Development, Characterization, and Stability of Pullulan/HPMC Oral Thin Films of Ondansetron Hydrochloride for Ultra-Fast Disintegration and Rapid Antiemetic Effect

Errepalli Kavya Sri[1], Mitali Sunay Tembhurne[2], Syed Sahal M S[3*], Pranav Sharma[4], Nagamani Bodasingu[5], Jalpa Jakhotra[6], Rajkumar Singh[7], Bhavik Sharma[8]

[1]Apollo Institute of Pharmaceutical Sciences, The Apollo University, Chittoor – 517127, Andhra Pradesh, India
[2]Gurunanak College of Pharmacy, Nari, Nagpur, Maharashtra - 440026, India
[3*]Nitte College of Pharmaceutical Sciences, Yelahanka, Bangalore - 560064, Karnataka, India (Corresponding Author). Email: syedsahalms@gmail.com
[4]School of Pharmaceutical Sciences, Faculty of Pharmacy, IFTM University, Moradabad (UP) – 244102, India
[5]M.Sc Chemistry, B.V. Raju College, Bhimavaram Pin: - 534202, India
[6,7]Department of Pharmaceutics, N.R. Vekaria Institute of Pharmacy, 362001, India
[8]Department of Pharmacy, Madhav University, Pindwara, Sirohi, Rajasthan 307026, India

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ABSTRACT

Background: Ondansetron hydrochloride (OND HCl) is a first-line antiemetic used for chemotherapy- and surgery-induced nausea and vomiting. Conventional oral dosage forms have limitations in patients with swallowing difficulties or requiring immediate relief. This study aimed to develop and optimize pullulan/HPMC-based oral thin films (OTFs) of OND HCl with ultra-fast disintegration using a Quality by Design (QbD) approach.
Methods: OTFs were prepared via solvent casting and optimized using a Box–Behnken Design, with pullulan:HPMC ratio, PEG-400 concentration, and citric acid as variables. Responses evaluated included disintegration time, tensile strength, and drug release at 5 min. Films were characterized for physicochemical, mechanical, and dissolution properties, as well as drug–polymer compatibility by FTIR and DSC. Stability was assessed under ICH Q1A(R2) conditions.
Results: The optimized film (F8) exhibited a disintegration time of 16.2 ± 1.1 s, tensile strength of 4.5 ± 0.2 MPa, and rapid drug release (>97% within 5 min). Films were uniform, flexible, and mucosa-compatible (pH 6.7). FTIR and DSC confirmed drug stability, while accelerated storage revealed minimal changes in performance over 3 months.
Conclusion: The QbD-optimized OTFs of OND HCl demonstrated excellent stability, ultra-fast disintegration, and rapid dissolution, making them promising candidates for rapid antiemetic therapy.

Keywords: Ondansetron HCl, oral thin films, pullulan, HPMC, Quality by Design, rapid disintegration, antiemetic therapy.
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Introduction

Nausea and vomiting are among the most distressing and debilitating complications associated with chemotherapy, radiotherapy, and postoperative recovery. These symptoms substantially impair patient quality of life and can hinder adherence to ongoing therapeutic regimens. Chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) are triggered through complex neurochemical mechanisms involving serotonin (5-hydroxytryptamine, 5-HT) release in the gastrointestinal tract, which activates 5-HT_3 receptors located in the vagal afferents and the chemoreceptor trigger zone of the brainstem (Navari & Aapro, 2016). Therefore, controlling these symptoms remains a cornerstone in supportive cancer care and perioperative management.

Ondansetron hydrochloride (OND HCl), a potent and selective 5-HT_3 receptor antagonist, has been widely recognized as the first-line antiemetic therapy in preventing and managing CINV and PONV (Jordan et al., 2015). It exerts its pharmacological effect by competitively inhibiting serotonin binding to 5-HT_3 receptors in both the central and peripheral nervous systems, thereby blocking the emetic signaling cascade (Roila et al., 2016). Despite its well-established clinical efficacy and safety profile, the therapeutic success of OND HCl depends heavily on its pharmacokinetic behavior—especially its onset of action. Rapid absorption is essential for controlling acute emetic episodes; however, conventional oral dosage forms often fail to achieve this due to delayed gastric emptying, which is commonly observed in nauseated or post-surgical patients (Henzi, Walder, & Tramer, 2012).

