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# FORMULATION AND EVALUATION OF BUCCAL TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE

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**ABSTRACT:**
The present study aimed to develop and evaluate mucoadhesive buccal tablets of Metoclopramide Hydrochloride for prolonged drug release, enhanced bioavailability, and avoidance of hepatic first-pass metabolism. A $3^2$ full factorial design was employed to investigate the influence of Carbopol 940 (CP) and Guar Gum (GG) on drug release and mucoadhesive performance. Buccal tablets were prepared by direct compression and evaluated for physicochemical characteristics, including hardness, friability, weight variation, drug content, surface pH, swelling index, mucoadhesive strength, and in vitro drug release. FTIR studies confirmed compatibility between the drug and excipients. The cumulative drug release from different formulations ranged between 74.83% and 100.41%, with formulation F9 exhibiting the most desirable balance of sustained drug release and mucoadhesive properties. Drug release kinetics were best described by the Korsmeyer–Peppas model, indicating a non-Fickian diffusion mechanism. Stability studies conducted under accelerated conditions demonstrated the stability of the optimized formulation.The optimized formulation (F9) was further subjected to in vivo evaluation in New Zealand White rabbits. The formulation exhibited prolonged buccal residence time (6.42 ± 0.58 h), excellent mucosal tolerability, and sustained plasma drug concentrations up to 24 h. Pharmacokinetic studies revealed a significantly delayed Tmax (8.0 ± 0.6 h) and higher $AUC_{0–24}$ (2946 ± 185 ng·h/mL) compared with the marketed oral tablet, indicating enhanced systemic exposure and improved bioavailability through buccal administration. The findings demonstrate that the optimized mucoadhesive buccal tablet effectively prolongs drug release, enhances bioavailability, and provides sustained therapeutic plasma concentrations. Therefore, the developed buccal delivery system represents a promising alternative to conventional oral administration of Metoclopramide Hydrochloride.

**KEYWORDS:** Metoclopramide Hydrochloride, Buccal Tablet, Mucoadhesion, Carbopol 940, Guar Gum, Sustained Release, Pharmacokinetics, Bioavailability, Buccal Drug Delivery, In Vivo Evaluation.

## INTRODUCTION

The development of alternative drug delivery routes has garnered significant attention in recent years, especially in improving the therapeutic efficacy of drugs with poor oral bioavailability.[1] Among these, buccal drug delivery systems represent a promising and innovative platform for systemic delivery of drugs via the mucosal lining of the cheek. Buccal administration offers multiple advantages over conventional oral dosage forms, including avoidance of first-pass hepatic metabolism, ease of administration, rapid onset of action, improved patient compliance, and better control over drug release profiles. Such systems are especially useful for drugs with short half-lives or those that undergo extensive first-pass metabolism.[2]

Metoclopramide hydrochloride, a dopamine D2 receptor antagonist, is widely used as an antiemetic and gastroprokinetic agent in the management of nausea, vomiting, gastroparesis, and gastroesophageal reflux disease (GERD). However, its conventional oral administration is often associated with limitations such as erratic gastrointestinal absorption, short biological half-life (approximately 4–6 hours), and significant hepatic first-pass metabolism, which reduces its bioavailability to nearly 30–40%. These pharmacokinetic challenges necessitate the development of an alternative delivery system that can ensure more consistent plasma levels and enhanced therapeutic efficacy.[3]

Buccal tablets present a viable strategy to overcome these drawbacks by providing a sustained release of Metoclopramide hydrochloride directly into systemic circulation through the rich vasculature of the buccal mucosa. This route bypasses the gastrointestinal tract and first-pass metabolism, potentially leading to increased bioavailability and prolonged drug action. Furthermore, buccal tablets can be designed to adhere to the mucosal surface for a designated period, thereby enabling controlled and site-specific drug release.

The formulation of buccal tablets involves careful selection of mucoadhesive polymers, excipients, and formulation techniques to achieve desired drug release kinetics, mechanical strength, and adhesion properties. Polymers such as Carbopol, HPMC, and sodium carboxymethylcellulose have been extensively studied for their excellent mucoadhesive properties and ability to control drug release. Additional formulation parameters such as tablet hardness, swelling index, surface pH, and in vitro residence time play a crucial role in determining the success of the buccal delivery system.[4]

Therefore, the present study aims to formulate and evaluate buccal tablets of Metoclopramide hydrochloride using different bioadhesive polymers and excipients, with the goal of optimizing drug release characteristics, mucoadhesive strength, and overall performance. The study also involves comprehensive physicochemical characterization and in vitro drug release profiling to assess the suitability of the developed formulation as a potential buccal delivery system for enhanced bioavailability and patient compliance.[5]

## MATERIALS AND METHODS

### MATERIALS

Metoclopramide Hydrochloride, almond gum, Carbopol 940, talc, ethyl cellulose, direct compressible lactose, and magnesium stearate were procured from A.G. Traders, Pune, Maharashtra. All the chemicals used in the study were of analytical reagent (AR) or laboratory reagent (LR) grade and were used.

