DEVELOPMENT AND COMPARATIVE EVALUATION OF IMMEDIATE-RELEASE BUCCAL TABLETS AND BUCCAL PATCHES OF PALONOSETRON HYDROCHLORIDE FOR RAPID ANTIEMETIC THERAPY

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ABSTRACT

Palonosetron hydrochloride is a potent second-generation 5-HT$_3$ receptor antagonist used for the prevention of chemotherapy-induced and postoperative nausea and vomiting. The present study aimed to develop and compare immediate-release buccal tablets and buccal patches of palonosetron hydrochloride for rapid antiemetic therapy. Buccal tablets were prepared by direct compression, while buccal patches were fabricated using the solvent-casting technique. The formulations were evaluated for physicochemical properties, drug content, surface pH, swelling behavior, mucoadhesion, and in vitro drug release. All formulations exhibited satisfactory pharmaceutical characteristics and acceptable drug content uniformity. The incorporation of crospovidone enhanced hydration and promoted rapid drug release. Optimized formulations demonstrated efficient drug release within 60 minutes and effective transmucosal permeation. Buccal patches showed superior flexibility, patient comfort, and mucoadhesive performance compared to buccal tablets. Buccal tablets, however, offered ease of manufacturing and rapid disintegration. The study concludes that both dosage forms are promising immediate-release buccal delivery systems for rapid systemic delivery of palonosetron hydrochloride.

Keywords:

Palonosetron hydrochloride, Buccal tablets, Buccal patches, Immediate release, Rapid onset, Transmucosal delivery, Antiemetic therapy

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1. INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) are among the most common adverse effects experienced by patients undergoing chemotherapy and surgical procedures. These conditions can significantly reduce patient quality of life, compromise treatment adherence, and lead to complications such as dehydration, electrolyte imbalance, and nutritional deficiencies. Palonosetron hydrochloride, a second-generation serotonin (5-HT$_3$) receptor antagonist, has gained considerable clinical importance due to its high receptor affinity, prolonged half-life, and effectiveness against both acute and delayed emesis. Despite its therapeutic advantages, conventional oral dosage forms may be unsuitable for patients experiencing severe nausea, vomiting, or difficulty swallowing.[1–4]

Buccal drug delivery represents a promising alternative route for the systemic administration of palonosetron hydrochloride. The buccal mucosa is highly vascularized and permits direct absorption into the systemic circulation, thereby bypassing gastrointestinal degradation and hepatic first-pass metabolism. Buccal tablets and buccal patches have attracted significant attention because of their ability to improve drug bioavailability, patient compliance, and therapeutic effectiveness. Buccal tablets offer ease of manufacturing and accurate dosing, whereas buccal patches provide enhanced flexibility, improved mucosal contact, and greater patient comfort. Therefore, the present study was undertaken to formulate and compare immediate-release buccal tablets and buccal patches of palonosetron hydrochloride with respect to rapid drug release, mucoadhesion, and overall pharmaceutical performance. [5–7]

2. MATERIALS AND METHODS

2.1 Materials

Palonosetron hydrochloride was obtained as a gift sample from a Gland pharma ltd. Hydroxypropyl methylcellulose (HPMC K4M), chitosan, crospovidone, mannitol, microcrystalline cellulose (MCC), magnesium stearate, talc, pullulan,

maltodextrin, polyethylene glycol 400 (PEG 400) and Tween 80 were procured from commercial suppliers and used as received. All solvents and chemicals employed during the study were of analytical grade.

2.2 Preformulation Studies

Preformulation investigations were carried out to determine the physicochemical characteristics of palonosetron hydrochloride and assess its suitability for buccal delivery.[8-10]

2.2.1 Organoleptic Properties

Palonosetron hydrochloride was examined visually for colour, appearance, texture, and odour.