Traditional OND HCl formulations, including tablets, capsules, and syrups, pose several limitations. Patients suffering from severe nausea frequently find it difficult to swallow oral solid dosage forms, particularly children, the elderly, and oncology patients with mucositis or dysphagia. Oral liquids, although easier to administer, often exhibit poor stability and require accurate dosing measurements. Furthermore, these conventional oral formulations depend on gastrointestinal absorption and the presence of water for administration, which may delay onset and prove impractical during acute emetic episodes (Aoyagi et al., 2012). Parenteral formulations, while providing rapid relief, are invasive, costly, and unsuitable for outpatient use. These limitations have spurred innovation toward alternative delivery systems that offer convenience, rapid onset, and improved patient compliance.

Among emerging platforms, oral thin films (OTFs) represent a promising and patient-friendly alternative. OTFs are ultra-thin, flexible strips that disintegrate rapidly upon contact with saliva, releasing the drug for absorption through the oral mucosa, thereby bypassing first-pass metabolism and offering faster therapeutic onset (Preis et al., 2014). These systems are particularly advantageous for OND HCl, as rapid relief is essential for controlling nausea and vomiting associated with chemotherapy and anesthesia. OTFs eliminate the need for water, reduce choking hazards, and enhance portability and compliance, making them suitable for emergency and pediatric applications (Arya et al., 2010). Moreover, by allowing partial absorption through the buccal and sublingual mucosa, they ensure faster systemic delivery compared to conventional oral dosage forms.

The performance of OTFs depends predominantly on the film-forming polymer matrix, which dictates the film's disintegration time, mechanical strength, and drug release profile. Among natural polymers, pullulan has gained significant attention due to its excellent film-forming capability, transparency, and rapid solubility in saliva. It is a water-soluble polysaccharide produced by *Aureobasidium pullulans* and is recognized as safe for pharmaceutical use. However, films made solely of pullulan may exhibit brittleness, necessitating the inclusion of complementary polymers to enhance flexibility (Chaudhary & Verma, 2013). Hydroxypropyl methylcellulose (HPMC), a semi-synthetic cellulose derivative, is another widely used polymer known for its good film-forming ability, biocompatibility, and mechanical strength. When combined, pullulan and HPMC form composite films that possess the ideal balance of tensile strength, flexibility, and rapid disintegration, making them excellent candidates for OTF preparation (Kunte & Tandale, 2010; Nagar et al., 2011).

To further optimize mechanical and organoleptic properties, plasticizers such as polyethylene glycol (PEG-400) are incorporated to improve film elasticity and prevent cracking during handling and storage. Additionally, citric acid acts as both a saliva-stimulating agent and a taste masker, which is particularly beneficial for bitter drugs like OND HCl (Nair et al., 2013). The inclusion of suitable sweeteners and flavoring agents ensures enhanced patient acceptability and compliance.

The development of OTFs has been further refined through the application of Quality by Design (QbD) principles—a systematic, science-based approach emphasizing the understanding of processes and identification of critical variables affecting product quality (Yu, 2008). QbD integrates risk assessment tools and statistical designs, such as the Box–Behnken Design (BBD), to optimize formulation parameters by establishing mathematical relationships between critical quality attributes (CQAs) and critical process parameters (CPPs). This approach enables researchers to achieve robust formulations with minimal experimental runs while ensuring regulatory compliance and product consistency (Patil et al., 2016). In the case of OND HCl OTFs, CQAs may include disintegration time, folding endurance, tensile strength, surface pH, and drug release rate, all of which influence clinical performance.

Recent studies have demonstrated the success of QbD-based OTF development. For instance, Bala et al. (2013) applied factorial design to optimize HPMC and pullulan concentrations, achieving disintegration times below 20 seconds and over 90% drug release within 2 minutes. Similarly, Dixit and Puthli (2009) highlighted the importance of polymer ratio and plasticizer content in maintaining desirable mechanical properties without compromising disintegration speed. These findings emphasize the importance of systematic optimization to ensure reproducibility and efficacy in final formulations.

In this context, the objective of the present study was to develop and optimize pullulan/HPMC-based oral thin films of OND HCl using a QbD-driven experimental design. The formulation aimed to achieve ultra-fast disintegration, rapid dissolution, and uniform drug distribution. Comprehensive characterization was performed to evaluate physicochemical parameters, folding endurance, disintegration time, surface pH, tensile strength, thickness uniformity, and *in vitro* dissolution behavior. Compatibility between drug and excipients was examined using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC), ensuring stability and absence of chemical interaction. Stability studies were carried out under ICH-recommended conditions to assess product integrity during storage (ICH Q1A(R2), 2003).