### Preformulation Studies[6-10]

Preformulation studies are critical in the initial stages of pharmaceutical development, offering a comprehensive understanding of the physicochemical properties of the drug substance alone and in combination with selected excipients. These studies help in the rational design of a stable and effective dosage form by identifying potential challenges such as solubility limitations, incompatibility with excipients, and thermal instability. In the present study, preformulation was initiated to evaluate the physical and chemical behavior of Metoclopramide Hydrochloride, a drug known for its extensive first-pass metabolism, making it a suitable candidate for buccal delivery.

### Physical Characterization of Drug[11-13]

The drug sample of Metoclopramide Hydrochloride was evaluated for its basic physical properties. The nature and color of the sample were observed visually and under a compound microscope to assess its morphological characteristics. The solubility profile was determined by adding 100 mg of the drug to 100 ml of various solvents and shaking the mixture for 24 hours at 20°C to ensure saturation. Solubility influences drug dissolution and bioavailability, particularly in oral formulations. The melting point, an essential parameter for confirming drug identity and purity, was assessed using the capillary method. A small amount of drug was placed in a capillary tube, inserted into a Thiele's tube immersed in a paraffin oil bath, and heated gradually. The temperature at which the drug melted was recorded in triplicate, and the average value was calculated.

### Identification of Drug[14-18]

#### UV Spectroscopic Analysis

For confirmation of drug identity, UV spectrophotometric scanning was performed. A 10 µg/mL solution of Metoclopramide Hydrochloride was prepared in phosphate buffer (pH 6.8), and the solution was scanned in the UV range of 200–400 nm using a double-beam spectrophotometer. The wavelength of maximum absorbance (λmax) was determined in triplicate to ensure precision.

### Preparation of Phosphate Buffer (pH 6.8)

Phosphate buffer of pH 6.8 was prepared by dissolving 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate in 900 mL of distilled water. The pH was adjusted using sodium hydroxide solution and finalized at 6.8 with the aid of a digital pH meter. The volume was then made up to 1000 mL with distilled water.

### Calibration Curve for Metoclopramide Hydrochloride

A standard stock solution (1000 µg/mL) was prepared by dissolving 100 mg of Metoclopramide Hydrochloride in phosphate buffer (pH 6.8) and sonicating for 5 minutes. Serial dilutions were performed to obtain concentrations ranging from 2 to 20 µg/mL. The absorbance of each dilution was measured at 309 nm using a UV spectrophotometer, and a standard calibration curve was plotted.

### Drug-Excipients Compatibility Studies[19-25]

#### Fourier Transform Infrared (FTIR) Spectroscopy

Compatibility between Metoclopramide Hydrochloride and selected excipients was investigated using FTIR spectroscopy. Spectra of the pure drug and its physical mixtures with excipients (1:1 ratio) were recorded using the KBr pellet method. Each sample was compressed into a transparent disc under 5 tons of pressure and scanned in the range of 4000–500 $cm^{-1}$ to detect any potential shifts or disappearance of characteristic peaks, which would indicate possible interactions.

### Differential Scanning Calorimetry (DSC)[26-30]

Thermal behavior and possible interactions between the drug and excipients were further assessed by Differential Scanning Calorimetry (DSC). Accurately weighed samples were sealed in aluminum pans and analyzed using a Shimadzu DSC-60 instrument under a nitrogen purge. The heating was carried out from 50°C to 300°C at a rate of 10°C/min. Indium was used for calibration. Thermograms of the pure drug and physical mixtures were compared for any changes in peak onset, melting point, or enthalpy that might indicate incompatibility.

**Pre-compression Parameters**[31-33]

Pre-compression evaluation is a vital step in solid dosage form development, as it provides critical insight into the flowability, compressibility, and packing characteristics of the powder blend. These parameters play a key role in ensuring uniform die filling, consistent tablet weight, and overall manufacturing efficiency.

**Angle of Repose:**

The flow behavior of the powder blend was evaluated by measuring the angle of repose using the fixed funnel method. This parameter reflects the internal friction between particles and gives an indirect measure of flowability. In general, lower angle values are indicative of good flow, whereas higher values suggest cohesive or poorly flowing powders.

**Bulk Density and Tapped Density:**

Bulk density was assessed by measuring the volume occupied by a known mass of powder in an untapped state. In contrast, tapped density was determined after subjecting the powder to mechanical tapping until a constant volume was achieved. These densities provide information about the packing characteristics of the blend and its potential behavior during die filling.

**Carr's Compressibility Index:**

This index is derived from the difference between tapped and bulk densities, offering a measure of the blend's ability to compress. Lower compressibility index values are generally associated with better flow properties, while higher values indicate poor flow and greater cohesiveness.

**Hausner's Ratio:**

Hausner's ratio is another widely used parameter to evaluate powder flowability. It is calculated from the ratio of tapped to bulk density. A low Hausner's ratio typically reflects excellent flow characteristics, whereas higher values suggest poor flow and possible handling challenges during tableting.

These pre-compression evaluations are essential in predicting the behavior of the powder blend during direct compression and help in identifying the need for flow enhancers or other formulation modifications.