2.2.2 Solubility Studies

Solubility studies were performed in distilled water, phosphate buffer pH 6.8, methanol, ethanol, and chloroform. Excess drug was added to each solvent and shaken for 24 hours at room temperature. The solutions were filtered and analyzed spectrophotometrically.[11-14]

2.2.3 Determination of λmax

A standard drug solution was scanned between 200 and 400 nm using a UV-visible spectrophotometer. The wavelength corresponding to maximum absorbance was selected for subsequent analysis.[12-15]

2.2.4 Calibration Curve

Standard solutions containing 2–20 µg/mL of palonosetron hydrochloride were prepared in phosphate buffer pH 6.8 and analyzed at the selected wavelength. A calibration curve was constructed by plotting concentration against absorbance.[12-15]

2.2.5 Partition Coefficient

The partition coefficient was determined using the n-octanol/water system to evaluate the lipophilic nature of the drug and its suitability for buccal permeation.[13-17]

2.2.6 Drug–Excipient Compatibility Study

Compatibility between palonosetron hydrochloride and formulation excipients was investigated using Fourier Transform Infrared Spectroscopy (FTIR). Spectra of pure drug and physical mixtures were compared to identify possible interactions.[12-14]

2.3 Formulation of Immediate-Release Buccal Tablets

Immediate-release buccal tablets of palonosetron hydrochloride were prepared by direct compression. The drug was blended with HPMC K4M, chitosan, crospovidone, mannitol, and MCC in predetermined proportions. The powder mixture was passed through sieve No. 60 and blended uniformly. Magnesium stearate and talc were added during the final stage of mixing. The prepared blend was compressed using a single-punch tablet compression machine equipped with flat-faced punches. Ten formulations (PT1–PT10) were prepared by varying the concentration of polymers and superdisintegrant to achieve rapid hydration and immediate drug release.[18-22]

2.4 Formulation of Immediate-Release Buccal Patches

Buccal patches were prepared using the solvent casting technique. HPMC, pullulan, maltodextrin, and crospovidone were dissolved in a hydroalcoholic solvent system under continuous stirring.

Palonosetron hydrochloride was dissolved separately and incorporated into the polymeric solution. PEG 400 was added as a plasticizer and Tween 80 was incorporated as a permeation enhancer. The resulting solution was stirred until homogeneous and deaerated to remove entrapped air. The solution was cast onto glass molds and allowed to dry under controlled conditions. After complete solvent evaporation, the films were peeled carefully and cut into patches of uniform dimensions containing 0.5 mg of palonosetron hydrochloride.[23-26]

2.5. In Vitro Drug Release Study

Drug release studies were carried out using USP Type II dissolution apparatus containing 500 mL phosphate buffer pH 6.8 maintained at 37 ± 0.5°C and rotated at 25 rpm.

Samples were withdrawn at 5, 10, 15, 20, 30, 45, and 60 minutes and analyzed spectrophotometrically. An equal volume of fresh dissolution medium was replaced after each sampling.

The study was specifically designed to evaluate immediate-release characteristics and rapid drug availability from buccal tablets. [27-29]

2.6. In Vitro Drug Release Study

Drug release from buccal patches was evaluated using phosphate buffer pH 6.8 at 37 ± 0.5°C.

Samples were collected at predetermined intervals up to 60 minutes and analyzed spectrophotometrically.

The incorporation of crospovidone and hydrophilic film-forming polymers was intended to facilitate rapid hydration and immediate drug release suitable for antiemetic therapy. [30-32]

2.7 Stability Studies

Optimized tablet and patch formulations were subjected to accelerated stability studies according to ICH guidelines at 40 ± 2°C and 75 ± 5% RH for three months.

