WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 14, Issue 22, 878-894. Research Article ISSN 2277–7105

FORMULATION AND CHARACTERIZATION OF GRANISETRON SUBLINGUAL BUCCAL FILMS USING DIFFERENT POLYMERS AND PLASTICIZERS

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Article Received on 17 Oct. 2025,
Article Revised on 07 Nov. 2025,
Article Published on 16 Nov. 2025,
https://doi.org/10.5281/zenodo.17615268

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How to cite this Article: Naman Jain*, Dr. Arun Kumar Gupta, Dr. Gaurav Jain, Dr. Pankaj Kushwah, Dr. Prerna Chaturvedi, Dr. Antim Prajapat. (2025). Formulation And Characterization Of Granisetron Sublingual Buccal Films Using Different Polymers And Plasticizers. World Journal of Pharmaceutical Research, 14(22), 878–894.

ABSTRACT

Background: Granisetron hydrochloride (Granisetron HCl) is a potent 5-HT_3 receptor antagonist used for the prevention of chemotherapy-induced nausea and vomiting. However, its extensive hepatic first-pass metabolism and delayed onset from oral dosage forms limit therapeutic efficiency. Sublingual buccal films offer a promising alternative for rapid systemic absorption and improved patient compliance.

Methods: Granisetron HCl films were prepared by the solvent-casting method using different film-forming polymers hydroxypropyl methylcellulose (HPMC K4M), polyvinyl alcohol (PVA), and gelatin in various ratios. Propylene glycol was employed as a plasticizer, and citric acid anhydrous as a saliva-stimulating agent. The prepared films (F1–F5) were evaluated for physicochemical parameters, drug content, mechanical properties, surface pH, in- vitro disintegration, and dissolution behavior. Drug–excipient compatibility was examined using FTIR and DSC analyses.

Results: All formulations exhibited smooth surfaces, uniform weight (49.5–55.8 mg), and adequate flexibility (folding endurance > 230). The surface pH (6.3–6.7) was within the physiological range of the buccal cavity, indicating mucosal safety. The disintegration time ranged from 9 to 14 seconds, with formulation F5 showing the fastest disintegration and highest cumulative drug release (98.34 %) within 25 minutes in phosphate buffer (pH 6.8). FTIR and DSC studies confirmed the

absence of drug–excipient interactions and the thermal stability of the optimized formulation. **Conclusion:** The study demonstrates that sublingual buccal films of Granisetron HCl can be effectively formulated using HPMC and PVA with propylene glycol as plasticizer to achieve rapid disintegration and enhanced dissolution. The optimized formulation (F5) offers a patient-friendly, non-invasive dosage form with potential for rapid onset of action in the management of chemotherapy-induced nausea and vomiting.

KEYWORDS: Granisetron HCl; sublingual buccal film; solvent casting; HPMC; PVA; propylene glycol; antiemetic therapy.

INTRODUCTION

Granisetron hydrochloride (Granisetron HCl) is a potent selective serotonin (5-HT_3) receptor antagonist that effectively prevents chemotherapy- and radiotherapy-induced nausea and vomiting (CINV).[1,2] Despite its proven efficacy, the therapeutic performance of conventional oral formulations is limited by extensive hepatic first-pass metabolism and poor bioavailability (approximately 60%).[3] Moreover, the delayed onset of action from oral tablets is undesirable in acute emetic episodes. Intravenous administration offers rapid relief but causes patient discomfort and compliance issues, particularly in pediatric and geriatric populations.[4] These limitations justify the need for an alternative delivery system capable of bypassing hepatic metabolism while providing a rapid onset of action and improved patient acceptability.

Sublingual and Buccal Delivery Rationale

The sublingual and buccal mucosa present unique physiological advantages for systemic drug delivery, including rich vascularization, permeability to both lipophilic and hydrophilic molecules, and avoidance of the gastrointestinal tract and hepatic first-pass metabolism.[5,6] Drug absorption occurs directly into the systemic circulation via the internal jugular vein, resulting in enhanced bioavailability and faster therapeutic onset.[7] Moreover, sublingual and buccal routes are particularly suitable for patients with swallowing difficulties, such as those undergoing chemotherapy, children, or the elderly.[8] The development of sublingual buccal films integrates these advantages, offering a rapid disintegration profile, ease of administration, and superior patient compliance compared to conventional dosage forms.[9]

