Design of a Mucoadhesive Film for Buccal Delivery Using FITC-Dextran 4000 (FD4) as a Model Compound For Peptides

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STATE-OF-THE-ART

Peptides are a major class of therapeutic drugs. The majority of commercially available peptide therapeutics are administered by injection. Because of their high molecular weight, sensitivity to proteolysis, and low intestinal permeability when administered orally, this results in low bioavailability[1]. This project aims to establish the buccal route as a non-invasive alternative route for the delivery of therapeutic peptides.

HYPOTHESIS

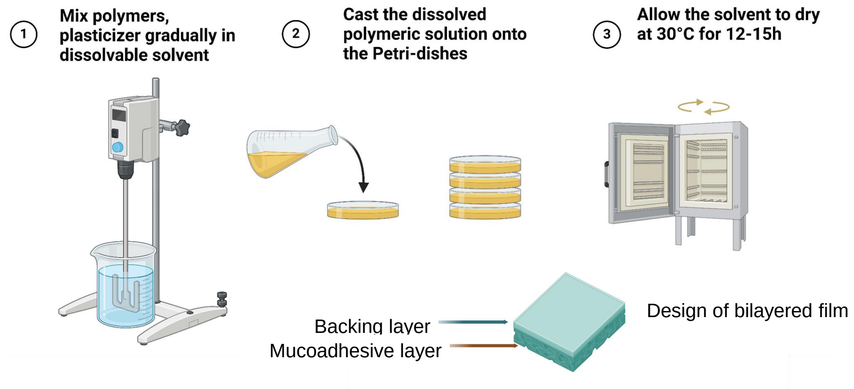
The optimised film prototype will overcome the buccal mucosal barrier through integration of permeation enhancers with biomaterials and a peptide payload. It will release the payload in a controlled manner, leading to enhanced buccal bioavailability.

OBJECTIVES

1. Preparation of bilayer buccal films using a fluorescent model molecule, FITC-Dextran 4000 (FD4).
2. Enhance mucosal permeability using permeation enhancers and mucoadhesive polymers.
3. Conduct permeability study in ex vivo porcine buccal mucosa and in vitro in human TR-146 keratinocyte cells.

METHODOLOGY

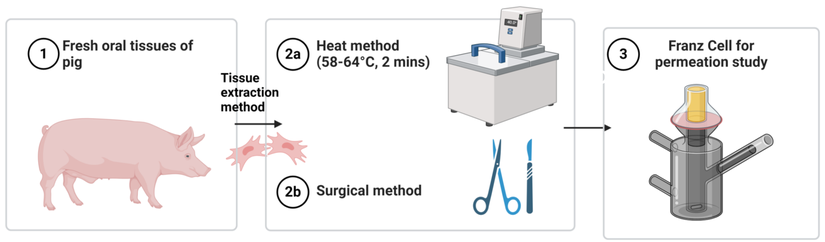
1. Synthesis of FD4-loaded bilayer films



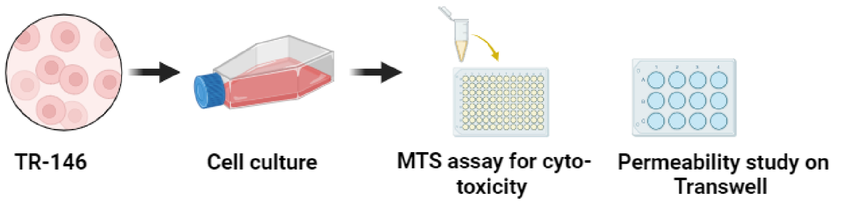
2. Physical characterisation of bilayer films

Morphology, drug disintegration, mucoadhesion (Texture Analyser), and rheological characterisation

3. Ex vivo flux study on isolated porcine buccal mucosa



4. TR-146 human buccal cells



RESULTS

Morphology of FD4 loaded prototype film

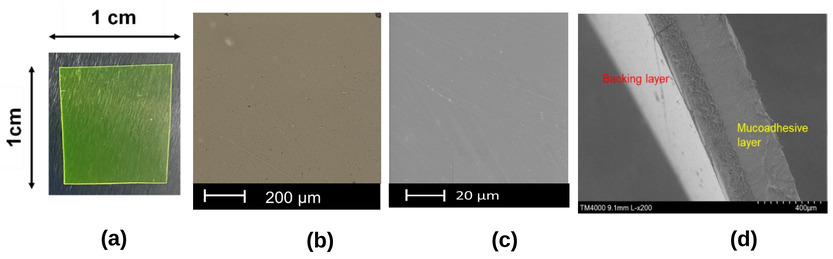


Fig. 1. Morphology of FD4 loaded PVA/Na CMC-based films (a) physical appearance b) Optical image (c) SEM image (d) SEM image showing bilayer longitudinally