**Formulation Using $3^2$ Full Factorial Design**[34-36]

A $3^2$ full factorial design was employed to systematically investigate the effects of two independent variables—Carbopol 940 ($X_1$) and Guar gum ($X_2$)—each at three different levels. This design allows for the evaluation of both individual and interactive effects of formulation variables on the tablet properties. The levels for each factor were selected based on prior optimization studies. All other formulation and process conditions were kept constant. The coded and actual values, along with the experimental combinations and runs, are detailed in Tables 1 and 2.

**Table 1: Amount of variables in $3^2$ factorial design batches**

| Coded Values | Actual Values (mg) | |
|---|---|---|
| | $X_1$ | $X_2$ |
| -1 | 10 | 6 |
| 0 | 15 | 12 |
| +1 | 20 | 18 |

**Table 2: A $3^2$ full factorial experimental design layout**

| Formulation Code | Coded Values | |
|---|---|---|
| | $X_1$ | $X_2$ |
| **F1** | -1 | -1 |
| **F2** | -1 | 0 |
| **F3** | -1 | +1 |
| **F4** | 0 | -1 |
| **F5** | 0 | 0 |
| **F6** | 0 | +1 |
| **F7** | +1 | -1 |
| **F8** | +1 | 0 |
| **F9** | +1 | +1 |

**Preparation of Buccoadhesive tablets**[37-42]

Table 3 lists the composition of different buccoadhesive formulations prepared using varying amounts of Carbopol 940 (CP), Guar gum, Direct Compressible Lactose (DCL) along with a fixed quantity of Aerosil, PVP and Ethyl cellulose. Buccoadheive bilayer tablets were prepared by a direct compression method involving two steps. In first step drug, polymers (CP and Guar gum) and diluents were mixed homogeneously in a blender for 15 minutes. Finally lubricant was

added and mixed for 5 minutes. The mixture was then compressed using a 10 station tablet punching machine using 6 mm punches at a pressure of approximately 5-6 kgs /$cm^2$ In the second step, upper punch was raised and the backing layer of ethyl cellulose was placed on the above compact, two layers were then compressed.

**Formulae of various buccoadhesive formulations in $3^2$ factorial design**

**Table 3: Actual values of ingredients taken for buccoadhesive tablet**

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **Metoclopramide** | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| **Carbopol 940** | 10 | 10 | 10 | 15 | 15 | 15 | 20 | 20 | 20 |
| **Guar gum** | 6 | 12 | 18 | 6 | 12 | 18 | 6 | 12 | 18 |
| **DCL** | 26 | 20 | 14 | 21 | 15 | 9 | 16 | 10 | 4 |
| **PVP K30** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Aerosil** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Ethyl cellulose as Backing Layer** | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| **Total** | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 |

**Evaluation of Buccal Tablets**[43-48]

All prepared buccal tablet formulations were subjected to thorough physicochemical evaluation to ensure consistent quality, efficacy, and patient acceptability. The following parameters were assessed as per standard pharmacopeial guidelines:

**a) Appearance**

Tablets were visually inspected for color, shape, uniformity, and any surface defects. An ideal tablet must exhibit a smooth finish without cracks or discoloration. Uniform appearance ensures proper mixing of excipients and active drug.

**b) Thickness and Diameter**

Ten tablets from each formulation were randomly selected, and their thickness and diameter were measured using a calibrated vernier caliper. Consistency in these dimensions is crucial for dosage accuracy and packaging compatibility.

**c) Hardness**

Tablet hardness was tested using a Monsanto hardness tester to assess mechanical strength. Adequate hardness ensures that tablets withstand handling and transportation without breaking, while still disintegrating appropriately upon administration.

**d) Friability**

Friability was determined using a Roche friabilator to assess tablet resistance to abrasion. Twenty tablets were subjected to mechanical agitation, and the weight loss was calculated. Friability below 0.8% indicates acceptable durability of tablets.

**e) Weight Variation**

Twenty tablets were individually weighed, and the average weight was calculated. The percentage deviation from the mean was determined and compared with Indian Pharmacopoeia limits to confirm uniformity in drug dosage.

**f) Drug Content Uniformity**

To ensure dose precision, five tablets were powdered and analyzed spectrophotometrically for drug content. Each tablet should contain the drug within an acceptable range (typically 90–110%) to maintain therapeutic efficacy.

**Surface pH Study**

Surface pH of hydrated buccal tablets was measured by placing the moistened tablet on a pH meter electrode. The study ensures that the formulation's pH is near-neutral (around pH 6–7), minimizing the risk of mucosal irritation during administration.

**Swelling Index**

Swelling studies were performed by immersing tablets in phosphate buffer (pH 6.8) at 37°C and measuring weight gain at regular intervals up to 8 hours. Swelling behavior indicates polymer hydration and plays a key role in mucoadhesion and drug release.

**Mucoadhesive Strength**

Mucoadhesive strength was evaluated using a modified balance method, wherein the force required to detach the tablet from a sheep buccal mucosa was measured. Stronger adhesion ensures prolonged residence time and better therapeutic action at the site.

**In-vitro Dissolution Studies**

Dissolution testing was conducted using USP Type II apparatus with phosphate buffer (pH 6.8) as the medium. Samples were withdrawn at set time intervals, and the drug release was quantified spectrophotometrically at 309 nm to study release kinetics.