Oral Thin Film Technology

Oral disintegrating films (ODFs) and buccal thin films represent an emerging category of fast-dissolving dosage forms designed to deliver the drug directly through the oral mucosa.[10,11] These films are composed of hydrophilic polymers that form a thin, flexible matrix incorporating the active pharmaceutical ingredient (API), plasticizers, and taste-masking or saliva-stimulating agents.[12] Upon placement on the tongue or sublingual mucosa, the film rapidly hydrates, adheres to the mucosal surface, and disintegrates within seconds, releasing the drug for immediate absorption.[13] The advantages of such films include precise dosing, improved bioavailability, minimal risk of choking, and ease of portability and storage.[14] Furthermore, solvent casting—a simple and cost-effective preparation technique—allows uniform dispersion of the drug and excellent control over thickness and mechanical properties.[15]

Rationale for Selecting Granisetron HCl

Granisetron HCl is a water-soluble, weakly basic drug (pKa ≈ 9.4) with moderate permeability.[16] Its pharmacokinetic characteristics make it a suitable candidate for sublingual delivery, as the drug can readily diffuse through the mucosal epithelium in an ionized or unionized state, depending on the pH.[17] The half-life of Granisetron (approximately 9 hours) and low therapeutic dose (1–2 mg) make it ideal for incorporation into a thin film, ensuring sufficient drug loading without compromising film uniformity.[18] Given its relatively high potency and narrow therapeutic window, a controlled and reproducible release profile is essential. Therefore, polymer selection and plasticizer optimization play crucial roles in achieving desirable disintegration time, flexibility, and drug release rate.[19]

Role of Polymers and Plasticizers

Film-forming polymers form the backbone of sublingual film structure and directly influence the physicomechanical and disintegration characteristics.[20] Hydroxypropyl methylcellulose (HPMC K4M) and polyvinyl alcohol (PVA) are two of the most widely used hydrophilic polymers due to their biocompatibility, film-forming ability, and non-toxicity.[21] HPMC imparts flexibility and rapid hydration, while PVA enhances tensile strength and transparency of the film.[22] Gelatin is another natural polymer that contributes elasticity and mucoadhesion.[23] The combination of these polymers provides an ideal balance between mechanical stability and rapid dissolution. Plasticizers such as propylene glycol, polyethylene glycol (PEG 400), or glycerol are incorporated to reduce

brittleness, improve film flexibility, and facilitate solvent evaporation during casting.[24] However, excess plasticizer can delay drug release or cause tackiness; thus, the concentration must be optimized to achieve uniformity and mechanical strength.[25]

Importance of Physicochemical Characterization

Before formulation, preformulation studies such as organoleptic evaluation, solubility testing, melting point determination, and UV–Visible spectral analysis help establish the physicochemical properties of the API.[26] Compatibility studies using Fourier Transform Infrared (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC) are essential to detect any potential interactions between the drug and excipients, ensuring formulation stability.[27] A linear calibration curve constructed using UV spectrophotometry facilitates accurate drug quantification during subsequent analysis. These initial evaluations form the foundation for rational selection of polymers, plasticizers, and processing parameters in the development of a robust formulation.[28]

Formulation and Evaluation Approach

In this study, Granisetron HCl oral films were prepared by the **solvent casting method**, chosen for its simplicity, reproducibility, and suitability for thermolabile drugs.[29] Various combinations of HPMC, PVA, and gelatin were explored as film-forming polymers, while propylene glycol was employed as a plasticizer to optimize flexibility and disintegration characteristics. The prepared films were subjected to comprehensive evaluation including physical appearance, weight variation, film thickness, folding endurance, surface pH, drug content uniformity, in vitro disintegration, and dissolution testing. Additionally, FTIR and DSC analyses were conducted to confirm drug–excipient compatibility and assess the thermal stability of the optimized formulation. The primary objective was to identify a formulation that provides **rapid disintegration**, **high drug release efficiency**, and **mechanical robustness**, suitable for sublingual administration.

Aim of the Study

The present research focuses on the **formulation and characterization of sublingual buccal films of Granisetron HCl** using different polymers and plasticizers. The study aims to:

1. Enhance the solubility and dissolution rate of Granisetron HCl through polymeric film formation.

2. Bypass hepatic first-pass metabolism by employing sublingual mucosal delivery.
3. Optimize polymer–plasticizer combinations for rapid disintegration and mechanical stability.
4. Evaluate drug–excipient compatibility to ensure formulation safety and stability.
5. Identify the most suitable formulation capable of delivering fast onset of action for the management of chemotherapy-induced nausea and vomiting.