PVA/PVPK-based formulations exhibited the excellent mucoadhesion

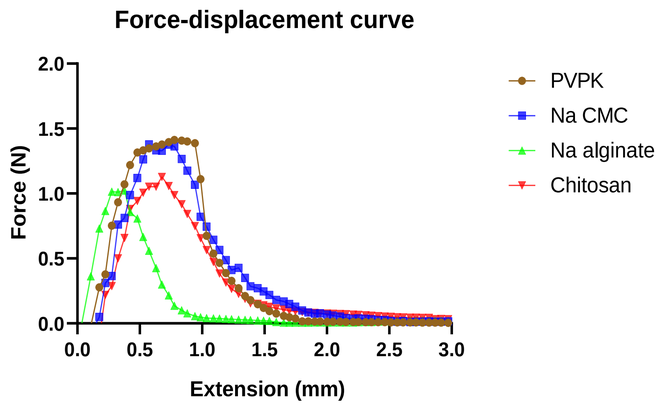


Fig. 2. Force displacement for polymer formulations.

Prototype formulation released in ~30 mins

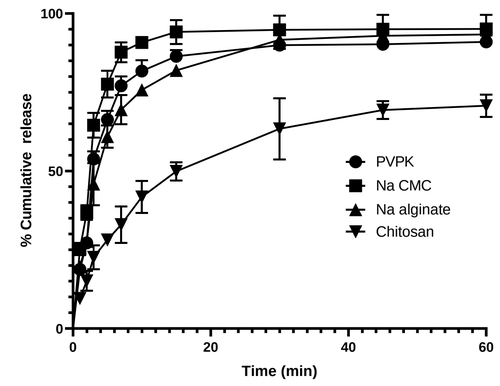


Fig. 3. In vitro release of FD4 loaded in polymer formulations

MTS assay in TR-146 cells showed no cytotoxicity at low concentrations of GDC

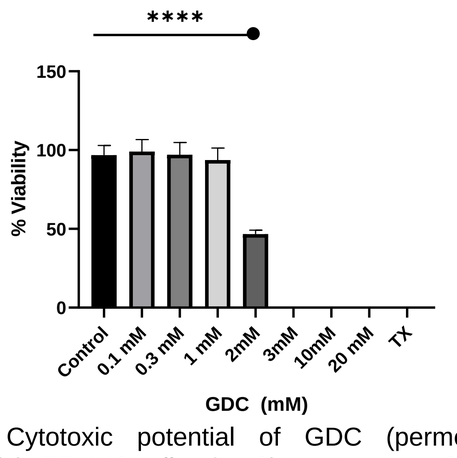


Fig. 4. Cytotoxic potential of GDC (permeation enhancer) in TR-146 cells after 3h treatment, n=3.

1 mM GDC increased FD4 permeability in TR-146 cells

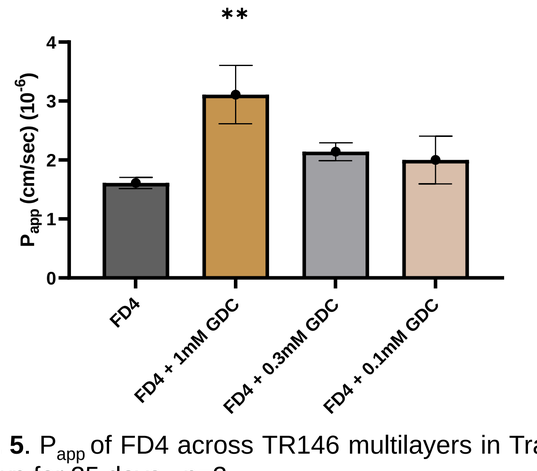


Fig. 5. P_{app} of FD4 across TR146 multilayers in Transwell® grown for 35 days, n=3.