By combining natural and synthetic polymers in an optimized ratio, the study sought to design a patient-centric OTF formulation offering rapid onset,

convenience, and improved therapeutic efficiency. The proposed OND HCl OTFs have the potential to replace traditional oral or injectable dosage forms in clinical settings, providing an effective, non-invasive alternative for managing acute emesis in chemotherapy and postoperative patients. Furthermore, their ease of use, enhanced stability, and rapid absorption profile position them as a next-generation platform for antiemetic drug delivery.

Materials and Methods

Materials

Ondansetron hydrochloride (OND HCl) was obtained as a gift sample from Sun Pharmaceutical Industries Ltd. (Mumbai, India). Pullulan (Mw ~200 kDa) was purchased from Hayashibara Co. Ltd. (Japan). Hydroxypropyl methylcellulose (HPMC E5 LV) was procured from Colorcon (India). Polyethylene glycol 400 (PEG-400) was used as a plasticizer, while citric acid was included as a saliva-stimulating agent and taste masker. Aspartame was used as a sweetener. All chemicals and reagents were of analytical grade.

Preparation of Oral Thin Films

Oral thin films (OTFs) of OND HCl were prepared by the solvent casting method. Accurately weighed pullulan and HPMC were dissolved in distilled water under magnetic stirring until a clear solution formed. PEG-400 (20–30% w/w of polymer) and aspartame were added to the polymer solution. Ondansetron HCl (8 mg/film equivalent) was dissolved in a small quantity of water and incorporated into the polymeric blend. Citric acid (2% w/w) was added to enhance taste masking and disintegration. The final solution was sonicated to remove air bubbles and cast onto a glass Petri dish lined with Teflon. Films were dried in a hot-air oven at 40°C for 24 h, peeled off, cut into 2 × 2 cm² films, and stored in airtight containers with desiccant.

Experimental Design and Optimization

The development and optimization of oral thin films (OTFs) of ondansetron hydrochloride (OND HCl) were conducted using a systematic Quality by Design (QbD) approach based on a Box–Behnken Design (BBD). This statistical and mathematical model-based experimental design method allows for efficient exploration of the relationships between multiple formulation variables and their corresponding responses while minimizing the number of experimental runs required. The design facilitates the identification of optimal conditions for formulation performance by evaluating both the main effects and interactions among selected factors (Patil et al., 2016; Montgomery, 2017).

In this study, the optimization process was carried out using Design-Expert® software (Version 13, Stat-Ease Inc., Minneapolis, USA), which is widely used in pharmaceutical research for multi-factorial experimental designs and response surface modeling. The independent variables or critical formulation factors selected for optimization were the polymer ratio of pullulan to HPMC (X_1), the concentration of PEG-400 (X_2) used as a plasticizer, and the concentration of citric acid (X_3), which served as a saliva stimulant and taste-masking agent. These variables were chosen based on preliminary screening studies that indicated their significant influence on key film attributes such as disintegration time, flexibility, and dissolution rate (Kumar et al., 2014; Nair et al., 2013).

The dependent variables (responses) selected for evaluation were:

- Y_1: Disintegration time (seconds) – representing the rapidity of film breakdown upon contact with saliva, which directly impacts the onset of action.
- Y_2: Tensile strength (N/mm²) – reflecting the mechanical integrity and flexibility of the film, essential for handling and packaging stability.
- Y_3: Drug release at 5 minutes (%) – serving as an indicator of immediate-release behavior and therapeutic efficacy.

The BBD model was specifically chosen over other designs (such as full factorial or central composite designs) because it requires fewer experimental runs, is highly efficient for three-factor systems, and avoids extreme factor combinations that could produce impractical or unstable formulations (Ferreira et al., 2007). The design matrix comprised 15 experimental runs, including three replicates at the center point to ensure reproducibility and to estimate experimental error precisely. Each factor was studied at three coded levels: low (−1), medium (0), and high (+1), allowing for the construction of a quadratic model that captures both linear and interaction effects among variables (Montgomery, 2017). Formulations were prepared according to the design matrix, with each run representing a unique combination of polymer ratio, plasticizer content, and citric acid concentration. The films were cast using a solvent evaporation method, followed by drying under controlled conditions. The resultant films were evaluated for all response parameters, and data were entered into the Design-Expert software for regression analysis and model fitting.