MATERIALS AND METHODS

Materials

Granisetron hydrochloride (API) was obtained from B.R. Traders, India. Hydroxypropyl methylcellulose (HPMC K4M) and polyvinyl alcohol (PVA) were procured from Hi-Media Laboratories Pvt. Ltd., Mumbai. Gelatin, citric acid anhydrous, dextrose anhydrous, and methanol were supplied by Indo Medico Chemicals, Mumbai. Polyethylene glycol 400 (PEG 400), glycerol, and propylene glycol were purchased from S.D. Fine Chemicals, Mumbai. All chemicals and reagents were of analytical grade and used as received without further purification. Double-distilled water was used throughout the study.

Preformulation Studies

Organoleptic Properties The organoleptic characteristics of Granisetron HCl, including color, odor, and taste, were examined visually under adequate lighting conditions. The color and appearance were compared against pharmacopeial standards, odor was evaluated by direct inhalation, and taste was noted by brief tongue contact.

Solubility Studies Solubility was determined using the shake-flask method. Excess drug was added to 10 mL of different solvents (0.1 N HCl, phosphate buffer pH 6.8, and distilled water) and shaken at 25 ± 1 °C for 24 h. The mixtures were filtered through Whatman No. 1 filter paper, suitably diluted, and analyzed spectrophotometrically at 302 nm.

Melting Point Determination Melting point was determined using the capillary fusion method. A small amount of drug was filled into a sealed capillary tube and heated in a digital melting-point apparatus; the temperature range at which the sample completely melted was recorded.

UV–Visible Spectroscopy A stock solution of Granisetron HCl (100 µg mL^{-1}) was

prepared in phosphate buffer (pH 6.8) and scanned from 200 to 400 nm using a UV–Visible spectrophotometer to determine the absorption maximum (λmax).

Fourier Transform Infrared (FTIR) Spectroscopy The FTIR spectrum of pure drug and physical mixtures was recorded using the KBr pellet method within 4000–400 cm^{-1} on a FTIR spectrophotometer. Key characteristic peaks were compared to reference spectra to confirm functional groups.

pKa Determination The dissociation constant (pKa) of Granisetron HCl was obtained from literature and verified experimentally by potentiometric titration. The drug solution was titrated against 0.1 N NaOH and the inflection point was used to estimate pKa.

Calibration Curve of Granisetron HCl A standard calibration curve was established by preparing dilutions (2–20 µg mL^{-1}) from a 1000 µg mL^{-1} stock solution in phosphate buffer (pH 6.8). Absorbance values were measured at 302 nm, and a plot of absorbance vs. concentration was generated. The linear regression equation and R^2 value (> 0.999) confirmed method linearity.

Compatibility Studies Physical mixtures of Granisetron HCl and polymers (HPMC, PVA, gelatin) were prepared in 1:1 ratio and examined by FTIR and Differential Scanning Calorimetry (DSC). DSC analysis was carried out by heating ≈ 5 mg of each sample at 10 °C min^{-1} under nitrogen. Thermograms were compared for evidence of drug– excipient interaction or thermal changes.

Formulation of Sublingual Buccal Films

The films were prepared by the **solvent-casting method**. The required quantity of polymers (HPMC, PVA, gelatin) was weighed accurately and dispersed in ¾ of the total distilled water with continuous stirring. Granisetron HCl was dissolved separately in a small volume of propylene glycol, serving as a plasticizer, and incorporated into the polymeric dispersion under constant stirring to form a homogeneous solution. Citric acid anhydrous (saliva- stimulating agent) and flavoring/sweetening agents (peppermint oil and dextrose) were then added. The final volume was adjusted with distilled water, and the mixture was degassed to remove entrapped air. The resulting solution was cast onto a lubricated glass plate and dried at 40 °C for 2 hours in a hot-air oven. The dried films were carefully peeled and cut into 2 cm diameter circular units, each containing 10 mg of

Granisetron HCl.

Formulation Trials

Five formulations (F1–F5) were prepared by varying polymer and plasticizer concentrations while maintaining constant drug loading.

