Buccal Delivery of GLP-1 Analogue: Insights into Local Peptide Release from Multi-layer Films

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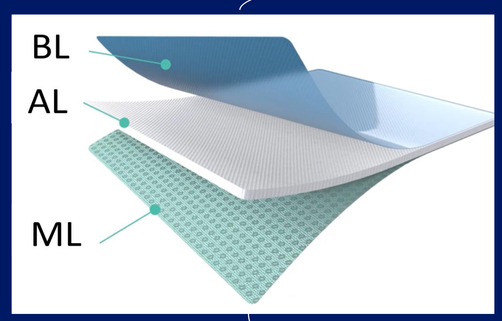
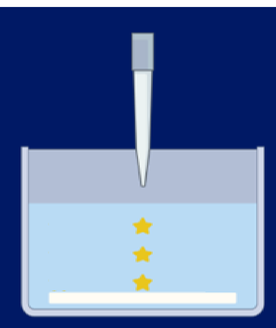
Optical Coherence Tomography combined with an automatic dissolution sampling instrument give insights into local release behavior from multi-layer films.





Background

The buccal route is a considered promising alternative to the traditional oral route for drug delivery by leveraging highly vascularized regions and bypassing the harsh gastrointestinal environment and first-pass metabolism [1]. Strong *in vitro* tools are essential for ethical, cost-effective, and knowledge-driven drug delivery system development. Here, we aim to combine the structural analysis with local drug release profiling in buccal local environment conditions to capture the local release dynamics for buccal film formulations.

Methods

A Glucagon-like peptide 1 receptor analogue (GLP-1 RA) from Novo Nordisk was used as model drug in this work. Sodium glycodeoxycholate (GDC), a bile salt, was used as epithelial permeation enhancer. The multilayers films were composed of successive layers defined as mucoadhesive layer (ML) containing the GDC, active layer (AL) containing the GLP-1 RA, and protective poorly water-soluble backing layer (BL). The tested films were positioned at the bottom of a culture cell plate and observed under dry or wet conditions with 1mL of Phosphate Buffer Saline (PBS) at pH 7.4 at room temperature under static conditions. Spectral domain Optical Coherence Tomography (SD-OCT) provided visualization of the film's internal architecture. The *in vitro* release assay used the FlowbotONE instrument, and GLP-1 RA and GDC in the samples were quantified using UPLC (Waters Acquity). This study centered on assessing the impact of the layer structure, the sampling distance from the film, and assessing unidirectional release.

Key Results

- Utilizing OCT in a dry state enables visualization of each film layer due to the distinct scattering properties. (Figure 1)
- Utilizing OCT in a wet state enables visualization of disintegration mechanisms for each film layer, including swelling, water penetration, and layer appearance. (Figure 2)
- The presence of diffusion-driven release is supported by the decrease in the detected amount of GLP-1 and GDC with sampling distance from the film. (Figure 3)
- The release of GDC was 3-fold less from a tri-layered structure compared to a bi-layered structure. No GLP-1 released was observed from the tri-layered film, emphasizing the importance of the film structure. (Figure 4)
- Directional release was observed as the release of GLP-1 RA and GDC through the BL is 7-fold less compared to through the MAL after 60 minutes. (Figure 5)