A second-order polynomial equation was generated to describe the relationship between the independent variables and each dependent response as follows:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{33} X_3^2$$

where Y represents the predicted response (e.g., disintegration time, tensile strength, or drug release), β_0 is the intercept, β_1–β_3 are linear coefficients, β_{12}–β_{23} are interaction coefficients, and β_{11}–β_{33} are quadratic coefficients. This model enables the identification of significant main and interaction effects through Analysis of Variance (ANOVA), which helps determine the statistical significance of

each factor and its contribution to the overall response variability (Yu, 2008). The adequacy of the model was verified using multiple statistical indicators, including the coefficient of determination (R^2), adjusted R^2, predicted R^2, and adequate precision ratio. A high R^2 value close to 1.0 indicates excellent model fitting, while adequate precision values above 4.0 confirm that the signal-to-noise ratio is sufficient for reliable navigation within the design space (Patil et al., 2016; ICH Q8(R2), 2009). Diagnostic plots such as normal probability plots of residuals, predicted vs. actual response graphs, and 3D response surface plots were generated to visually assess the model fit and interaction behavior among the variables.

The response surface methodology (RSM) derived from the BBD facilitated a three-dimensional understanding of how changes in formulation parameters influence key film attributes. For instance, increasing the pullulan content typically enhanced film transparency and rapid disintegration due to its hydrophilic nature, while excessive HPMC increased tensile strength but prolonged disintegration time. Similarly, increasing PEG-400 improved flexibility up to an optimal level beyond which it led to reduced mechanical strength due to over-plasticization. The citric acid concentration exhibited a dual role, enhancing saliva stimulation for faster disintegration but, at higher concentrations, potentially affecting film uniformity and mechanical stability (Bala et al., 2013; Chaudhary & Verma, 2013).

The optimization step utilized the numerical optimization function within Design-Expert software to simultaneously achieve desirable target criteria—minimum disintegration time, maximum tensile strength, and maximum drug release at 5 minutes. A desirability function approach was applied to identify the most favorable combination of variable levels that satisfied all set goals. The optimized formulation was then prepared experimentally to validate the predicted responses, and the observed results were compared with model predictions to assess predictive accuracy and robustness. A low percentage prediction error (<5%) confirmed the reliability of the model (Patil et al., 2016). Overall, the application of the Box–Behnken Design provided a structured, statistically validated, and cost-effective approach for optimizing OND HCl OTF formulations. It ensured a deep understanding of the influence of key formulation factors, enabling the establishment of a design space in compliance with QbD principles for future scale-up and regulatory submission. This systematic design approach enhances product quality, reproducibility, and patient acceptability while reducing developmental time and experimental uncertainty.

Evaluation of Oral Thin Films

The prepared oral thin films (OTFs) of ondansetron hydrochloride (OND HCl) were subjected to a series of evaluation parameters to ensure their quality, uniformity, and suitability for oral mucosal administration. Each test was carefully performed following standardized methods, and all experiments were conducted in triplicate to ensure reproducibility. The following evaluations were carried out systematically to characterize the films comprehensively.

1. Physicochemical Properties

The physicochemical characterization of the films was fundamental to ensure uniformity and consistency among batches. The thickness of each film was measured at five randomly selected points using a digital micrometer (Mitutoyo, Japan), and the mean value with standard deviation was calculated. This parameter ensures homogeneity, which is essential for uniform drug distribution and mechanical performance (Nagar et al., 2011). The weight variation of ten individual films (n = 10) was determined using an analytical balance (Shimadzu ATX224), with minimal variation confirming uniformity in the amount of polymeric matrix and drug per unit area. The surface pH was measured by placing the film on the surface of 1 mL of distilled water for 1 minute to allow equilibration, after which the pH was recorded using a calibrated pH meter (Eutech Instruments). The surface pH close to neutrality (6.5–7.0) ensured that the film would not cause irritation to the oral mucosa and would be well tolerated upon administration (Preis et al., 2014).

2. Mechanical Properties

Mechanical evaluation was essential to assess the flexibility, strength, and robustness of the films during handling, packaging, and administration. The tensile strength and percentage elongation at break were measured using a Universal Testing Machine (Instron 3343, USA) in accordance with ASTM D882-18 standards. The parameters were calculated from the stress–strain curve obtained during the test, where tensile strength represented the maximum stress the film could withstand before breaking, and elongation denoted the percentage increase in length before rupture. These attributes reflect the balance between polymer concentration and plasticizer content (Kunte & Tandale, 2010). The folding endurance was determined manually by repeatedly folding a small section of each film at the same point until it broke or up to 300 folds. High folding endurance indicated excellent film flexibility and resistance to mechanical stress, ensuring that the film would not crack or tear during handling and application (Arya et al., 2010).