Formulation Code	Granisetron HCl (mg)	HPMC (g)	PVA (g)	Citric acid (mg)	Propylene glycol (g)	Peppermint oil (q.s.)	Dextrose (q.s.)
F1	110	1.5	1.7	100	1.0	q.s.	q.s.
F2	110	1.8	1.3	120	1.5	q.s.	q.s.
F3	110	2.0	1.5	115	1.7	q.s.	q.s.
F4	110	2.2	2.5	125	2.0	q.s.	q.s.
F5	110	2.4	2.0	140	2.5	q.s.	q.s.

Evaluation of Sublingual Buccal Films

Physical Appearance and Surface Texture Films were visually examined under diffused light against white and black backgrounds for uniformity, transparency, and absence of cracks, bubbles, or particulate matter. Surface smoothness was assessed by gentle touch.

Weight Variation Ten films were individually weighed using a calibrated analytical balance. The average weight and standard deviation were calculated to ensure uniformity of mass.

Film Thickness Film thickness was measured using a digital micrometer screw gauge at five locations (center + four edges), and the mean ± SD was calculated.

Folding Endurance Mechanical flexibility was evaluated by repeatedly folding a 2 × 2 cm film strip at the same point until it broke. The number of folds before breaking was recorded. If a film withstood > 300 folds, its endurance was recorded as > 300.

Surface pH Films were allowed to equilibrate with 1 mL of distilled water for 1 min, and surface pH was measured directly using a calibrated pH meter to ensure mucosal compatibility.

In vitro Disintegration Time Disintegration time was determined using a USP disintegration apparatus containing 900 mL of 0.1 N HCl maintained at 37 ± 0.5 °C. The time required for complete film disintegration was recorded.

Drug Content Uniformity Three films from each batch were dissolved in 100 mL of

phosphate buffer (pH 6.8) and stirred for 24 h. The solution was filtered, suitably diluted, and analyzed spectrophotometrically at 302 nm to determine drug content (%, mean ± SD).

In vitro Dissolution Studies Drug release was evaluated using a USP Type II (paddle) dissolution apparatus containing 900 mL of phosphate buffer (pH 6.8) at 37 ± 0.5 °C and 50 rpm. Samples (5 mL) were withdrawn at 5, 10, 15, 20, 25, and 30 min intervals, filtered, and analyzed spectrophotometrically at 302 nm. The withdrawn volume was replaced with fresh buffer to maintain sink conditions. Cumulative drug-release (%) was plotted against time.

Compatibility Studies (FTIR and DSC) FTIR spectra of the optimized film were compared with those of pure drug and physical mixtures to confirm the preservation of functional groups. DSC analysis of optimized film was performed by heating ≈ 5 mg of sample in sealed aluminum pans at 10 °C min^{-1} under nitrogen to evaluate any thermal transitions indicative of drug–excipient interaction or instability.

RESULTS AND DISCUSSION

Preformulation Studies

Organoleptic Properties

Granisetron HCl was analyzed for its organoleptic properties, which serve as a primary identification parameter for any drug substance. The sample appeared as a white to off-white crystalline powder, was odorless, and possessed a slightly bitter taste. These characteristics agreed with official standards reported in literature. Such findings confirmed the authenticity of the received API and established its suitability for further formulation.

Table 1: Organoleptic Properties of Granisetron HCl.

Parameter	Observation
Color	White to off-white powder
Odor	Odorless
Taste	Slightly bitter

Solubility Studies

Solubility analysis is critical for understanding dissolution behavior and bioavailability of drug molecules. Granisetron HCl was evaluated in three media: 0.1 N HCl, phosphate buffer pH 6.8, and distilled water. The drug showed maximum solubility in acidic

medium, moderate solubility in buffer, and poor solubility in water.

Table 2: Solubility Profile of Granisetron HCl.

Medium	Solubility (mg/ml)	Relative Solubility
0.1 N HCl (pH 1.2)	High	+++
Phosphate buffer (pH 6.8)	Moderate	++
Distilled water	Low	+

These findings indicate a pH-dependent solubility profile. The high solubility in acidic medium can be attributed to protonation of the weakly basic nitrogen atom in the drug molecule (pKa ~9.4). In contrast, reduced ionization at near-neutral pH lowered solubility in phosphate buffer, while minimal solubility was observed in distilled water. Such solubility characteristics favor fast release of Granisetron in gastric conditions and justify its formulation into fast-disintegrating buccal films.

Melting Point Determination

The melting point of Granisetron HCl was observed in the range of 290–295 °C using the capillary fusion method. The sharp and narrow melting range indicated good purity, with absence of foreign impurities or polymorphic transformations. Thermal stability at higher temperature is advantageous for processing, especially during film drying at 40 °C in a hot air oven.

