Quest Journals
Journal of Research in Pharmaceutical Science
Volume 12 ~ Issue 3 (May- June 2026) pp: 98-103
ISSN(Online): 2347-2995
www.questjournals.org

Research Paper

Development And Evaluation of Mucoadhesive Buccal Film of Semaglutide Using Permeation Enhancers: A Novel Approach for Enhanced Bioavailability in Type 2 Diabetes Mellitus Patients with Obesity

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Abstract:
Buccal administration of drugs is an attractive route for peptides as it allows avoidance offirst-pass metabolism and increased bioavailability. The objective of the study was todevelop and assess mucoadhesive buccal films of semaglutide to improve drug transport, deliver sustained drug release and enhance patient compliance. Solvent casting technique was used for preparing buccal films with appropriate polymers and penetration enhancers. Preformulation studies showed compatibility of drug with excipients by FTIR and dissolution in phosphate buffer pH 6.8. The films were uniform, smooth, flexible and had acceptable thickness, weight variation, surface pH (6.5-6.9), drug content (95.9-99.2%) and folding endurance (160-220 folds). The in-vitro release studies showed sustained drug release for 8 hours, with F5 showing the maximum release (~98%). Ex-vivo permeation studies revealed faster drug permeation across buccal mucosa with F5 having the highest permeation flux (180 µg/cm²/hr) and permeability coefficient (0.018). Mucoadhesive force (0.22-0.34 N) provides longer residence time. In conclusion, the optimized semaglutide buccal film formulation F5 had ideal physicochemical properties, sustained drug release, enhanced permeation and effective mucoadhesion; hence, semaglutide buccal films could be a potential approach to enhance bioavailability and efficacy in the treatment of type 2 diabetes.

Keywords: *Semaglutide, Mucoadhesive buccal film, Buccal drug delivery, Permeation enhancers, Bioavailability, Sustained release, Ex-vivo permeation, Mucoadhesion, Type 2 diabetes mellitus, Peptide drug delivery.*

*Received 06 June., 2026; **R**evised 15 June., 2026; **A**ccepted 17 June., 2026 © The author(s) 2026.*
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I. Introduction

Type 2 diabetes mellitus (T2DM) is a significant global health burden, which is associatedwith obesity and physical inactivity **[1].** The presence of obesity and T2DM leads to rapid onset of insulin resistance and β-cell failure, as well as chronic cardiovascular and metabolic complications **[2].** In recent years, the development of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has gained attention for their ability to reduce blood glucose levels and body weight **[3].** Long-acting GLP-1 mimetic semaglutide has been shown to have greater HbA1c, weight, and cardiovascular risk reductions than many standard treatments **[4].**

Despite its therapeutic potential, current semaglutide formulations have several drawbacks. Injection-related issues include fear of needles, pain, cold storage and low patient compliance, especially with long-term treatment **[5].** While an oral formulation is available, it has very low oral bioavailability, variable absorption (affected by food consumption) and gastrointestinal adverse effects **[6].** Therefore, an alternative patient-preferred delivery method that enhances systemic delivery and efficacy is needed **[7].**

Buccal delivery is an attractive, non-invasive method for peptide administration which avoids gastrointestinal and hepatic metabolism, has rapid absorption and high patient compliance **[8].** Mucoadhesive buccal films, containing bioadhesive polymers and permeation enhancers, extend mucosal contact time and increase mucosal drug permeation through the buccal membrane **[9].** Hence, a mucoadhesive buccal film containing semaglutide is a new and promising strategy to improve bioavailability, ease the drug administration, and increase patient compliance in obese T2DM patients **[10].**

4. MATERIALS AND METHODS

4.1 Materials

The active pharmaceutical ingredient (API) was semaglutide (3 mg per film). Film forming and mucoadhesive polymers were sodium carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose (HPMC), Carbopol 934P and polyvinyl alcohol (PVA). Tween 80, oleic acid, and sodium taurocholate were used as permeation enhancers . Glycerol and polyethylene glycol 400 (PEG 400) were used as plasticizers and mannitol and aspartame as sweeteners. Water and ethanol were used as solvents. All the chemicals used were of analytical grade.

