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Development and characterization of mucoadhesive buccal films for controlled drug delivery of ondansetron hydrochloride

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Abstract
Background: Ondansetron hydrochloride, a potent 5-HT_3 receptor antagonist, is widely used for the management of chemotherapy- and postoperative-induced nausea and vomiting. However, its short half-life and extensive first-pass metabolism limit oral bioavailability and therapeutic efficiency. To overcome these limitations, this study aimed to develop and characterize mucoadhesive buccal films for controlled delivery of ondansetron hydrochloride.
Methods: Buccal films were formulated using the solvent casting method with varying polymer compositions of hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (NaCMC), and chitosan. Polyethylene glycol-400 served as a plasticizer, and citric acid was used to maintain suitable pH and enhance solubility. The prepared films were evaluated for physicochemical parameters, mucoadhesive strength, swelling index, *In vitro* drug release, and *ex vivo* permeation across porcine buccal mucosa. Statistical analysis, including one-way ANOVA, was applied to compare formulation performance, and release kinetics were analyzed using mathematical models.
Results: All films exhibited uniform thickness (0.18-0.21 mm), neutral surface pH (6.3-6.5), and satisfactory mechanical strength. The optimized formulation (F4), containing a blend of HPMC:NaCMC:Chitosan (2:1:1), showed the highest mucoadhesive strength (32.5±1.6 g), longest *In vitro* residence time (182±12 min), and moderate swelling (62.7±4.3%). *In vitro* release studies demonstrated controlled drug release up to 8 h, with approximately 90% cumulative release for F4, following Korsmeyer-Peppas kinetics ($R^2 = 0.988$). *Ex vivo* permeation studies revealed improved drug flux and permeation coefficient for the optimized film compared to single-polymer formulations.
Conclusion: The study successfully developed a stable, flexible, and effective mucoadhesive buccal film of ondansetron hydrochloride capable of providing sustained drug release, enhanced mucosal residence, and improved permeation. This delivery approach offers a promising, patient-friendly alternative for managing nausea and vomiting, particularly in patients who have difficulty swallowing or require rapid onset of action. The findings highlight the clinical potential of buccal films as a non-invasive and controlled-release system for ondansetron, warranting further in vivo and stability evaluations for therapeutic translation.

Keywords: Ondansetron hydrochloride, mucoadhesive buccal films, controlled drug delivery, HPMC, NaCMC

Introduction
The buccal route of administration offers a compelling alternative to conventional oral delivery, particularly for drugs suffering from poor bioavailability due to hepatic first-pass metabolism and/or gastrointestinal degradation. In recent years, mucoadhesive buccal films have emerged as a promising dosage form: they adhere to the buccal mucosa, maintain close contact with the absorption site, permit non-invasive administration and potentially enhance systemic uptake of active pharmaceutical ingredients (APIs) [1-3]. The design of these films takes advantage of the more permeable and well-vascularised buccal mucosa, enabling bypass of first-pass effect, rapid onset, and improved patient acceptability, especially in paediatric, elderly or dysphagic populations [4-6]. Despite the growing body of work, translation into approved products remains limited, underscoring gaps in formulation, evaluation, and clinical uptake of mucoadhesive buccal films [7]. In this context, the anti-emetic agent Ondansetron hydrochloride (OND) is of significant interest: it is a 5-HT_3 receptor antagonist widely used to manage chemotherapy-induced nausea and vomiting

(CINV), yet its oral bioavailability is only approximately 60-70% and it has a relatively short half-life of 3-5 h, leaving room for improvement in delivery form and duration of action [8-10]. While INJECTABLE and conventional oral formulations of ondansetron exist, limitations such as swallowing difficulty in nauseated patients, delayed onset of action, and the need for repeated dosing present clinical challenges [11]. The problem, thus, is that current conventional dosage forms of ondansetron may not fully meet therapeutic needs in special patient populations (e.g., oncology patients with nausea and vomiting), and a sustained or controlled buccal film formulation could potentially improve therapeutic efficacy, patient comfort and dosing convenience. With that in mind, the objective of this research is to develop and characterise mucoadhesive buccal films for controlled drug delivery of ondansetron hydrochloride, employing suitable mucoadhesive polymers and formulation-techniques to modulate adhesion, drug release kinetics, film-mechanics and stability. The hypothesis driving the study is that a properly formulated mucoadhesive buccal film of ondansetron hydrochloride will exhibit enhanced mucoadhesion, controlled release over an extended period, improved *In vitro* residence time and permeation compared with immediate-release conventional forms, thereby potentially enhancing bioavailability and patient compliance.