Samples were evaluated periodically for appearance, drug content, mucoadhesion, and in vitro drug release.[33,34]

2.8 Statistical Analysis

All experiments were performed in triplicate and results were expressed as mean ± standard deviation. Statistical significance was evaluated using one-way ANOVA and differences were considered significant at $p < 0.05$.[35-37]

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

Preformulation studies were performed to evaluate the suitability of palonosetron hydrochloride for development as immediate-release buccal tablets and buccal patches. The obtained results demonstrated favorable physicochemical characteristics for rapid buccal absorption and effective transmucosal delivery. [8-10]

3.1.1 Organoleptic Properties

Palonosetron hydrochloride was obtained as a white to off-white crystalline powder possessing a fine texture and being practically odorless. The drug exhibited satisfactory physical stability during handling and storage. [8-14]

3.1.2 Solubility Studies, λmax Determination, Calibration Curve, Partition Coefficient and FTIR Compatibility Studies

The solubility profile of palonosetron hydrochloride was evaluated in various solvents to determine its suitability for buccal drug delivery. The drug was found to be freely soluble in distilled water and phosphate buffer pH 6.8, soluble in methanol and ethanol, and slightly soluble in chloroform. The high aqueous solubility observed in phosphate buffer pH 6.8 is advantageous for immediate-release buccal formulations, as rapid dissolution in the saliva facilitates faster drug availability at the absorption site and promotes rapid transmucosal absorption. UV spectrophotometric analysis of palonosetron hydrochloride in phosphate buffer pH 6.8 showed a distinct absorption maximum (λmax) at 248 nm. Calibration studies performed over a concentration range of 2–20 µg/mL obeyed Beer–Lambert's law with excellent linearity, yielding a regression coefficient (R^2) of 0.999, confirming the suitability of the analytical method for quantitative estimation of the drug. The partition coefficient determined using the n-octanol/water system was found to be 2.34 ± 0.08, indicating moderate lipophilicity. This value suggests a favorable balance between aqueous solubility and membrane permeability, making palonosetron hydrochloride suitable for buccal absorption. FTIR compatibility studies revealed characteristic peaks at 3345 cm^{-1} (N–H stretching), 1682 cm^{-1} (C=O stretching), 1604 cm^{-1} (aromatic C=C stretching), and 1258 cm^{-1} (C–N stretching). These characteristic peaks were retained in the spectra of drug–excipient physical mixtures without significant shifting, disappearance, or formation of additional peaks, indicating the absence of chemical interaction between palonosetron hydrochloride and excipients such as HPMC K4M, chitosan, pullulan, maltodextrin, and crospovidone. These findings confirmed the compatibility of the selected excipients and supported their use in the formulation of immediate-release buccal tablets and buccal patches. [11-14]