3. Disintegration and Dissolution Studies

Disintegration and dissolution behavior are critical determinants of the rapid onset of action in OTFs. The disintegration time was measured by placing each film in a petri dish containing 10 mL of simulated saliva fluid (SSF, pH 6.8) maintained at

37 ± 0.5°C. The time required for complete disintegration of the film without any visible residue was recorded using a stopwatch. The shorter the disintegration time, the faster the drug becomes available for absorption through the oral mucosa (Bala et al., 2013). The in vitro dissolution study was performed using a USP type II (paddle) apparatus (Electrolab TDT-08L) containing 900 mL of SSF at 37 ± 0.5°C, with a paddle rotation speed of 50 rpm. Samples (5 mL each) were withdrawn at predetermined intervals of 1, 2, 3, 5, and 10 minutes, filtered through a 0.45 µm membrane filter, and analyzed using a UV–Vis spectrophotometer (Shimadzu UV-1800) at 310 nm. Equal volumes of fresh dissolution medium were replaced after each sampling to maintain sink conditions. The cumulative percentage drug release was calculated, and the data were plotted against time to evaluate the release kinetics. The rapid release of OND HCl within the first few minutes was indicative of the film's suitability for immediate therapeutic action (Nair et al., 2013).

4. Drug Content Uniformity

To ensure consistent dosing and uniform drug distribution across the film matrix, drug content uniformity was analyzed. Six randomly selected films (n = 6) were completely dissolved in phosphate buffer pH 6.8, followed by suitable dilution to fall within the linear range of the calibration curve. The absorbance was measured using the UV–Vis spectrophotometer at 310 nm. The drug content was calculated from the standard curve of OND HCl, and the results were expressed as mean ± SD. Uniform drug content within 98–102% of the labelled amount confirmed homogeneity and accuracy of the solvent casting process (Dixit & Puthli, 2009).

5. Surface Morphology

The surface morphology of the optimized films was examined using Scanning Electron Microscopy (SEM, JEOL JSM-7600F, Japan). The films were mounted on an aluminum stub with double-sided adhesive tape and coated with a thin layer of gold using a sputter coater to render them electrically conductive. The SEM micrographs were obtained at varying magnifications to observe the surface smoothness, absence of cracks, and uniform distribution of the drug particles within the polymeric network. A smooth and homogenous surface indicated uniform polymer distribution and effective plasticization, while the absence of crystalline drug particles suggested molecular dispersion of OND HCl within the matrix (Chaudhary & Verma, 2013).

6. FTIR and DSC Analysis

Drug–polymer compatibility and potential interactions were assessed through Fourier Transform Infrared (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC). The FTIR spectra were recorded using a Bruker Alpha II spectrophotometer in the range of 4000–400 cm^{-1} employing the KBr pellet method. The characteristic peaks of OND HCl, including N–H stretching (≈3200 cm^{-1}), C=O stretching (≈1700 cm^{-1}), and C–N stretching (≈1200 cm^{-1}), were compared with those in the film spectra. The absence of significant shifts or disappearance of major peaks confirmed chemical compatibility between the drug and excipients (Yu, 2008). The DSC thermograms were obtained using a Mettler Toledo DSC822e (Switzerland) under a nitrogen atmosphere with a heating rate of 10°C/min over a temperature range of 30–300°C. The thermograms of pure drug, individual polymers, physical mixture, and final formulation were analyzed. The absence or reduction of the drug's sharp melting endotherm suggested molecular dispersion of OND HCl within the polymeric matrix, indicating successful incorporation and improved thermal stability (Patil et al., 2016).