4.2 Pre-formulation Studies

- **Drug–Excipient Compatibility:** Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) were used to evaluate the compatibility of semaglutide with chosen excipients. FTIR was used to identify any chemical incompatibilities through shifts in peaks of functional groups, while DSC was used to study thermal characteristics, melting point and crystallinity to ensure drug stability in the formulation.
- **Solubility Study:** Solubility of semaglutide was tested in distilled water, ethanol and buffers at different pH. This helped in choosing an appropriate solvent system and drug loading/ release from polymer matrix.

4.3 Preparation of Mucoadhesive Buccal Films

Semaglutide mucoadhesive buccal films were prepared by solvent casting technique. Film-formers (HPMC, CMC, Carbopol 934P and PVA) were dissolved in water. Plasticizers were incorporated to enhance flexibility, followed by addition of semaglutide dissolved in ethanol-water mixture**.[11]** Permeation enhancers and sweeteners were added. The solution was deaerated, poured into Petri plates, air-dried at room temperature and cut to produce films with 3 mg of semaglutide.

4.4 Formulation Design

A series of six formulations (F1-F6) were prepared with different polymer, plasticizer, and permeation enhancer concentrations to achieve optimal mechanical properties, mucoadhesion, and drug release.

4.5 Evaluation of Buccal Films

Films were assessed for appearance, thickness, weight variation, foldability, and pH. Drug content was analysed by UV spectrophotometry. In vitro drug release was investigated using a USP dissolution apparatus in phosphate buffer (pH 6.8) and ex vivo drug permeation using a Franz diffusion cell with buccal mucosa. Mucoadhesive strength, swelling index and stability studies were carried out to validate the film's performance and stability.

4.6 Statistical Analysis

Triplicate experiments were conducted and data presented as mean ± SD. Formulations were analysed by one-way ANOVA with $p < 0.05$ as the level of significance. Post hoc tests were carried out when required.

5.RESULTS AND DISCUSSION

5.1 Preformulation Studies

Semaglutide was found to be suitable for development of a buccal film formulation. The FTIR spectrum showed the peaks for the functional groups of the drug remained unchanged when mixed with excipients, suggesting no interaction between the drug and excipient and hence compatibility with the chosen polymers and excipients. Further, the drug's high solubility in phosphate buffer pH 6.8 was shown to be suitable for buccal drug delivery **[12].**

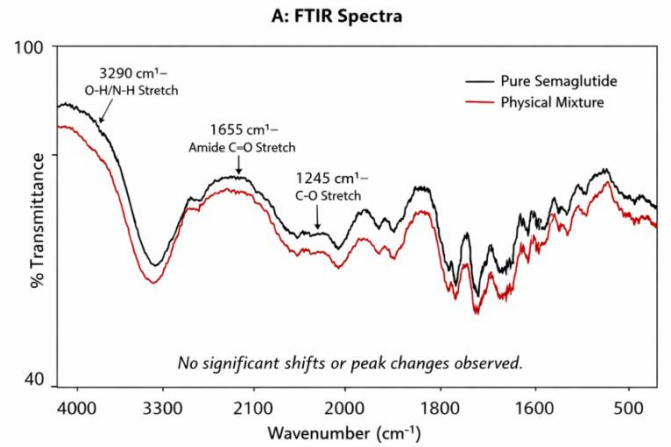

Figure 5.1: FTIR spectrum confirming drug–excipient compatibility.

5.2 Evaluation of Buccal Films

Buccal films (F1-F6) were smooth, flexible, transparent, and had a uniform appearance. Thickness (0.21-0.26 mm) and weight (48-53 mg) were uniform, thus indicating the reproducibility of solvent casting technique. The surface pH (6.5-6.9) was acceptable for buccal application and the drug content (95.9-99.2%) showed uniform distribution of the drug. Folding endurance (160-220 folds) indicated strong and flexible nature.