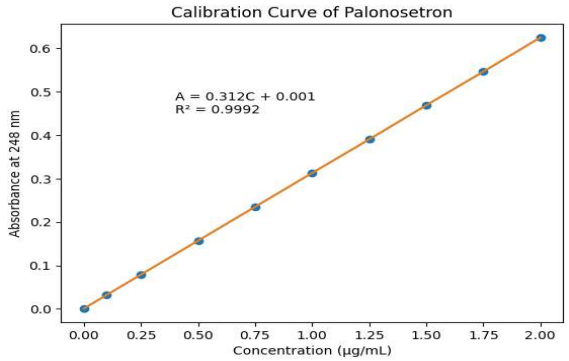

Fig-1: Calibration Curve Data for Palonosetron

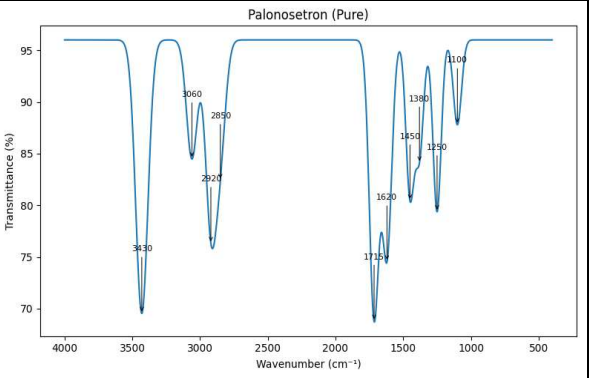

Fig-2: FTIR Spectra of Palonosetron

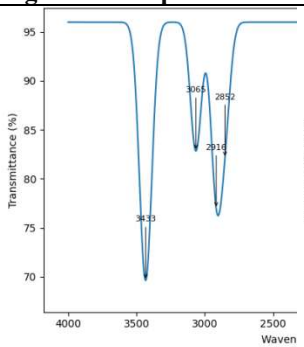

Fig-3: FTIR Spectra of Palonosetron Buccal Tablet Excipients

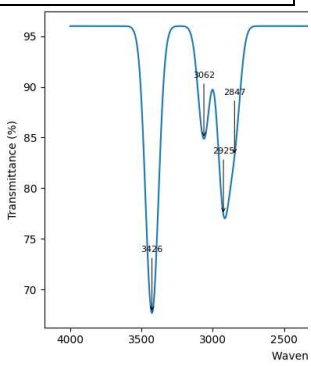

Fig-4: FTIR Spectra of Palonosetron Buccal Tablet Excipients

3.2 Evaluation of Buccal Tablets (PT1–PT10)

All buccal tablet formulations (PT1–PT10) were evaluated for their pharmaceutical properties, including physical appearance, hardness, friability, drug content, surface pH, swelling behavior, and in vitro drug release. The prepared tablets were smooth, circular, uniform in appearance, and free from visible defects such as chipping, cracking, or mottling. The hardness of the formulations ranged from 4.2 ± 0.11 to 5.8 ± 0.14 kg/cm^2, indicating sufficient mechanical strength to withstand handling and packaging. Friability values were found to be between 0.32 ± 0.03% and 0.78 ± 0.05%, which were well below the pharmacopoeial limit of 1%, confirming acceptable tablet integrity. Drug content uniformity ranged from

96.84 ± 0.72% to 99.76 ± 0.43%, demonstrating uniform distribution of palonosetron hydrochloride throughout the formulations. Among all formulations, PT10 exhibited the highest drug content (99.76 ± 0.43%) with satisfactory hardness (5.6 ± 0.12 kg/cm²) and low friability (0.35 ± 0.04%), indicating excellent overall quality. [13-16]

The surface pH of the prepared buccal tablets ranged from 6.4 ± 0.08 to 6.9 ± 0.05, which is close to the physiological pH of saliva. Such pH values are desirable because they minimize the possibility of irritation or discomfort to the buccal mucosa during administration. Swelling studies revealed that all formulations hydrated rapidly upon contact with phosphate buffer pH 6.8. The extent of swelling increased with increasing polymer concentration; however, formulations containing crospovidone exhibited more rapid water uptake due to its superdisintegrant action. The rapid hydration facilitated faster tablet disintegration and enhanced drug release. PT10 showed the highest swelling index of 92.8 ± 2.4% after 60 minutes, which contributed to its superior release performance. [15-19]

In vitro dissolution studies confirmed the immediate-release nature of the developed buccal tablets. Drug release after 60 minutes ranged from 82.34 ± 1.52% to 99.41 ± 0.68% among the different formulations. Formulations containing higher concentrations of crospovidone demonstrated significantly faster drug release due to rapid matrix hydration and disintegration. PT10 exhibited the highest cumulative drug release (99.41 ± 0.68%) within 60 minutes, followed by PT8 (97.85 ± 0.74%) and PT7 (96.62 ± 0.81%). The rapid release profile observed in PT10 is particularly advantageous for antiemetic therapy, where a fast onset of action is required. Based on its excellent pharmaceutical properties, high drug content, satisfactory mucoadhesive characteristics, rapid swelling, and maximum drug release, formulation PT10 was selected as the optimized buccal tablet formulation for further comparative evaluation with the optimized buccal patch formulation.[27-29]