**Permeation Studies**

Franz diffusion cells with sheep buccal mucosa were used to assess drug permeation over 8 hours. The cumulative amount of drug permeated through the mucosa was recorded to evaluate the efficiency of the buccal delivery system.

**Steady-State Flux**
Steady-state flux was calculated from the linear portion of the permeation curve. It reflects the rate of drug transport across the buccal mucosa and is essential for determining the therapeutic potential of the formulation.
**Permeability Coefficient**
The permeability coefficient (Kp) was calculated using the flux and drug concentration. It provides insight into how efficiently the drug diffuses across biological membranes and helps predict in vivo performance.
**Diffusivity (D)**
Diffusivity was derived using known parameters such as permeability coefficient and membrane thickness. This value helps to understand the movement of drug molecules within and across the mucosal membrane.
**Drug Release Kinetics**
Drug release profiles were fitted to various kinetic models—Zero order, First order, Higuchi, and Korsmeyer–Peppas—to determine the mechanism of release. The best-fit model was selected based on the highest regression coefficient ($R^2$) value.
**Statistical Data Analysis**
Design Expert software (v8.0.7.1) was used for statistical evaluation of the factorial design data. Polynomial equations were generated, and ANOVA was performed to determine the significance of formulation variables on response parameters.
**Stability Studies**
Stability studies were conducted at accelerated conditions (40 ± 2°C / 75 ± 5% RH) for 30 days according to ICH guidelines. Post-study evaluations included drug content, pH, and drug release profile to confirm formulation stability over time.
**Selection of Optimized Buccal Tablet Formulation**
The optimized buccal tablet formulation (F9) containing Metoclopramide Hydrochloride was selected for in vivo evaluation based on its superior in vitro performance, including high mucoadhesive strength, controlled swelling behavior, sustained drug release, enhanced permeation, adequate mechanical properties, and stability. The formulation comprised Carbopol 940 and Guar Gum as mucoadhesive polymers with an ethyl cellulose backing layer for unidirectional drug release.

**In vivo Pharmacological studies:**[49-57]
**Experimental Animals**
Healthy New Zealand White rabbits (2.0–2.5 kg) of either sex were used for the study. Animals were housed under controlled environmental conditions (22 ± 2°C, 55 ± 10% RH, 12 h light/dark cycle) with free access to standard pellet diet and water. Prior to experimentation, animals were acclimatized for seven days. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and conducted according to CPCSEA guidelines. The entire experimental protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of HSBPVT's Faculty of Pharmacy, Kashti, Ahilyanagar – 414701, Maharashtra. The study was conducted in strict accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. (Project Proposal Number: 1697/PO/Re/S/13/CPCSEA/2025/02)

**Experimental Design**
Fourteen rabbits were randomly divided into three groups: Group G1 (placebo buccal tablet, n=2), Group G2 (optimized buccal tablet F9, n=6), and Group G3 (marketed oral Metoclopramide Hydrochloride tablet, n=6). The study was designed to compare the pharmacokinetic performance and bioavailability of the optimized buccal formulation with the conventional oral formulation.

**Drug Administration**
For buccal administration, tablets were carefully placed in the buccal pouch using sterile forceps. Animals were monitored to ensure proper adhesion and retention of the tablet. For oral administration, the marketed tablet was crushed, dispersed in an aqueous vehicle, and administered orally using a feeding tube to ensure accurate dosing.

**Buccal Residence Time Study**
The buccal residence time of the optimized formulation was determined by recording the duration from tablet placement until complete erosion, dissolution, or dislodgement from the buccal cavity. Observations were made periodically, and residence time was expressed as mean ± SD.

**Pharmacokinetic Study**
The buccal absorption of Metoclopramide Hydrochloride was assessed through plasma drug concentration analysis following buccal administration. Blood samples were collected at predetermined intervals (0.5, 2, 4, 8, 12, and 24 h) using a staggered sampling design. Plasma was separated by centrifugation and analyzed using a validated RP-HPLC method. Plasma concentration–time profiles were generated for pharmacokinetic evaluation.

**Comparative Pharmacokinetic Evaluation**
Pharmacokinetic parameters including maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), and area under the plasma concentration–time curve (AUC) were calculated using non-compartmental analysis.

The pharmacokinetic profile of the optimized buccal tablet was compared with that of the marketed oral formulation to evaluate enhancement in systemic bioavailability.

**Statistical Analysis**

All experimental data were expressed as mean ± standard deviation (SD) and analyzed using GraphPad Prism software (Version 8.0). Statistical comparisons were performed using Student's t-test, one-way ANOVA followed by Tukey's post hoc test, or two-way ANOVA with Bonferroni's correction where appropriate. Differences were considered statistically significant at $p < 0.05$.

## RESULTS AND DISCUSSIONS:

### Preformulation Studies

Preformulation studies are a critical step in the rational development of any pharmaceutical formulation. These studies provide fundamental information about the physicochemical properties of the active pharmaceutical ingredient (API) and excipients. In the present study, preformulation investigations involved both qualitative and quantitative assessments of the drug substance and tablet blend. This included physical and chemical characterization, evaluation of powder flow properties, and compatibility assessments to ensure efficient formulation development. The pre-compression parameters such as bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose were determined to assess the flowability and compressibility of the tablet blend, which are essential for uniform tablet production.