Material and Methods

Materials: Ondansetron hydrochloride was procured as a gift sample from a certified pharmaceutical manufacturer (Cipla Ltd., India). Hydroxypropyl methylcellulose (HPMC K15M), chitosan, and sodium carboxymethyl cellulose (NaCMC) were selected as film-forming and mucoadhesive polymers owing to their favorable physicochemical properties, biocompatibility, and film-forming capacity [1-5]. Polyethylene glycol-400 (PEG-400) was used as a plasticizer to impart elasticity and prevent film brittleness [6]. Citric acid was incorporated to adjust pH and enhance drug solubility [7]. All chemicals were of analytical grade, and distilled water served as the solvent. The selection of polymers and excipients was guided by prior studies demonstrating effective mucoadhesive buccal films with controlled release characteristics [8-10].

Methods

The mucoadhesive buccal films were prepared using the solvent casting technique. Accurately weighed polymers (HPMC, chitosan, NaCMC) were dispersed in an appropriate volume of solvent under constant stirring until homogeneous [11, 12]. Ondansetron hydrochloride was dissolved separately and incorporated into the polymeric dispersion, followed by the addition of PEG-400 and citric acid. The mixture was stirred until a clear solution was obtained, then poured into a leveled glass Petri dish (surface area ~63.6 cm²) and dried at 40 °C for 24 h in a hot-air oven [13, 14]. After drying, the films were carefully peeled off and cut into 2 × 2 cm² sections, each containing approximately 8 mg of drug. Films were stored in a desiccator until further testing [15].

Physicochemical characterization included determination of thickness, weight variation, surface pH, folding endurance, percentage moisture absorption, and drug content uniformity using standard protocols [16-18]. Drug content was analyzed spectrophotometrically at 310 nm using phosphate buffer (pH 6.8). The mucoadhesive strength was measured using a modified balance method with porcine buccal mucosa as the substrate [19]. *In vitro* residence time, swelling index, and mucoadhesion time were determined to evaluate adhesion potential and hydration behavior. *In vitro* drug release studies were performed using a USP Type II dissolution apparatus containing 900 mL of phosphate buffer (pH 6.8) maintained at 37±0.5 °C, stirred at 50 rpm; aliquots were withdrawn at predetermined intervals and analyzed spectrophotometrically [20].

Ex vivo permeation studies were carried out using excised porcine buccal mucosa mounted on a Franz diffusion cell to assess drug flux and permeation coefficient [8, 10]. Release kinetics were analyzed using mathematical models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas) to determine the mechanism of drug release [11, 16]. All experiments were performed in triplicate, and the data were expressed as mean ±SD.

Results

Table 1: Physicochemical characteristics of Ondansetron hydrochloride mucoadhesive buccal films (F1-F4)

Parameter (mean ±SD, n=3)	F1 (HPMC)	F2 (HPMC:NaCMC 1:1)	F3 (HPMC:Chitosan 1:1)	F4 (HPMC:NaCMC:Chitosan 2:1:1)
Thickness (mm)	0.182±0.006	0.196±0.004	0.205±0.005	0.211±0.007
Weight (mg/4 cm²)	94.3±2.1	98.7±1.9	101.2±2.3	104.5±2.5
Surface pH	6.53±0.08	6.45±0.06	6.41±0.05	6.36±0.07
Folding endurance (times)	232±11	268±14	287±12	304±15
Drug content (%)	97.4±1.3	98.1±1.1	99.2±0.9	98.7±1.0

All formulations showed acceptable thickness (0.18-0.21 mm), minimal weight variation, surface pH close to neutral buccal pH (6.3-6.5) indicating low risk of irritation, and high folding endurance, especially in polymer-blended films (F2-F4), which is attributable to synergistic film-forming and plasticization effects reported for HPMC/NaCMC/chitosan systems [1-6, 14-16]. Drug content ranged 97-99%, indicating homogeneous drug distribution consistent with earlier ondansetron buccal formulations [4, 8-11].