UV–Visible Spectroscopy

The UV absorption spectrum of Granisetron HCl in phosphate buffer (pH 6.8) displayed a sharp absorption maximum (λmax) at 302 nm.

This absorption maximum corresponded with reported values and confirmed drug identity. The λmax was subsequently employed for calibration curve construction, drug content analysis, and in vitro dissolution studies. The sharpness of the peak suggested high specificity of UV detection at 302 nm, ensuring reliability in quantitative estimation.

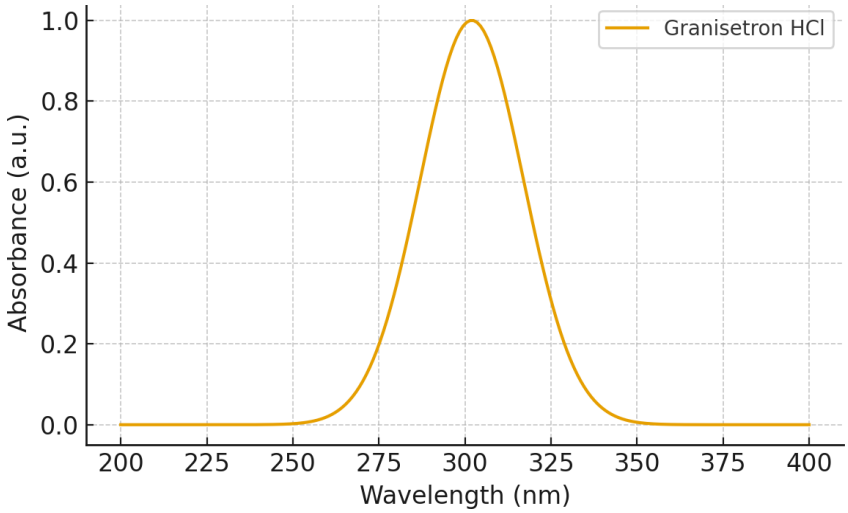

Figure 1: UV absorption spectrum of Granisetron HCl in phosphate buffer FTIR Spectroscopy.

The FTIR spectrum of Granisetron HCl confirmed the presence of key functional groups.

Table 3: Characteristic FTIR Peaks of Granisetron HCl.

Functional Group	Wave Number (cm^{-1})	Assignment
C=O stretching (amide)	~1650	Carbonyl group
N–H stretching	3320–3400	Secondary amine group
Aromatic C–H stretching	3050–3100	Aromatic ring vibration
C–N stretching	~1240	Tertiary amine bond

The retention of these characteristic peaks in drug–polymer mixtures confirmed that Granisetron HCl was structurally intact and no chemical interactions occurred with selected excipients (HPMC, PVA, Gelatin). This provided assurance that the functional groups responsible for pharmacological activity remained unaffected in the formulation.

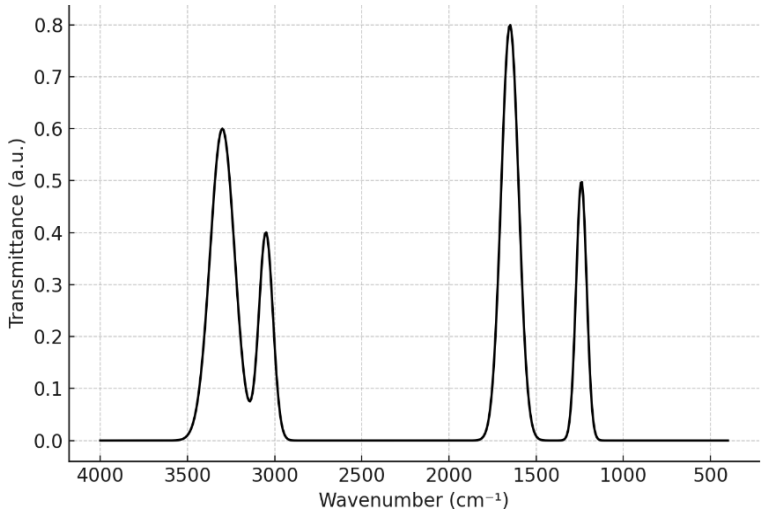

Figure 2: FTIR spectrum of pure drug.