### Physical Characterization of Drug Sample

**a) Description**

The physical appearance of Metoclopramide Hydrochloride was evaluated visually. The drug was found to be a white, crystalline, and odorless powder, which is consistent with the standard description reported in pharmacopoeial references. The absence of any discoloration or foreign particles indicates good purity and storage stability of the raw material.

**b) Melting Point**

The melting point of the drug is a key indicator of its purity and thermal behavior. The average melting point of Metoclopramide Hydrochloride was determined using the capillary method, performed in triplicate to ensure reproducibility. The observed melting point was 180°C, which falls within the reported standard range of 182–184°C, confirming the authenticity and purity of the drug substance.

**c) Solubility Profile**

Solubility analysis is essential for determining the appropriate medium for drug release and absorption. Metoclopramide Hydrochloride was tested for solubility in different solvents, including acidic, neutral, and basic media. The results revealed that the drug exhibits higher solubility in acidic (0.1 N HCl) and aqueous media, while its solubility significantly decreased in phosphate buffer, which mimics an alkaline environment. This indicates that Metoclopramide Hydrochloride is more soluble in the stomach's acidic environment, making it suitable for oral and buccal delivery systems where acidic conditions prevail.

**Table 4: Solubility of Metoclopramide Hydrochloride in Various Solvents**

| Sr. No. | Solvent | Solubility (mg/mL) |
|---|---|---|
| 1 | 0.1 N HCl | 5.1 mg/mL |
| 2 | Distilled Water | 5.0 mg/mL |
| 3 | Phosphate Buffer | 3.9 mg/mL |

The solubility order observed was: 0.1 N HCl > Distilled Water > Phosphate Buffer. This order clearly reflects the pH-dependent solubility behavior of Metoclopramide Hydrochloride, which must be considered when designing its formulation and predicting its bioavailability.

**UV Scanning of Metoclopramide Hydrochloride**

The UV spectrum of Metoclopramide Hydrochloride (10 µg/ml) was scanned between 200–400 nm using a UV spectrophotometer. The solution showed two prominent absorption maxima at 272.5 nm and 309 nm. Among these, 309 nm was consistently recorded as the λmax in triplicate, which matches well with literature values, confirming the drug's identity and purity.

**Construction of Calibration Curve**

A standard calibration curve of Metoclopramide Hydrochloride was developed in phosphate buffer pH 6.8. The absorbance values for concentrations ranging from 0 to 20 µg/ml were measured at 309 nm. The resulting graph showed a linear relationship with a regression equation of $y = 0.0325x + 0.005$ and a high correlation coefficient ($R^2 = 0.999$), indicating good linearity of the method within the tested range.

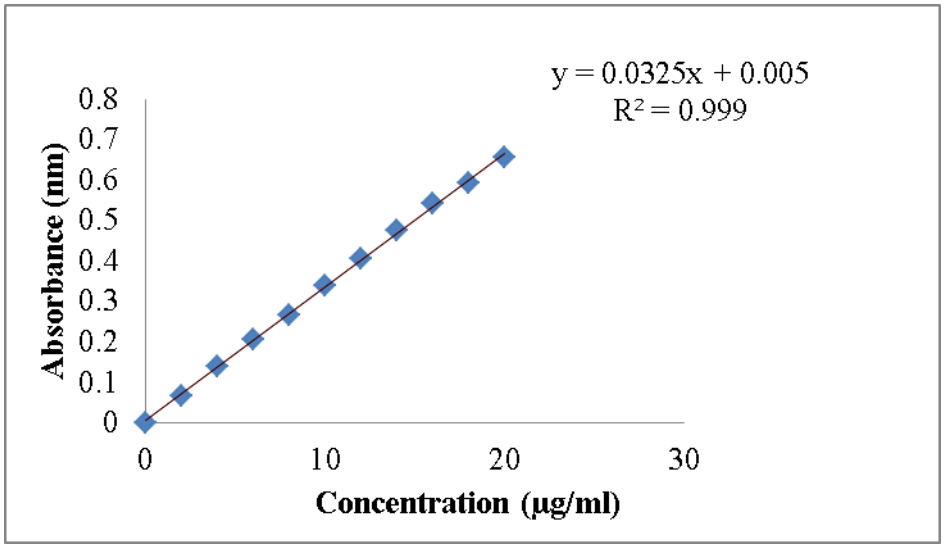


**Figure 1: Standard calibration curve of Metoclopramide Hydrochloride in PBS pH 6.8**

**Preformulation Studies**

**Drug-Polymer Compatibility Study by FT-IR**

FTIR analysis was conducted to assess any possible interactions between Metoclopramide Hydrochloride and the excipients used in the formulation. The spectra showed characteristic peaks of the drug, such as NH stretching (3393 $cm^{-1}$), C=O stretching (1639 $cm^{-1}$), and NH bending (1503 $cm^{-1}$). These peaks were also present in the formulation spectra with slight shifts but no disappearance or major changes, suggesting no chemical interaction between the drug and polymers.