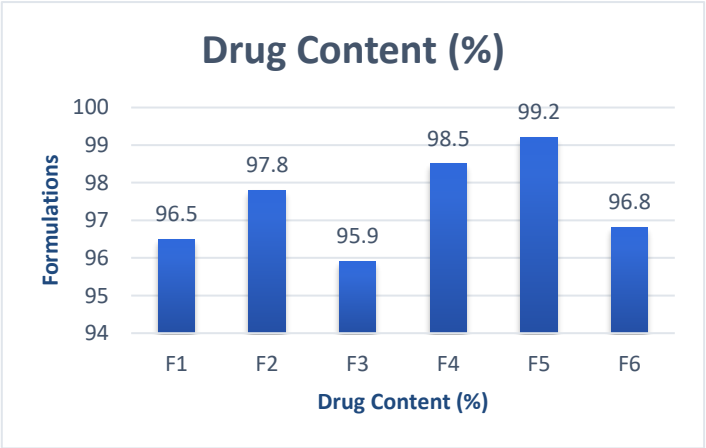

Figure 5.2: Physical appearance and uniformity of prepared buccal films.

5.3 In-Vitro Drug Release Study

The in-vitro drug release study exhibited sustained release for all formulations over 8 hours. The highest cumulative drug release was observed with F5 (~98%) followed by F4 (~94%). This sustained release is due to the combination of mucoadhesive and permeation enhancer polymers, suggesting the potential of buccal films for sustained release, lower dosing frequency and better patient compliance.

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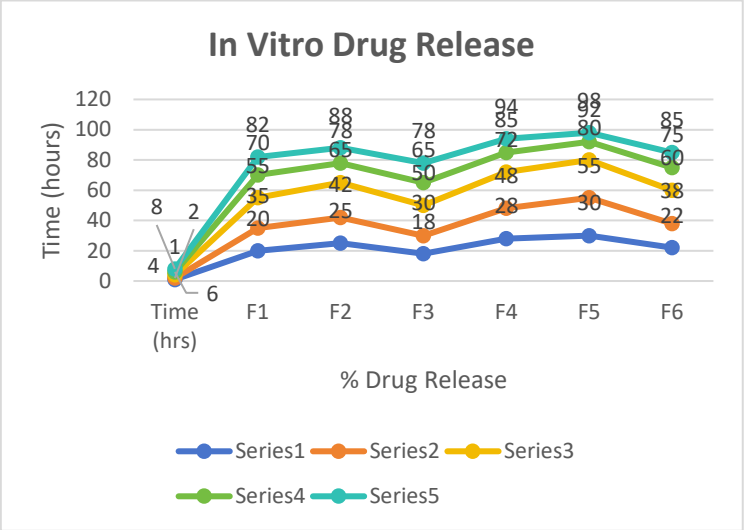

Figure 5.3: Comparative in-vitro drug release profile of formulations F1–F6.

5.4 Ex-Vivo Permeation Study

Ex-vivo permeation study revealed improved permeation through buccal mucosa. Highest permeation flux (180 µg/cm²/hr) and permeability coefficient (0.018) was observed with formulation F5, suggesting enhanced mucosal permeation of semaglutide and improved systemic bioavailability.

Table 5.9: Ex Vivo Permeation Parameters of Buccal Films (Flux and Permeability Coefficient)

Formulation	Flux (µg/cm²/hr)	Permeability Coefficient
F1	120	0.012
F2	140	0.014
F3	110	0.011
F4	160	0.016
F5	180	0.018
F6	135	0.013