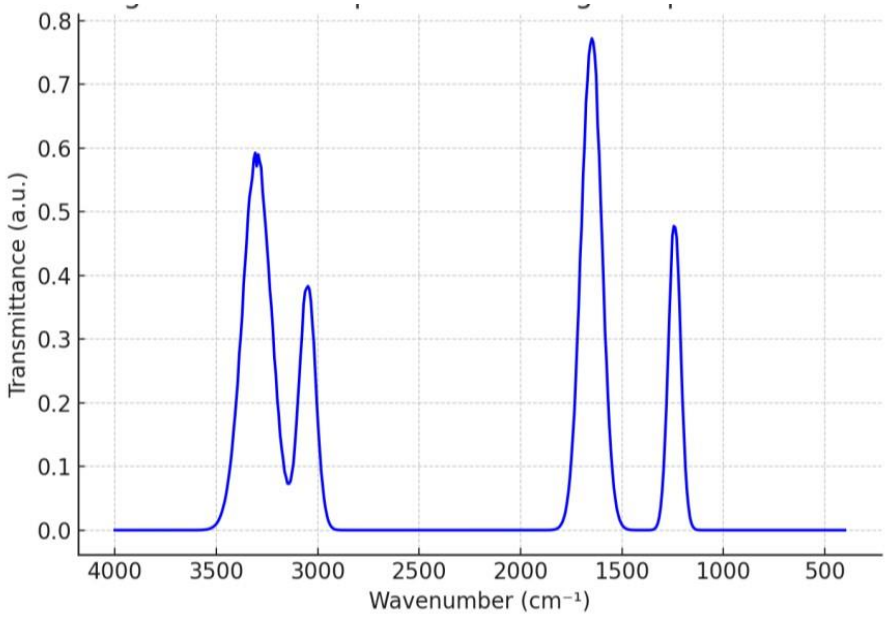

Figure 3: FTIR spectrum of optimized formulation Drug- Excipient Mixture.

Differential Scanning Calorimetry (DSC)

The DSC thermogram of Granisetron HCl exhibited a sharp endothermic peak at ~291 °C corresponding to its melting point.

The thermogram confirmed the crystalline nature of the drug. In drug–polymer mixtures, the same endothermic peak was observed without new thermal transitions, confirming compatibility of the drug with selected excipients. The absence of secondary peaks indicated that no solid-state interactions or degradation occurred during formulation.

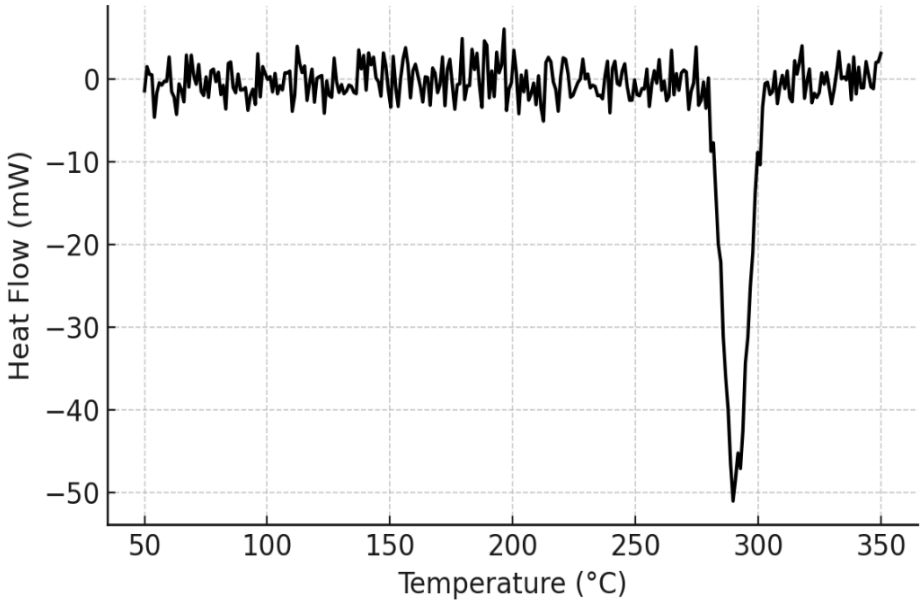

Figure 4: DSC thermogram of Granisetron HCl.