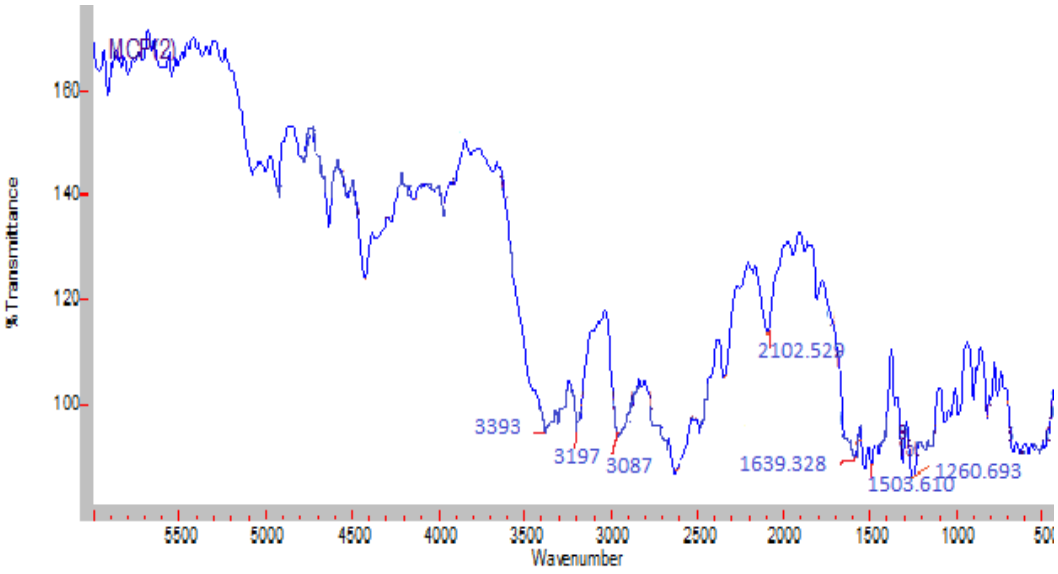


**Figure 2: IR spectra of Metoclopramide Hydrochloride**

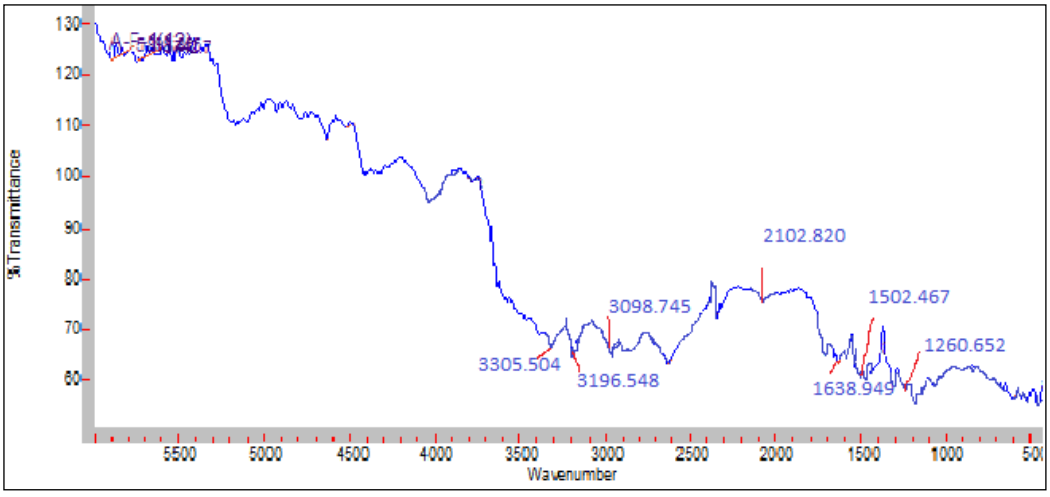


**Figure 3: IR spectra of Formulation**

**Drug-Polymer Compatibility Study by DSC**

Differential Scanning Calorimetry (DSC) was used to further confirm drug-excipient compatibility. The thermogram of Metoclopramide Hydrochloride showed a sharp endothermic peak at 97.27°C, indicating the loss of water of crystallization. A second major peak at 180.52°C corresponds to the melting point of the drug. These peaks were retained in the thermogram of the formulation, suggesting that the drug remains chemically stable and there is no interaction with the excipients. The crystalline nature and thermal behavior of the drug were preserved in the formulation.