10mM and 20mM increased FD4 permeability in porcine buccal tissue in Franz Cells

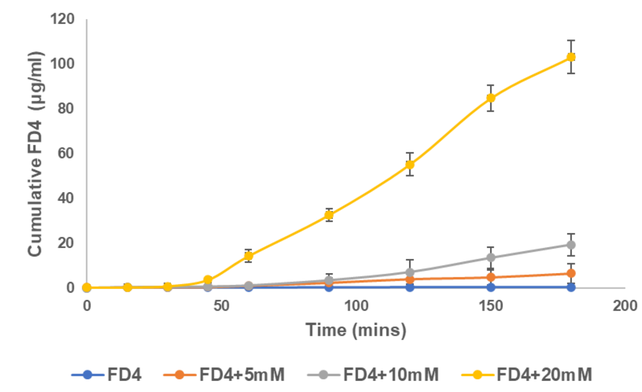


Fig. 6. Cumulative flux of FD4: control FD4, FD4 mixed with GDC at selected concentrations (n=4).

10mM and 20mM showed higher FD4 distribution across ex vivo porcine tissue

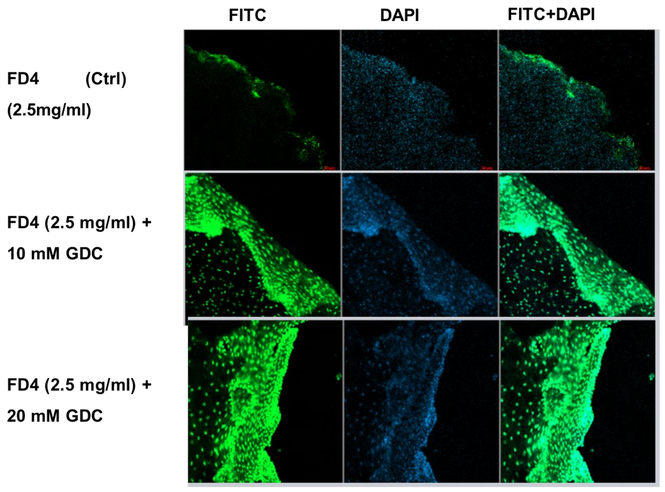


Fig. 7. Confocal imaging of ex vivo porcine buccal tissue exposed to FD4 with and without GDC at 3h

Some signs of porcine tissue damage at 20mM GDC

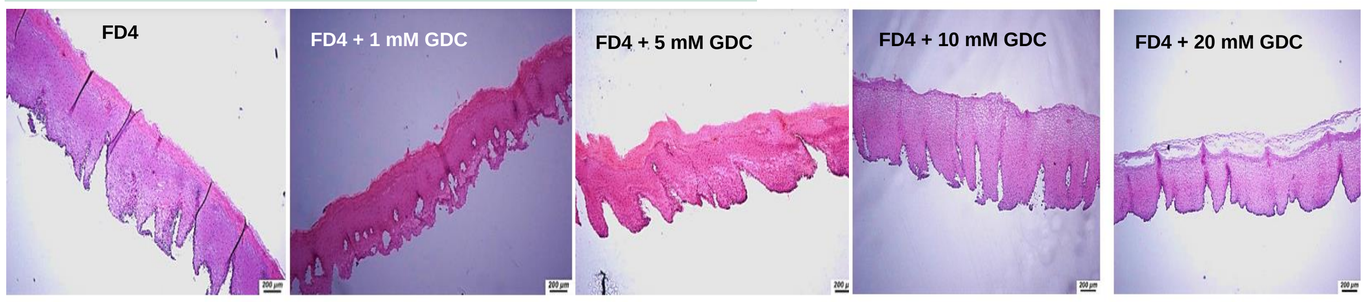


Fig. 8. H&E-stained porcine buccal tissue mounted in Franz cells and exposed to FD4 and selected concentration of GDC for 3h

CONCLUSIONS

- A prototype bilayer film based on a PVA/Na CMC mucoadhesive layer was selected.
- Based on in vitro and ex vivo results, GDC will be incorporated as an enhancer in the bilayer film.

IMPACT

- Potential to become first commercialised buccal patch for a GLP-1 peptide.
- Improve patient adherence and quality of life with another option for GLP-1 administration.
- Buccal platform for delivering other peptides.

REFERENCE

1. Morales J.O., et al. Int. J. Pharm. 2023, 636: 122789.

ACKNOWLEDGEMENTS

BUCCAL-PEP