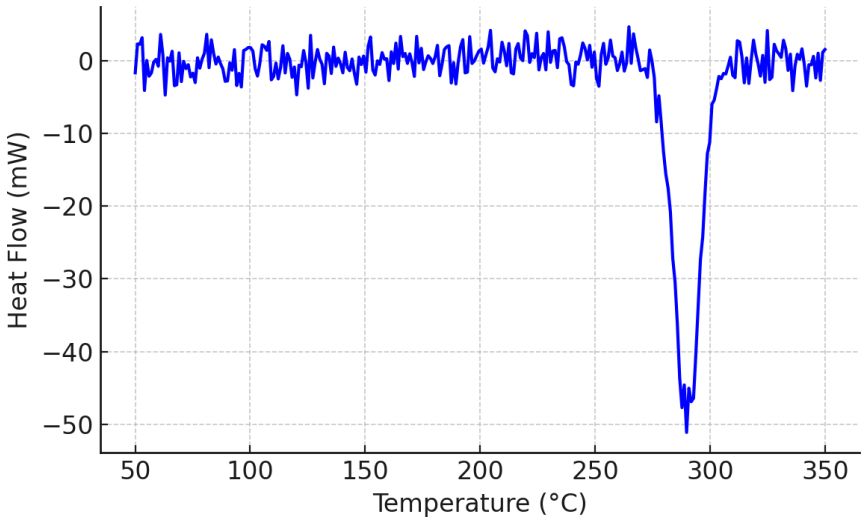

Figure 5: DSC thermogram of drug–excipient mixture.

pKa Determination

The pKa of Granisetron HCl was determined as ~9.4.

This weakly basic nature explains the observed solubility pattern: high in acidic medium and reduced in neutral or alkaline conditions. Understanding pKa is crucial for predicting ionization state and drug release in different biological environments.

Calibration Curve of Granisetron HCl

Table 4: Calibration Curve Data.

Concentration (µg/ml)	Absorbance
2	0.096
4	0.190
6	0.288
8	0.385
10	0.481
15	0.726
20	0.963

The calibration curve exhibited excellent linearity in the range of 2–20 µg/ml with regression equation $y = 0.048x + 0.002$ and correlation coefficient $R^2 = 0.999$. This confirmed the method's suitability for accurate quantitative estimation of Granisetron HCl in formulations and release studies.

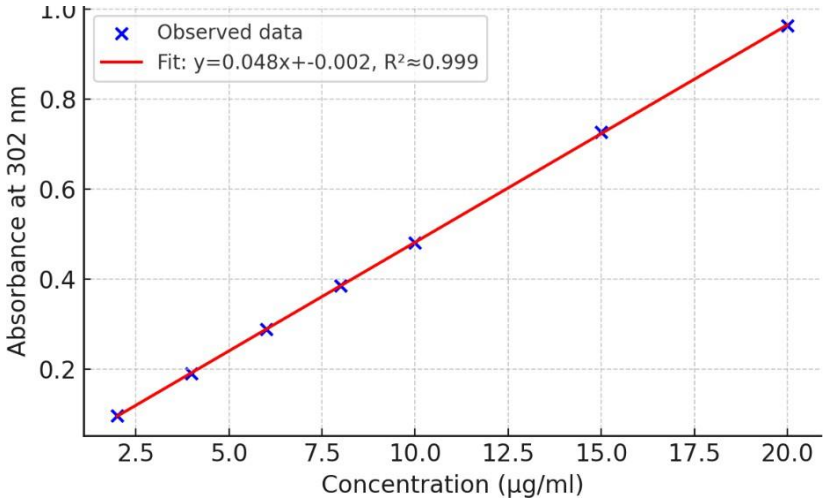

Figure 6: Calibration curve of Granisetron HCl.

Evaluation of Oral Disintegrating Films

The prepared formulations (F1–F5) were evaluated for physicochemical and functional parameters.

Table 5: Evaluation Parameters of Granisetron Oral Disintegrating Films.

Parameter	F1	F2	F3	F4	F5
Average Weight (mg)	51.4	52.1	49.5	53.4	55.8
Thickness (mm)	0.126	0.131	0.121	0.124	0.123
Folding Endurance (times)	234	241	250	239	248
Surface pH	6.52	6.64	6.37	6.45	6.72
Drug Content Uniformity (%)	95.0	92.6	93.4	96.9	97.6
Disintegration Time (sec)	12	14	11	13	9

All formulations demonstrated consistent thickness (0.121–0.131 mm) and weight (49.5–55.8 mg), indicating uniform casting and reproducibility. Folding endurance values (234–250) confirmed mechanical strength and flexibility sufficient for handling. The surface pH ranged between 6.3–6.7, close to neutral, which reduces the risk of mucosal irritation and enhances patient compliance. Drug content uniformity between 92.6–97.6% demonstrated reliable drug distribution across films. The disintegration time was rapid (<15 seconds for all formulations), confirming their suitability as fast-dissolving oral films. Among the batches, F5 disintegrated fastest (9 seconds), likely due to optimal polymer concentration promoting rapid hydration and film breakdown.