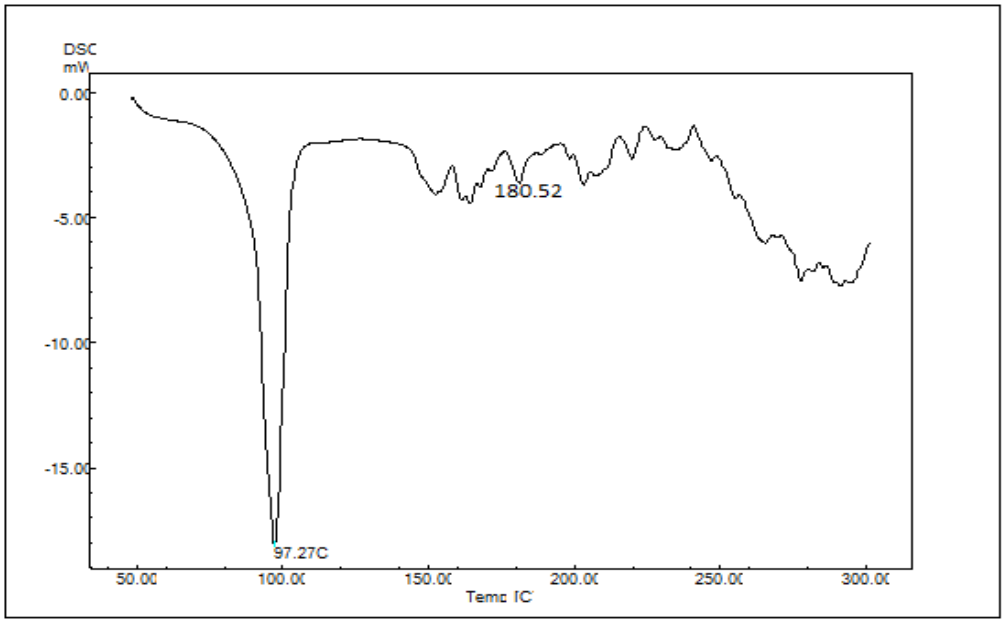


**Figure 4: DSC Analysis of Metoclopramide Hydrochloride**

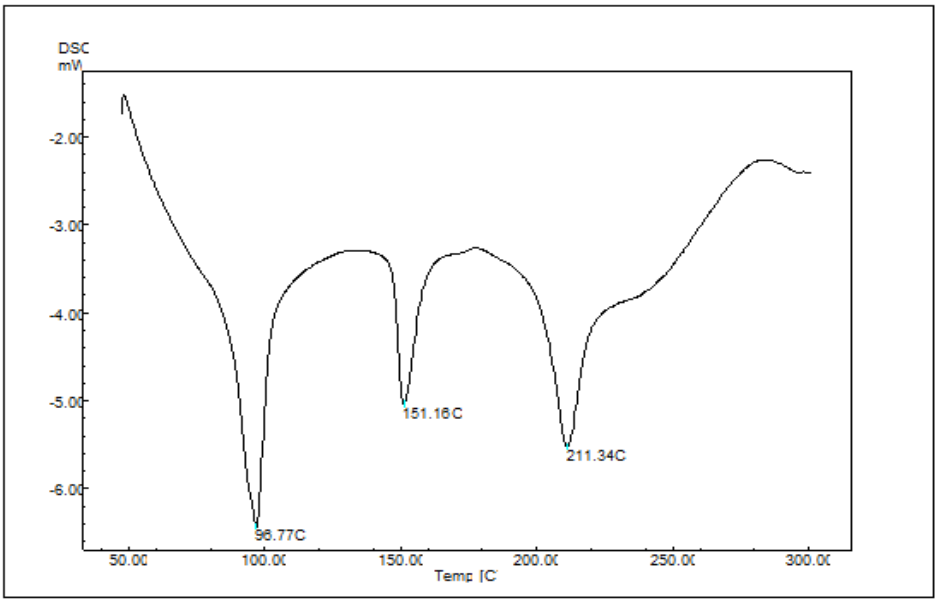


**Figure 5: DSC Analysis of Tablet Formulation**

**Evaluation of Precompression Parameters of Powder Blend**

The powder blends of all nine formulations (F1–F9) were subjected to precompression evaluation to assess their flow and packing characteristics, which are critical for consistent tablet production.

**Angle of Repose**

The angle of repose for the formulations ranged between 20.75° ± 0.92 (F7) and 24.80° ± 0.55 (F1), indicating good flowability of the powder blends. An angle of repose less than 30° typically signifies excellent to good flow properties, essential for uniform die filling and smooth tablet compression.

**Bulk Density and Tapped Density**

The bulk density of the blends was found between 0.386 ± 0.004 g/ml (F5) and 0.451 ± 0.003 g/ml (F3), while the tapped density ranged from 0.471 ± 0.003 g/ml to 0.540 ± 0.005 g/ml. These values reflect adequate packing ability of the powder, indicating minimal porosity and suitability for direct compression without segregation or flow issues.

**Compressibility Index (Carr's Index)**
The compressibility index values ranged from 14.26 ± 0.55% to 19.44 ± 0.58%, with most values falling below 20%, suggesting acceptable compressibility. These results support the suitability of the blends for tablet formation with minimal compression problems.

**Hausner's Ratio**
Hausner's ratio values were observed between 1.16 ± 0.012 and 1.24 ± 0.008, indicating good flow properties. A Hausner's ratio below 1.25 is indicative of freely flowing powders, further confirming the appropriateness of the blends for tablet manufacturing.