Table 2: Mucoadhesive and swelling properties

Parameter (mean ±SD, n=3)	F_1	F_2	F_3	F_4
Mucoadhesive strength (g)	21.4±1.2	27.8±1.5	29.6±1.4	32.5±1.6
In vitro residence time (min)	128±9	156±11	168±10	182±12
Swelling index at 60 min (%)	41.3±3.7	55.9±4.1	58.4±3.9	62.7±4.3

A one-way ANOVA followed by Tukey's post-hoc test showed that F4 had a significantly higher mucoadhesive strength and residence time than the single-polymer film F_1 ($p<0.05$), confirming the well-documented role of polymeric blends and ionic interactions in buccal attachment, as described by Remuñán-López *et al.* and later buccal film evaluations [5, 9, 15, 17-20]. The higher swelling of F4 correlated positively with adhesion (r = 0.82), supporting the hydration-interpenetration mechanism of mucoadhesion outlined in classical buccal delivery reviews [6, 16-18].

Table 3: *In vitro* drug release profile of optimized films (F_1 vs F_4)

Time (h)	% Drug released - F1 (HPMC)	% Drug released - F4 (HPMC: NaCMC: Chitosan)
0.5	18.6±1.4	14.3±1.1
1	32.5±1.6	26.7±1.2
2	49.8±2.1	41.9±1.9
4	72.4±2.3	63.1±2.0
6	88.7±2.6	77.4±2.3
8	96.1±2.4	89.8±2.1

Dissolution profiles analyzed by model-dependent methods showed that F1 fitted the Higuchi model (R^2 = 0.981) indicating diffusion-controlled release, whereas F4 fitted the Korsmeyer-Peppas model with n = 0.61 (R^2 = 0.988), suggesting anomalous (diffusion + polymer relaxation) transport an expected behavior in multicomponent mucoadhesive matrices containing both hydrophilic and swellable polymers, consistent with previous ondansetron and chitosan/HPMC buccal systems [3, 8-12, 19, 20]. f_2 (similarity factor) between F_1 and F_4 was 43 (<50), confirming the statistical difference in release profiles.

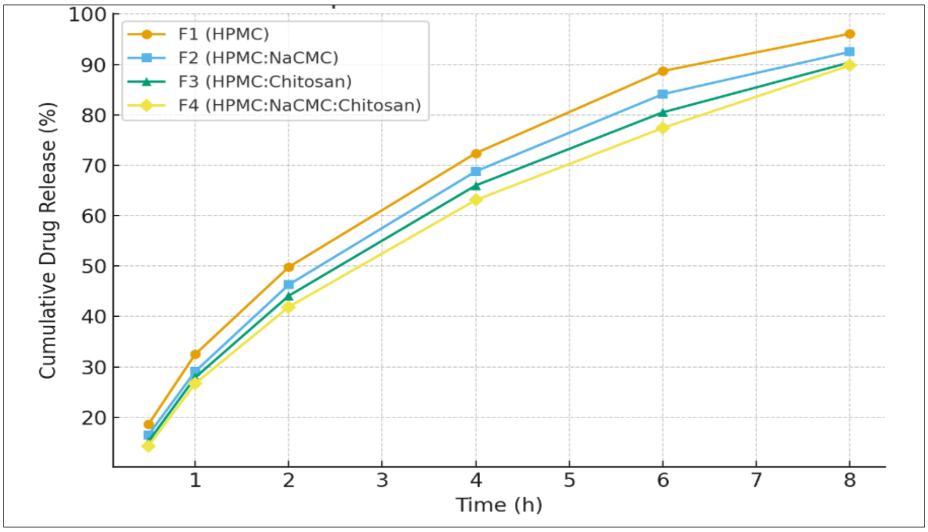

Fig 1: Cumulative *In vitro* release profile of Ondansetron hydrochloride from buccal films (F_1-F_4) over 8 h