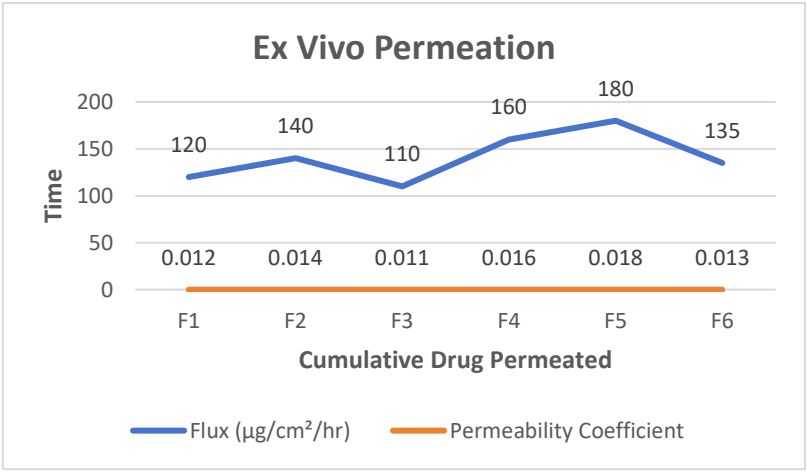

Figure 5.4: Ex Vivo Permeation Profile of Semaglutide Buccal Films (F1–F6)

5.5 Mucoadhesive Strength

Mucoadhesive strengths were between 0.22-0.34 N, with F5 being the strongest (0.34 N), for longer residence time.

Table 5.1: Mucoadhesive Strength of Buccal Films (F1–F6)

Formulation	Strength (N)
F1	0.25
F2	0.28
F3	0.22
F4	0.30
F5	0.34
F6	0.26

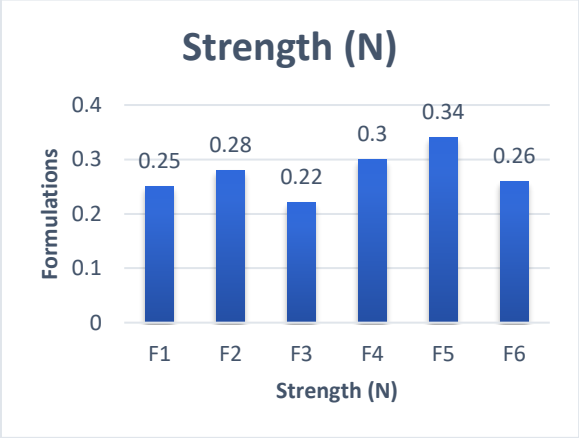

Figure 5.5: Mucoadhesive Strength of Mucoadhesive Buccal Films (F1–F6)

6.Discussion

Among the formulations prepared, F5 was found to be the optimized buccal film formulation that exhibited the optimal balance of physicochemical properties such as acceptable thickness, fold endurance, surface pH and drug content uniformity. It displayed good mucoadhesive force and swelling index, both crucial for sustained buccal residence time and steady drug delivery.

In addition, F5 also exhibited sustained drug release and high permeation, suggesting the successful incorporation of permeation enhancers promote drug penetration into the buccal membrane. The results of this study indicate that the development of mucoadhesive buccal films of semaglutide is a promising, non-invasive, and convenient delivery system with the potential to enhance bioavailability, efficacy and patient compliance for the chronic treatment of Type 2 Diabetes Mellitus.

7.Conclusion

This study successfully formulated and evaluated mucoadhesive buccal films of semaglutide as a potential substitute to conventional modes of drug delivery in the treatment of Type 2 Diabetes Mellitus. Compatibility and stability of the drug with the chosen polymers and excipients were confirmed in the preformulation studies, and the developed films showed acceptable physicochemical characteristics, uniform drug distribution and acceptable pH on the surface for the buccal application. In-vitro drug release and ex-vivo permeation studies showed sustained release and increased permeability, suggesting that buccal films have the potential to avoid first-pass metabolism and enhance systemic absorption.

The formulation F5 showed the highest mucoadhesive force, optimum swelling and highest permeation efficiency among all the formulations, indicating sustained residence time and enhanced therapeutic efficacy. In conclusion, semaglutide buccal films demonstrate a novel, patient-compliant and non-invasive delivery approach that may improve patient adherence and therapeutic outcomes in the treatment of diabetes.

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