drugs. The majority of commercially available peptide therapeutics are administered by injection because of their high molecular weights, proteolytic sensitivity, and low intestinal permeability when administered orally[1,2]. This project aims to overcome the buccal mucosa barrier, by co-administering a permeation enhancer, the bile salt, sodium glycodeoxycholate (GDC), and a lipidated long half-life Glucagon-Peptide-1 receptor peptide analogue (GLP-1-RA) in a mucoadhesive bilayer buccal film. We hypothesise that having the peptide and GDC in the same mucoadhesive layer that contacts the epithelium while supported with a backing layer is an advantageous design to achieve acceptable buccal bioavailability.

Aims

1. Preparation of bilayer buccal films using a GLP-1 RA and GDC
2. Enhance buccal mucosal permeability using GDC and mucoadhesive polymers
3. Conduct permeability studies with the GLP-1 RA in *ex-vivo* porcine buccal mucosa and *in-vitro* in human TR-146 multilayers

Methods

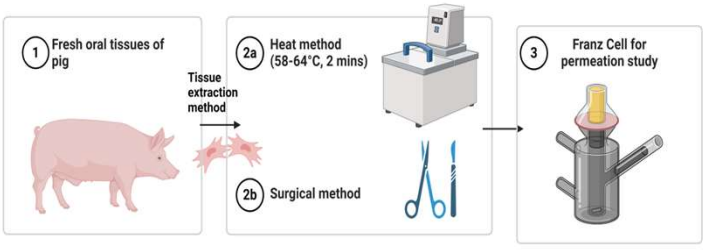
1. Fabrication of GLP-1 RA entrapped bilayer films



2. Physical characterization of bilayer films

- Morphology (SEM)
- Drug disintegration/dissolution in artificial saliva
- Muco-adhesion to *ex-vivo* porcine buccal membranes
- FTIR for drug-excipient compatibility
- Circular dichroism for peptide structure analysis
- Rheological characterization

3. *Ex-vivo* flux study on isolated porcine buccal mucosa



Results

Physicochemical properties of GLP-1 RA-entrapped films

Code	Polymers	pH	Disintegration (min)	Moisture content (%)	Mechanical strength F_{max} (N)
F1	Natural	7.09±0.04	**10.05±0.40**	8.94±0.25	**73.71±5.47**
F2	Semi-synthetic	6.75±0.06	16.1±1.37	9.25±0.34	0.73±0.08
F3	Synthetic	6.62±0.14	18.59±0.54	9.12±1.42	27.25± 2.07

Table 1. F2 exhibited the fastest disintegration and possessed the greatest mechanical strength (n=3)

SEM

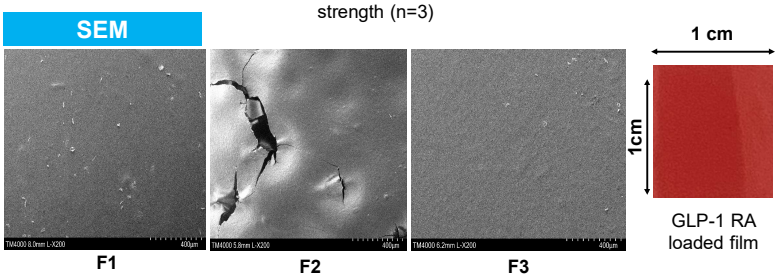


Fig. 1. SEM of GLP-1 RA loaded films (Bar = 400 μm). F1 and F3 surface were uniform and homogeneously distributed. However, F2 was brittle with pores on the surface

FTIR for chemical interaction

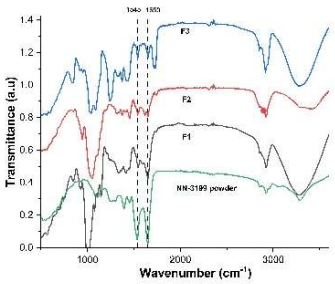
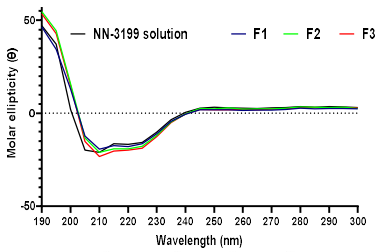


Fig. 2 ATR-FTIR graph of GLP-1 RA loaded films of F1, F2 and F3 along with the GLP-1 RA powder. Amide I/II peak in 1500−1700 cm^{-1} region was intact in all three formulations compared to reference powder

GLP-1 RA structure: CD



Day 1	α-helix (%)	β-sheet (%)
NN-3199 (0.25mg/ml)	95.39	0.03
F1	95.38	0.04
F2	95.34	0.04
F3	95.31	0.03

Fig. 3 Circular dichroism (CD) spectra of GLP-1 RA (0.25 mg/mL) and formulations (F1, F2 and F3). Secondary peptide structure was intact in all three formulations

GLP-1 RA Fluxes across in porcine buccal tissue in Franz Cells

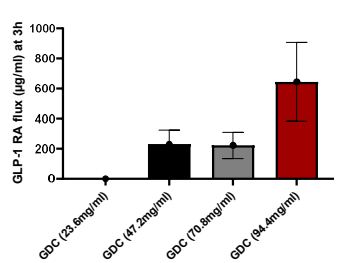


Fig. 4. *Ex-vivo* fluxes study across isolated porcine tissue with different GDC concentration and the GLP-1 RA (50 mg/mL) (n=4). GLP-1 RA flux increased with GDC concentration.

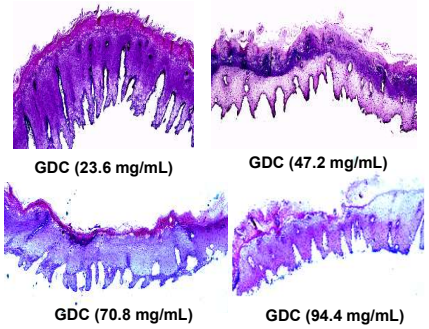


Fig. 5. Histology (H&E) of different GDC concentrations after 120 min (Bar = 250μm). The severity of tissue damage increased with increasing GDC dose

Conclusions

Based on excellent physicochemical properties, a buccal film a buccal film formulation using water-soluble biodegradable natural polymer was selected as prototype film for further development. The *ex-vivo* permeability study across porcine buccal mucosae demonstrated that the GLP-1 RA flux was the highest with a 1:2 ratio of the GLP-1 RA (50 mg/mL) to GDC (94.4 mg/mL). Although tissue damage increases with increasing GDC concentration *ex-vivo*, this will not be the case *in-vivo* where repair mechanisms are intact.

Acknowledgements

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Reference

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2. Brayden, D.J. et al., Advanced drug delivery reviews. 2020;157: 2-26