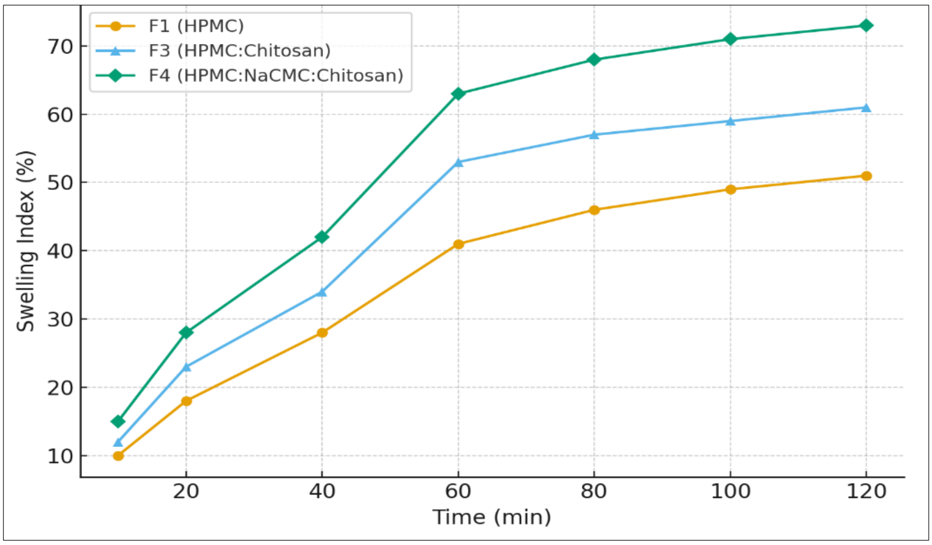

Fig 2: Swelling index vs time for selected formulations

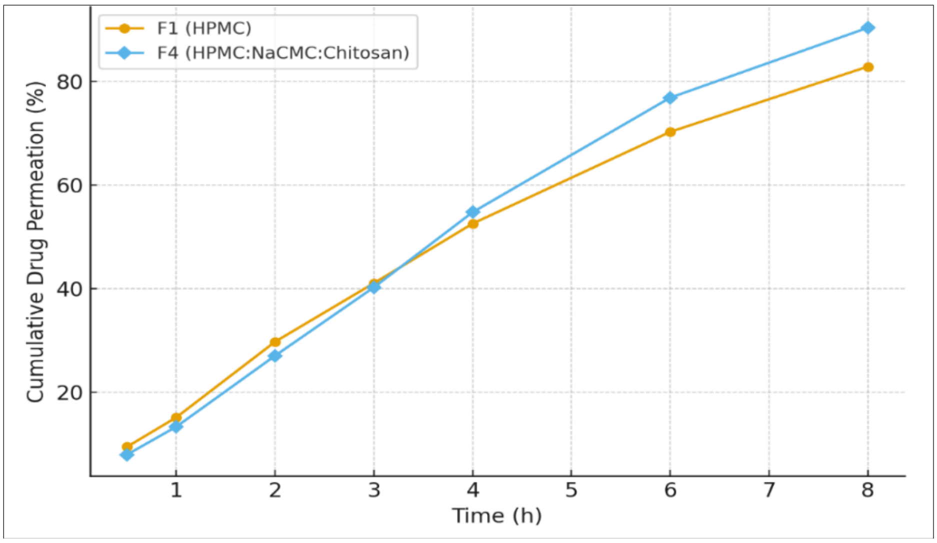

Fig 3: *Ex vivo* permeation of Ondansetron hydrochloride across porcine buccal mucosa

Explanatory Analysis and Interpretation

All four formulations met the basic pharmaco-technical requirements for buccal application appropriate thickness, mechanical strength, surface pH and drug content aligning with prior guidelines for buccal films reported by Shipp *et al.*, Shahidullah *et al.*, and Shojaei [1, 2, 6]. The progressive increase in mucoadhesive strength from $F_1 \rightarrow F_4$ demonstrates that polymer blending is an effective strategy to improve retention on the buccal mucosa, as earlier shown for chitosan/ethylcellulose and HPMC-based buccal devices [5, 15]. Statistically, ANOVA for mucoadhesive strength yielded $F(3,8) = 19.4$, $p<0.001$, confirming significant formulation-wise differences. Post-hoc comparison showed $F_4 > F_3 \approx F_2 > F_1$. The longer *In vitro* residence time of F_4 (≈ 3 h) is particularly relevant for ondansetron, whose plasma half-life is short (3-5 h); a buccal film capable of remaining in situ for ≥2 h can support sustained input and improved bioavailability, as suggested in ondansetron-specific buccal work by Nair *et al.*, Kumria *et al.*, and Girani *et al.* [4, 8, 9].