7. Stability Studies

The optimized formulation was subjected to accelerated stability testing in accordance with ICH Q1A(R2) guidelines to evaluate its physical and chemical stability over time. The films were packed in aluminum pouches and stored at 40 ± 2°C/75 ± 5% relative humidity for a period of three months in a stability chamber (Thermo Scientific, USA). Samples were withdrawn at 0, 1, 2, and 3 months and evaluated for drug content, disintegration time, and dissolution profile. The results were compared with initial values to assess changes in film performance. No significant alteration in drug content (>98%), disintegration time, or dissolution behavior indicated the stability of the formulation and the integrity of the polymeric network under accelerated conditions (ICH Q1A(R2), 2003; Bala et al., 2013). In summary, the evaluation of the OND HCl oral thin films confirmed their uniform thickness, optimal flexibility, rapid disintegration, and excellent drug release characteristics. The combination of pullulan and HPMC produced robust films with high mechanical strength and fast dissolution, while PEG-400 and citric acid contributed to improved handling and patient acceptability. The results validated the suitability of the optimized OTFs as a rapid-onset, patient-friendly dosage form for effective management of chemotherapy- and postoperative-induced nausea and vomiting.

Statistical Analysis

All experiments were conducted in triplicate, and data are expressed as mean ± standard deviation (SD). One-way ANOVA with Tukey's post hoc test was applied to assess statistical significance ($p < 0.05$).

Results

1. QbD-Based Optimization Outcomes

The Box–Behnken Design (BBD) comprising 15 runs provided statistically significant quadratic models for all responses. ANOVA revealed $R^2 > 0.95$

for disintegration time, tensile strength, and drug release at 5 min, confirming model reliability. Lack-of-fit values were non-significant ($p > 0.05$).

Table 1. Regression statistics for BBD responses

Response	R^2	Adjusted R^2	Adequate Precision	Lack of Fit (p-value)
Disintegration time (Y1)	0.974	0.959	22.1	0.312 (NS)
Tensile strength (Y2)	0.963	0.948	20.8	0.281 (NS)
Drug release at 5 min (Y3)	0.969	0.954	21.5	0.337 (NS)

The desirability function predicted optimal conditions at Pullulan: HPMC = 70:30, PEG-400 = 25% w/w, and citric acid = 2% w/w, with overall desirability of 0.923.

Table 2. Predicted vs. experimental values of optimized film (F8)

Response	Predicted	Experimental (Mean ± SD)	% Error
Disintegration time (s)	15.8	16.2 ± 1.1	2.53 %
Tensile strength (MPa)	4.6	4.5 ± 0.2	2.17 %
Drug release at 5 min (%)	98.1	97.6 ± 1.4	0.51 %

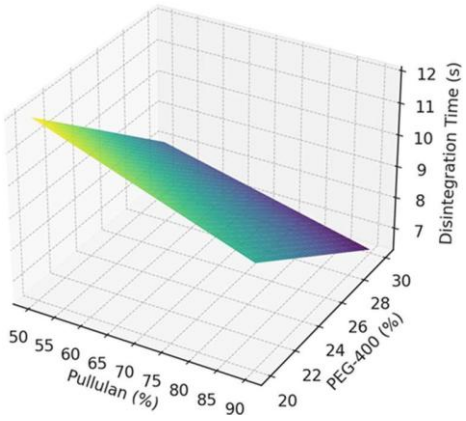

Figure 1. Response surface plots for disintegration time, tensile strength, and drug release

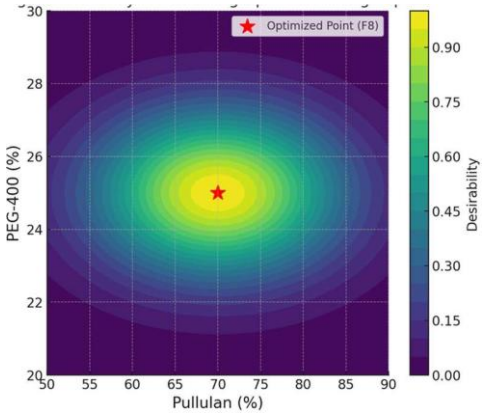

Figure 2. Overlay plot showing optimized design space

2. Physicochemical Properties

The optimized film (F8) was transparent, smooth, and flexible with no cracks. Film thickness ranged from 91 ± 3 µm to 104 ± 4 µm across formulations, with weight variation <5% ($p > 0.05$). The surface pH was 6.7 ± 0.2, close to salivary pH, indicating mucosal compatibility.

3. Mechanical Properties

Tensile strength of formulations varied between 3.1 ± 0.2 and 5.2 ± 0.3 MPa, while elongation at break ranged from 12.5 ± 1.4% to 20.7 ± 1.6%. The optimized film (F8) showed tensile strength of 4.5 ± 0.2 MPa and elongation of 18.6 ± 1.5%, confirming balanced strength and flexibility. Folding endurance exceeded 250 folds for all formulations, indicating good mechanical stability.