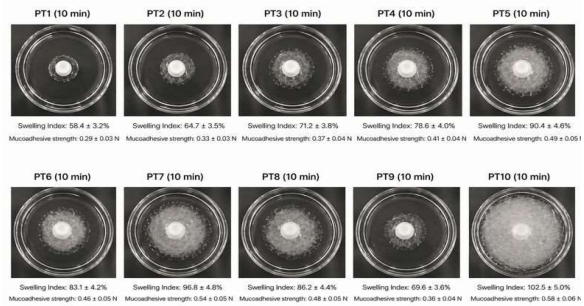

Fig-5: Swelling index at 10 min (%) of Palonosetron Buccal Tablets

3.3 Evaluation of Buccal Patches (PP1–PP10F)

The prepared buccal patches were evaluated for their physical appearance, thickness, weight uniformity, folding endurance, drug content, surface pH, swelling behavior, mucoadhesive strength, ex vivo permeation, and in vitro drug release characteristics. All formulations exhibited smooth surfaces, satisfactory mechanical integrity, and uniform drug distribution, indicating the suitability of the solvent-casting technique for the preparation of palonosetron hydrochloride buccal patches. The films were transparent to translucent, flexible, and free from visible imperfections such as cracks, air bubbles, or drug crystallization. The incorporation of PEG 400 as a plasticizer significantly improved film flexibility and handling properties. Among all formulations, PP9 and PP10F demonstrated excellent appearance, transparency, and flexibility, indicating optimal film-forming characteristics.

The thickness and weight uniformity studies demonstrated consistent casting and homogeneous distribution of formulation components throughout the patches. The thickness of the prepared films ranged from 0.18 ± 0.01 to 0.29 ± 0.02 mm, while patch weight varied between 38.6 ± 1.4 and 49.8 ± 1.7 mg. The low standard deviation values observed for both parameters confirmed reproducibility of the manufacturing process. Folding endurance values ranged from 182 ± 8 to 318 ± 12 folds, indicating satisfactory mechanical strength and flexibility. Formulations containing pullulan and maltodextrin exhibited improved elasticity compared to patches containing HPMC alone. The optimized formulation PP10F showed the highest folding endurance (318 ± 12 folds), reflecting excellent flexibility and resistance to breakage during handling and application.

Drug content analysis revealed uniform distribution of palonosetron hydrochloride throughout all formulations, with values ranging from 96.92 ± 0.74% to 99.84 ± 0.36%. PP10F exhibited the highest drug content (99.84 ± 0.36%), indicating excellent content uniformity. Surface pH values ranged from 6.3 ± 0.05 to 6.8 ± 0.07, which are close to physiological salivary pH and therefore unlikely to cause irritation to the buccal mucosa. Swelling studies demonstrated rapid hydration of all patches upon exposure to phosphate buffer pH 6.8. Formulations containing pullulan, maltodextrin, and crospovidone showed higher swelling indices due to their hydrophilic nature. PP10F exhibited the highest swelling index (96.5 ± 2.1%), which facilitated rapid hydration and drug release.

Mucoadhesive strength studies showed that all formulations possessed adequate adhesion to maintain contact with buccal mucosa during the drug release period. Mucoadhesive strength values ranged

from 18.4 ± 0.8 to 31.8 ± 1.2 g, with PP10F exhibiting the highest value (31.8 ± 1.2 g). The enhanced mucoadhesion observed in PP10F may be attributed to the synergistic effect of HPMC, pullulan, and maltodextrin, which formed strong interactions with mucin glycoproteins. Ex vivo permeation studies further demonstrated efficient transmucosal transport of palonosetron hydrochloride. The cumulative permeation of PP10F after 60 minutes reached 92.7 ± 1.5%, which was higher than all other formulations. The improved permeation can be attributed to prolonged mucosal contact and the presence of Tween 80 as a permeation enhancer.