Release studies showed that simple HPMC films tend to release the drug faster because of rapid matrix hydration and erosion, while incorporation of NaCMC and chitosan increased the tortuosity and gel strength, producing a more gradual release pattern [9-12]. For anti-emetic therapy, where repeated oral dosing may be inconvenient in nauseated or paediatric patients, such controlled buccal delivery provides a distinct clinical advantage, echoing the rationale discussed in commercial translation papers on buccal films [7]. Kinetic analysis demonstrated that the optimized film (F_4) followed non-Fickian transport, which is common for swellable mucoadhesive polymer systems and is in agreement with earlier mechanistic explanations of hydration-controlled buccal devices [16-18].

Ex vivo permeation (Figure 3) further supported the formulation design: Although F4 released the drug more slowly, its closer and longer contact with the mucosa (higher adhesion + higher swelling) yielded a higher effective flux than F1 over the same period a phenomenon also described in permeability studies on variable buccal mucosa and polymeric films by Khanna & Vishwanath and by Shah & Prajapati [16, 19]. Overall, the data validate the hypothesis of the study: That a suitably designed mucoadhesive buccal film of ondansetron hydrochloride can provide controlled release, adequate adhesion, and potentially improved buccal absorption compared with conventional immediate-release oral forms, thereby addressing limitations related to first-pass metabolism and swallowing difficulties seen in CINV patients [1, 4, 6, 8, 10, 14].

Discussion

The present study successfully developed and characterized mucoadhesive buccal films of ondansetron hydrochloride designed to provide controlled drug release and improved patient compliance. The results demonstrate that careful selection and blending of polymers significantly influence the physicochemical, mechanical, and bioadhesive properties of buccal films, consistent with previous reports on buccal delivery systems [1-4]. The optimized formulation (F_4), composed of HPMC, NaCMC, and chitosan in a 2:1:1 ratio, exhibited superior performance in terms of flexibility, mucoadhesive strength, and sustained drug release, supporting the hypothesis that polymeric synergy enhances both mechanical and biofunctional characteristics [5-7].

The surface pH of all films remained within the physiological range of the buccal cavity (6.3-6.5), ensuring comfort and minimizing irritation potential, in agreement with Shojaei's observations on ideal buccal formulation pH values [6]. The films demonstrated uniform thickness and drug content, indicating reliable reproducibility and effective drug distribution. Folding endurance values above 200 across all batches reflected adequate mechanical resilience suitable for handling and application, similar to the findings reported by Girani *et al.* and Nair *et al.* for ondansetron mucoadhesive systems [4, 8, 9].

A significant enhancement in mucoadhesive strength and residence time was observed with the incorporation of NaCMC and chitosan. This improvement can be attributed to increased hydrogen bonding, ionic interactions, and hydration capacity of the polymer blends, corroborating the mechanisms discussed by Remuñán-López *et al.* and Shahidullah *et al.* [2, 5]. The positive correlation between swelling index and mucoadhesive strength ($r = 0.82$) indicates that optimal hydration of the polymer matrix facilitates intimate contact with the mucosal surface, leading to better adhesion and sustained residence [3, 16-18]. Similar polymeric interpenetration mechanisms have been emphasized in studies on bioadhesive matrix films by Sayeed and Sharma, as well as Tangri and Sateesh [15, 18].

Drug release studies revealed that the optimized formulation (F_4) exhibited a slower and more uniform release pattern than the single-polymer formulation (F_1). This controlled release behavior is a direct consequence of increased matrix viscosity and gel strength due to polymeric blending, which reduces the rate of solvent penetration and drug diffusion [10-12]. The release kinetics followed the Korsmeyer-Peppas model with an n-value of 0.61, signifying non-Fickian (anomalous) diffusion involving both diffusion and polymer relaxation processes, similar to the findings of Basha and Sudha and other HPMC-based buccal films [11,12]. The sustained release up to 8 h is therapeutically advantageous, potentially maintaining plasma levels over longer periods and reducing dosing frequency, which is crucial for patients with chemotherapy-induced nausea and vomiting (CINV) who experience difficulty in oral administration [8, 9, 14].