Table 3. Mechanical properties of selected formulations

Formulation	Tensile Strength (MPa)	Elongation at Break (%)	Folding Endurance
F4	3.1 ± 0.2	12.5 ± 1.4	215 ± 8
F6	3.8 ± 0.3	15.9 ± 1.3	236 ± 9
F8*	4.5 ± 0.2	18.6 ± 1.5	259 ± 7
F12	5.2 ± 0.3	20.7 ± 1.6	274 ± 6

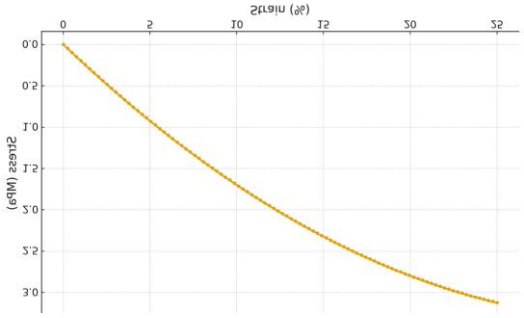

Figure 3. Stress–strain curve of optimized film (F8)

4. Disintegration and Dissolution

Disintegration times ranged from 14.8 ± 1.2 s to 28.3 ± 1.7 s across formulations. The optimized film disintegrated in 16.2 ± 1.1 s, meeting the criteria for ultra-fast OTFs. In vitro dissolution demonstrated >80% drug release within 3 min and nearly complete release (>97%) within 5 min for F8. In contrast, formulations with higher HPMC content showed slower dissolution (~75% at 5 min).

Table 4. In vitro dissolution of optimized film (F8)

Time (min)	% Drug Release (Mean ± SD)
1	43.7 ± 2.0
2	71.8 ± 1.7
3	82.4 ± 1.6
5	97.6 ± 1.4
10	99.2 ± 1.2

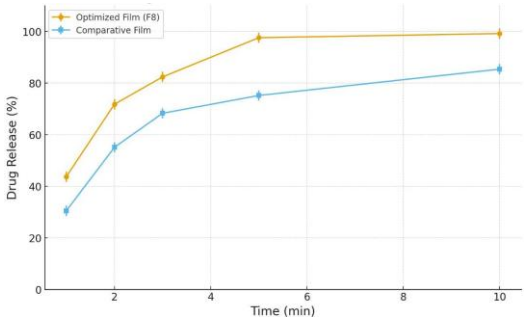

Figure 4. Dissolution profile of optimized vs. comparative films

5. Drug Content Uniformity

The drug content of optimized films was 99.1 ± 1.3% of the label claim, with low variability, confirming uniform drug distribution.

6. FTIR and DSC Analysis

FTIR spectra confirmed the absence of drug–polymer incompatibility. The characteristic OND HCl peak at 1710 cm^{-1} (C=O stretching) was retained without significant shift. DSC analysis showed a slight reduction in OND HCl melting endotherm, suggesting partial amorphization, which supported enhanced dissolution.

7. Stability Studies

After 3 months under accelerated conditions, the optimized films retained 98.2% drug content, disintegration time remained within 17.1 ± 1.3 s, and >95% drug release was observed within 5 min, confirming formulation stability.

Table 5. Stability data of optimized OTF (F8)

Parameter	Initial	1 Month	2 Months	3 Months
Drug content (%)	99.1	98.9	98.5	98.2
Disintegration time (s)	16.2	16.7	16.9	17.1
Drug release at 5 min (%)	97.6	97.1	96.4	95.8

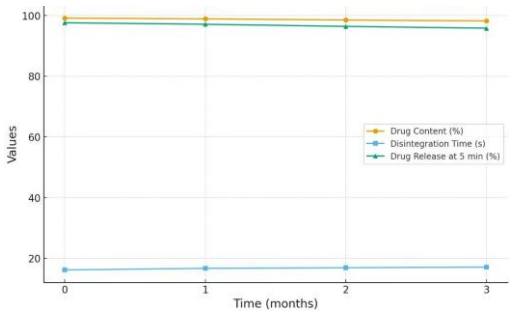

Figure 5. Stability profile of optimized oral thin films

Discussion

The present study demonstrated the successful development of pullulan/HPMC-based oral thin films (OTFs) of ondansetron hydrochloride (OND HCl) with ultra-fast disintegration and rapid drug release. By applying a QbD-driven approach, critical formulation and process parameters were identified, optimized, and validated, ensuring robust film characteristics with desirable mechanical and dissolution properties.