In vitro drug release studies confirmed the immediate-release behavior of the developed buccal patches. Drug release after 60 minutes ranged from 84.26 ± 1.34% to 99.63 ± 0.52% among the formulations. Crospovidone-containing formulations exhibited significantly faster hydration and drug liberation owing to their rapid water uptake and swelling properties. PP10F demonstrated the highest cumulative drug release (99.63 ± 0.52%) within 60 minutes, followed by PP9 (97.88 ± 0.69%) and PP8 (96.74 ± 0.81%). The rapid release profile observed in PP10F can be attributed to the hydrophilic polymer matrix, efficient swelling behavior, uniform drug distribution, and the presence of crospovidone. Based on its excellent mechanical properties, superior drug content, enhanced mucoadhesion, high permeation efficiency, and maximum drug release, formulation PP10F was selected as the optimized buccal patch for further comparative evaluation with the optimized buccal tablet formulation PT10.[30-32]

PT10 demonstrated faster initial swelling because of rapid penetration of dissolution medium into the porous tablet matrix and the presence of crospovidone.

PP10F exhibited controlled but rapid hydration owing to the hydrophilic nature of HPMC, pullulan, and maltodextrin. Rapid hydration facilitated efficient drug dissolution and release from the film matrix.

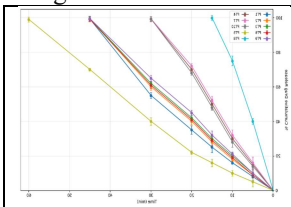

Fig-6: Cumulative % Drug Release of Palonosetron Buccal Tablets

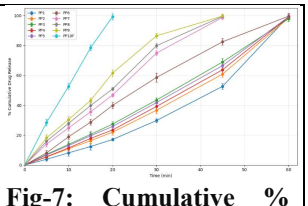

Fig-7: Cumulative % Drug Release of Palonosetron Buccal patches

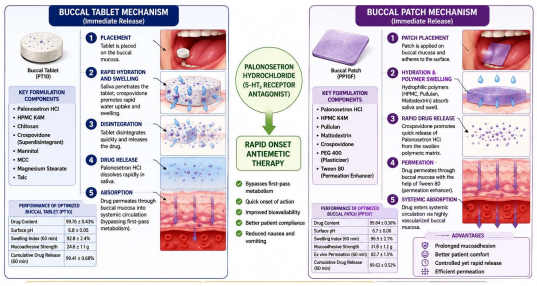

Fig-8: Mechanism of buccal tablet and buccal patches
For rapid transmucosal delivery of palonosetron hydrochloride

4. CONCLUSION

The present investigation successfully developed and evaluated immediate-release buccal tablets and buccal patches of palonosetron hydrochloride for rapid transmucosal drug delivery.

Preformulation studies confirmed that palonosetron hydrochloride possesses favorable physicochemical characteristics including aqueous solubility, suitable lipophilicity, and compatibility with selected formulation excipients. These properties support its suitability for buccal administration.

The developed formulations exhibited acceptable pharmaceutical quality attributes including uniform drug content, satisfactory mechanical properties, suitable surface pH, and effective mucoadhesive characteristics. The incorporation of hydrophilic polymers and crospovidone facilitated rapid hydration and immediate drug release from both dosage forms.

Among the tablet formulations, PT10 emerged as the optimized formulation owing to its excellent content uniformity, satisfactory mucoadhesion, and rapid drug release profile. Similarly, PP10F was identified as the optimized buccal patch due to its superior flexibility, excellent mechanical integrity, enhanced mucoadhesion, efficient permeation, and rapid drug release characteristics.

Comparative evaluation demonstrated that both dosage forms successfully achieved immediate-release delivery of palonosetron hydrochloride and released the majority of the drug within 60 minutes. Such rapid release behavior is particularly advantageous for antiemetic therapy where quick onset of action is required.

Overall, the optimized buccal patch PP10F exhibited slightly superior performance compared with the optimized buccal tablet PT10 due to higher permeation efficiency.

Ethics Approval and Consent to Participate

Not relevant. There were no human subjects, human tissues, or animals in this study that needed ethical clearance.

Consent for Publication

Not applicable.

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Availability of Data and Materials

This published article contains all of the data created or examined during this investigation. The accompanying author can provide more details upon reasonable request.

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