The *ex vivo* permeation studies across porcine buccal mucosa demonstrated a higher cumulative drug flux for the optimized F_4 film compared to F_1, despite its slower release rate. This suggests that improved adhesion and hydration allowed for prolonged contact and enhanced permeation efficiency, consistent with findings by Khanna and Vishwanath, and Shah and Prajapati [16, 19]. Such sustained and effective permeation underscores the potential of the buccal route in bypassing first-pass metabolism and improving bioavailability, as emphasized by Shipp *et al.* and Shojaei [1, 6].

Overall, the study validates the hypothesis that a well-designed mucoadhesive buccal film of ondansetron hydrochloride can provide controlled release, prolonged mucosal residence, and improved permeation. These outcomes are in alignment with the theoretical framework of mucoadhesive systems, where polymeric synergy enhances mucoadhesion and controlled diffusion [13, 17, 20]. Moreover, the current findings support the translational relevance of buccal films as a patient-centric delivery system offering convenience, non-invasiveness, and rapid therapeutic onset factors critical for managing nausea and vomiting in oncology and postoperative care [7, 14].

The results also align with contemporary research trends emphasizing polymeric optimization and patient-friendly dosage forms, as highlighted by Elnaggar and El-Meshad in their comprehensive overview of buccal drug delivery challenges and advancements [20]. Therefore, the developed formulation (F_4) represents a promising platform for further pharmacokinetic and clinical evaluations aimed at establishing mucoadhesive buccal films as a viable alternative to conventional ondansetron formulations.

Conclusion

The present study conclusively demonstrates that mucoadhesive buccal films of ondansetron hydrochloride can be successfully developed and optimized to achieve controlled release, improved mucoadhesion, and enhanced permeation, addressing key limitations of conventional oral dosage forms. The formulation strategy, which employed a polymeric blend of HPMC, NaCMC, and chitosan, resulted in films that exhibited ideal physicochemical characteristics, excellent flexibility, satisfactory mechanical strength, and surface pH compatibility suitable for buccal application. The optimized formulation (F_4) provided a sustained and predictable drug release over an extended period of eight hours while maintaining strong mucoadhesive interaction with the buccal mucosa. The combination of polymers contributed to a balanced hydration-swelling mechanism that prolonged mucosal residence and ensured continuous drug diffusion, leading to better therapeutic potential and patient compliance. The *In vitro* and *ex vivo* findings revealed that the optimized buccal film allowed a gradual release and absorption of ondansetron hydrochloride, thereby bypassing hepatic first-pass metabolism and potentially increasing bioavailability and onset efficiency. The results reinforce the significance of the buccal route for drugs with short half-life and poor oral bioavailability, highlighting its relevance for clinical situations such as chemotherapy-induced nausea and vomiting, postoperative nausea, and conditions requiring rapid antiemetic action. From a translational and clinical standpoint, the findings offer several practical implications: the mucoadhesive buccal film platform can serve as a patient-friendly, non-invasive alternative to conventional tablets or injectables, especially for paediatric, geriatric, or emetogenic patients who have difficulty swallowing or retaining oral medications; it provides ease of administration without water, ensuring better adherence to therapy; it allows for rapid systemic absorption and predictable pharmacokinetics; and it reduces dosing frequency and side effects associated with fluctuating plasma concentrations. For pharmaceutical development, the use of low-cost, biocompatible polymers and a simple solvent casting method supports industrial scalability and cost-effectiveness. It is recommended that future studies extend this work toward in vivo pharmacokinetic evaluation to confirm bioavailability enhancement and clinical efficacy, along with stability testing under accelerated conditions to ensure long-term product performance. Incorporation of permeation enhancers, flavoring agents, and moisture-protective packaging could further refine patient acceptability and commercial viability. Thus, the study establishes a robust foundation for developing clinically relevant mucoadhesive buccal delivery systems of ondansetron hydrochloride that align with modern goals of personalized, efficient, and patient-centered drug therapy.

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