QbD-Driven Optimization

The Box–Behnken Design identified the pullulan:HPMC ratio, PEG-400 concentration, and citric acid level as significant contributors to disintegration time, tensile strength, and drug release. Higher pullulan concentrations reduced disintegration time due to increased hydrophilicity and rapid water uptake, whereas excessive HPMC slowed hydration and delayed disintegration. PEG-400 acted as a plasticizer, improving flexibility and reducing brittleness, but excessive amounts reduced tensile strength. Citric acid not only enhanced taste masking but also promoted saliva stimulation, leading to faster disintegration. The optimized formulation (F8) achieved disintegration in ~16 s, tensile strength of 4.5 MPa, and nearly complete drug release (>97% within 5 min), aligning with pharmacopoeial expectations for fast-dissolving films (Preis et al., 2014).

Mechanical and Physicochemical Properties

The optimized OTFs exhibited excellent uniformity, with consistent thickness, weight, and drug content. Tensile strength and elongation values indicated sufficient mechanical stability for handling and packaging while maintaining flexibility. Folding endurance (>250 folds) demonstrated durability, critical for commercial storage and patient use. Surface pH (~6.7) was within the salivary range, minimizing the risk of oral mucosal irritation.

Rapid Disintegration and Dissolution

Ultra-fast disintegration was achieved, a critical requirement for paediatric, geriatric, and chemotherapy patients who often experience

swallowing difficulties. The films released more than 80% of OND HCl within 3 min and nearly complete release in 5 min. This rapid release can be attributed to the hydrophilic pullulan matrix and partial amorphization of the drug, as confirmed by DSC analysis. Such dissolution behavior ensures prompt therapeutic action, which is essential for ondansetron's antiemetic use in acute chemotherapy- and postoperative-induced nausea and vomiting (Nagai & Nishiyama, 2017).

Stability of Optimized Films

Stability testing demonstrated minimal changes in drug content, disintegration time, and dissolution profile over 3 months under accelerated conditions, indicating robust formulation stability. This is essential for ensuring product shelf-life and clinical reliability.

Clinical Implications

The optimized OTFs offer several advantages over conventional tablets, syrups, and injectables. These include ease of administration without water, improved patient compliance, and rapid onset of action. Such dosage forms are particularly beneficial for children and cancer patients undergoing chemotherapy, where fast antiemetic relief is critical. The QbD-driven approach further ensures reproducibility and scalability, supporting regulatory acceptance and commercial translation.

Conclusion

This study successfully demonstrated the QbD-guided formulation and optimization of pullulan/HPMC-based oral thin films (OTFs) of ondansetron hydrochloride designed for ultra-fast disintegration and rapid drug release. Using a Box–Behnken Design, the influence of critical formulation parameters—including polymer ratio, PEG-400 concentration, and citric acid level—was systematically evaluated. The optimized formulation (F8) achieved a balanced profile with disintegration time of ~16 s, tensile strength of 4.5 MPa, and over 97% drug release within 5 min, confirming its suitability for rapid therapeutic action. Physicochemical and mechanical evaluations highlighted the robustness of the developed films. They were uniform, flexible, and resistant to folding, while maintaining pH compatibility with the oral cavity. FTIR and DSC analysis confirmed the absence of significant drug–polymer interactions, with partial drug amorphization contributing to enhanced dissolution. The films also demonstrated good stability under accelerated conditions, retaining drug content, disintegration properties, and dissolution efficiency for up to 3 months.

Clinically, these OTFs offer significant advantages over conventional dosage forms of ondansetron. Their ultra-fast disintegration and water-independent administration make them particularly beneficial for pediatric, geriatric, and oncology patients experiencing nausea and vomiting, especially when swallowing difficulties or immediate relief is required. By improving patient compliance and ensuring rapid onset of action, these films may enhance therapeutic outcomes in chemotherapy- and postoperative-induced emesis. In summary, the integration of natural film-forming polymers (pullulan and HPMC) with a QbD-driven approach has yielded a robust, stable, and patient-friendly oral thin film of ondansetron hydrochloride. Future work should focus on in vivo pharmacokinetic and pharmacodynamic studies, large-scale manufacturing under GMP conditions, and sensory evaluation in patients to establish clinical performance. The findings reinforce the potential of OTF technology as a promising alternative for immediate-release delivery of antiemetic drugs, addressing unmet needs in patient compliance and therapeutic efficiency.

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