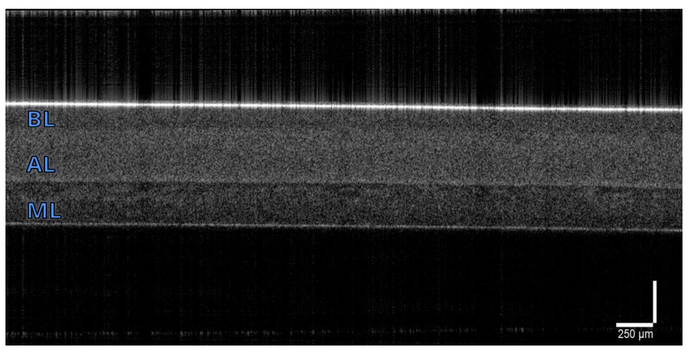


Figure 1. ML-AL-BL film observed by SD-OCT

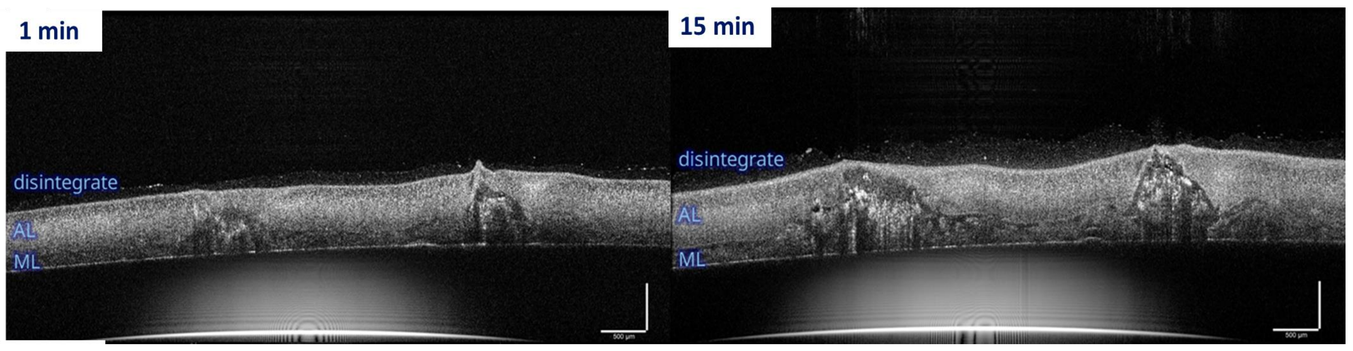


Figure 2. Disintegration of the ML-AL film in PBS observed by SD-OCT

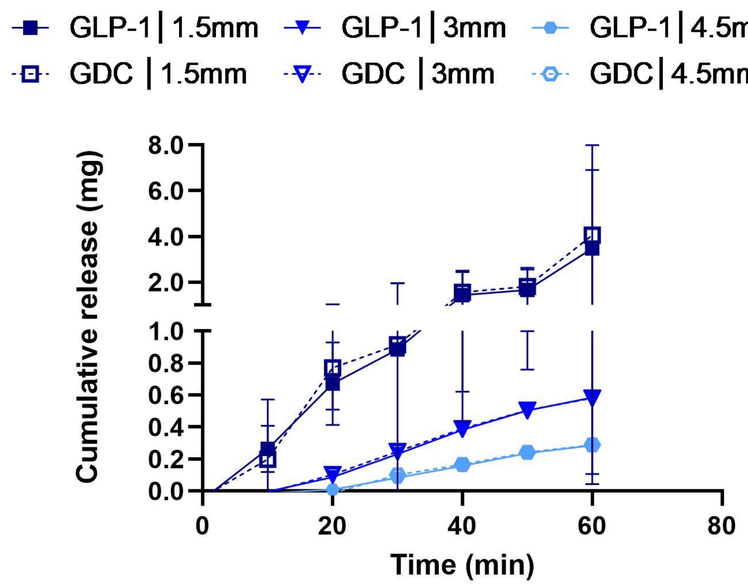


Figure 3. Cumulative release of GLP-1 and GDC, sampled at various heights from MAL-BL films. (Dose 1.6mg for GLP-1 and GDC)

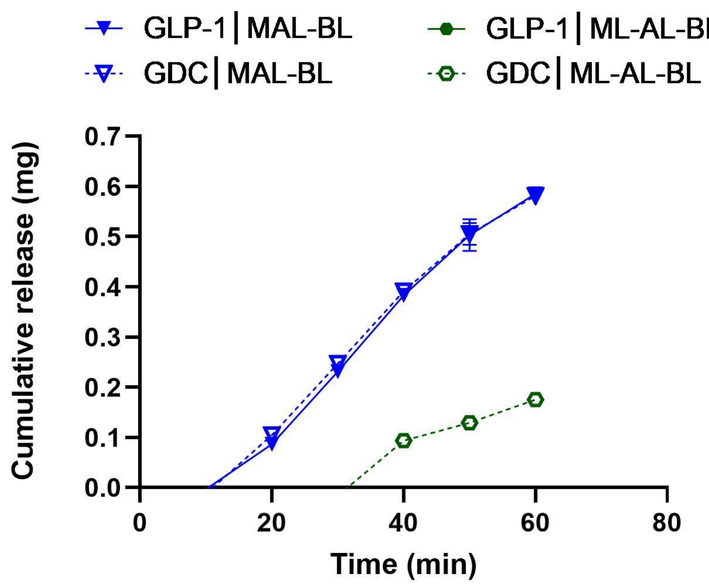


Figure 4. Cumulative release of GLP-1 and GDC from MAL-BL or ML-AL-BL films, sampled at 3mm. (Dose 1.6mg for GLP-1 and GDC)

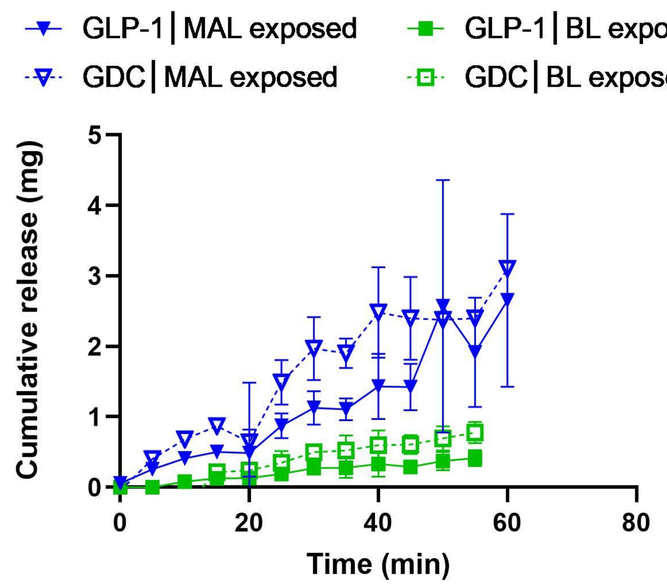


Figure 5. Cumulative release of GLP-1 and GDC varying layer exposition to medium, sampled at 3mm. (Dose 10mg for GLP-1 and 15mg for GDC)

Conclusion

Structural analysis revealed swelling, water penetration, and progressive layer disintegration, while *in vitro* release studies gave insights into local release behavior of GLP-1 and GDC, highlighting the significant influence of film structure on release dynamics. Combining OCT and precise and automatic dissolution sampling instrument provide a basis for method development in understanding optimizing buccal film formulations for enhanced peptide delivery.

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[1] F. Veuillez et al., Factors and strategies for improving buccal absorption of peptides, Eur. J. Pharm. Biopharm, 2001, 51, 93-109, doi:10.1016/S0939-6411(00)00144-2

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