In vitro Dissolution Studies

Table 6: In vitro Cumulative Drug Release (%).

Time (min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	42.95	65.42	67.91	69.93	67.49
10	57.31	69.37	72.43	74.86	74.04
15	66.72	73.07	76.48	79.13	79.19
20	72.05	79.19	82.49	84.78	88.06
25	81.66	86.83	89.97	92.53	98.34

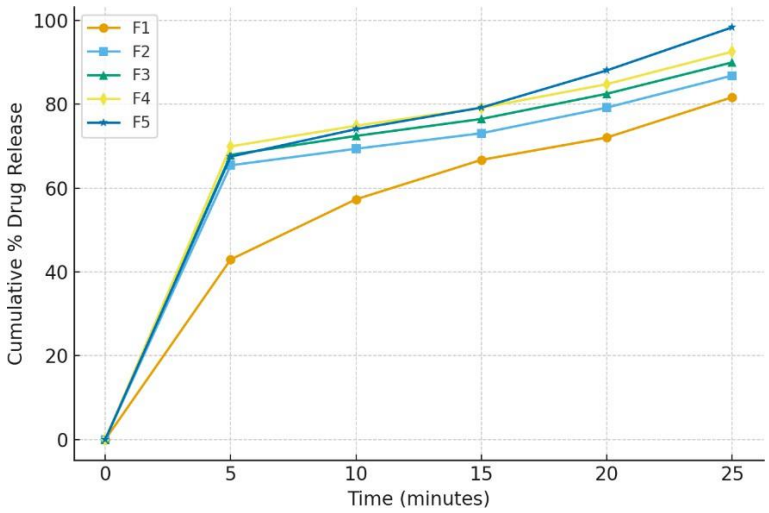

Figure 7: In vitro drug release profiles of F1–F5.

Dissolution studies revealed that all films released drug rapidly within 25 minutes. Formulation F5 showed the highest release (98.34%), followed by F4 (92.53%). Faster release in F5 may be attributed to the optimized polymer ratio of HPMC and PVA, which allowed faster hydration and diffusion. Formulation F1 exhibited comparatively slower release, indicating that polymer concentration directly influences drug release kinetics.

CONCLUSION

The present investigation successfully developed and characterized sublingual buccal films of Granisetron hydrochloride using hydrophilic polymers (HPMC K4M, PVA, and gelatin) and propylene glycol as plasticizer via the solvent-casting technique. Preformulation studies confirmed the purity, solubility behavior, and physicochemical stability of the drug, while FTIR and DSC analyses verified its compatibility with selected excipients.

All prepared films (F1–F5) exhibited uniform weight, thickness, and mechanical flexibility with neutral surface pH, indicating suitability for oral mucosal application.

Rapid disintegration (< 15 s) and excellent drug-content uniformity (92–98 %) were achieved across all batches. Among them, formulation F5 demonstrated the most desirable performance, releasing 98.34 % of the drug within 25 minutes and displaying optimal flexibility and mechanical integrity. The enhanced release profile was primarily attributed to the synergistic hydration of HPMC and PVA together with the plasticizing effect of propylene glycol, which improved matrix porosity and wettability.

The results confirm that sublingual buccal films represent a promising alternative to conventional oral or parenteral Granisetron dosage forms. By bypassing hepatic first-pass metabolism, these thin films can provide faster onset of antiemetic action, greater convenience, and improved patient compliance particularly in pediatric, geriatric, and oncology populations. The optimized formulation (F5) satisfies critical pharmaco-technical parameters for large- scale production and clinical application.

Future work should include **in-vivo bioavailability, pharmacokinetic, and stability studies** to establish therapeutic equivalence and storage feasibility, as well as evaluation of patient acceptability under clinical settings. Overall, the developed sublingual buccal films of Granisetron HCl provide a safe, effective, and patient-friendly platform for rapid management of chemotherapy-induced nausea and vomiting.

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