**Table 5: Rheological properties of powder blend of F1 to F9**

| Batch | Angle of Repose (°)* ± S.D | Bulk Density (g/ml)* ± S.D | Tapped Density (g/ml)* ± S.D | Compressibility Index (%)* ± S.D | Hausner's Ratio* ± S.D |
|---|---|---|---|---|---|
| F1 | 24.80 ± 0.55 | 0.445 ± 0.005 | 0.521 ± 0.003 | 14.58 ± 0.196 | 1.17 ± 0.012 |
| F2 | 23.21 ± 0.31 | 0.435 ± 0.005 | 0.540 ± 0.005 | 19.44 ± 0.583 | 1.24 ± 0.008 |
| F3 | 23.26 ± 0.31 | 0.451 ± 0.003 | 0.526 ± 0.004 | 14.26 ± 0.553 | 1.16 ± 0.012 |
| F4 | 22.76 ± 0.12 | 0.423 ± 0.003 | 0.507 ± 0.006 | 16.57 ± 0.705 | 1.19 ± 0.012 |
| F5 | 24.48 ± 0.41 | 0.386 ± 0.004 | 0.471 ± 0.003 | 18.05 ± 0.799 | 1.22 ± 0.008 |
| F6 | 23.53 ± 0.45 | 0.398 ± 0.006 | 0.490 ± 0.003 | 18.77 ± 0.525 | 1.23 ± 0.016 |
| F7 | 20.75 ± 0.92 | 0.423 ± 0.008 | 0.512 ± 0.003 | 17.38 ± 0.745 | 1.21 ± 0.016 |
| F8 | 22.12 ± 0.40 | 0.436 ± 0.008 | 0.535 ± 0.004 | 18.50 ± 0.617 | 1.23 ± 0.012 |
| F9 | 22.67 ± 0.62 | 0.422 ± 0.004 | 0.510 ± 0.005 | 17.25 ± 0.642 | 1.21 ± 0.012 |

Note: All values represent mean ± standard deviation (n = 3).

**Post-Compression Evaluation of Buccoadhesive Tablet Formulations**
The post-compression evaluation of all nine buccoadhesive tablet formulations of Metoclopramide Hydrochloride revealed consistent and acceptable physicochemical properties. The thickness of the tablets ranged between 2.45 ± 0.029 mm to 2.47 ± 0.037 mm, and the diameter remained uniform at around 6.0 mm, indicating uniform compression across batches. The hardness values ranged from 5.13 ± 0.18 to 6.03 ± 0.12 kg/cm², confirming adequate mechanical strength for handling. Friability values were well below 1% (0.371% to 0.717%), indicating the tablets had sufficient resistance to abrasion. The weight variation for all batches was within the acceptable limit (79.55 ± 1.13 mg to 80.08 ± 0.21 mg), complying with pharmacopeial standards. Drug content uniformity across batches was satisfactory, ranging from 97.16 ± 0.59% to 99.50 ± 0.31%, indicating uniform distribution of the drug within each formulation. Overall, all tablet batches passed the evaluation tests, confirming their suitability for further studies.

**Table 6: Evaluation parameters of formulations**

| Formulation Code | Thickness (mm) ± S.D. | Hardness (kg/cm²) ± S.D. | Friability (%) | Weight (mg) ± S.D. | Drug Content (%) ± S.D. |
|---|---|---|---|---|---|
| F1 | 2.46 ± 0.038 | 5.43 ± 0.41 | 0.621 | 79.9 ± 1.64 | 97.16 ± 0.59 |
| F2 | 2.45 ± 0.029 | 5.56 ± 0.41 | 0.717 | 80.0 ± 0.32 | 98.82 ± 0.17 |
| F3 | 2.45 ± 0.046 | 5.73 ± 0.24 | 0.622 | 80.05 ± 0.11 | 97.99 ± 0.12 |
| F4 | 2.47 ± 0.032 | 5.46 ± 0.36 | 0.598 | 80.05 ± 0.23 | 99.50 ± 0.31 |
| F5 | 2.47 ± 0.037 | 5.73 ± 0.20 | 0.433 | 80.0 ± 0.48 | 98.78 ± 0.21 |
| F6 | 2.46 ± 0.046 | 6.03 ± 0.12 | 0.474 | 79.9 ± 1.25 | 98.54 ± 0.22 |
| F7 | 2.45 ± 0.037 | 5.76 ± 0.28 | 0.371 | 79.55 ± 1.13 | 97.67 ± 0.27 |
| F8 | 2.46 ± 0.040 | 5.73 ± 0.20 | 0.434 | 79.95 ± 1.65 | 97.75 ± 0.52 |
| F9 | 2.45 ± 0.038 | 5.13 ± 0.18 | 0.495 | 80.08 ± 0.21 | 99.11 ± 0.99 |

*Average of three values (n=3) ± Standard Deviation:

**Evaluation of Surface pH, Swelling Index, and Mucoadhesive Strength of Buccoadhesive Tablets**
**Surface pH Study:** The surface pH of all formulations ranged from 5.97 ± 0.06 to 6.30 ± 0.08, which is close to the natural salivary pH (5.5–7.0). This suggests that the buccoadhesive tablets are unlikely to cause irritation or discomfort upon administration, making them suitable for buccal use. All formulations showed surface pH values within the safe range, indicating good biocompatibility.

**Swelling Index Study:** The swelling behavior of the formulations was assessed over 8 hours. It was observed that the swelling index increased with time, and higher polymer content (particularly Carbopol 940 and guar gum) led to greater swelling. The trend observed in swelling capacity was F9 > F8 > F7 > F6 > F5 > F4 > F3 > F2 > F1. Maximum swelling index was observed in F9 (448.76 ± 0.49%), while F1 showed the lowest (379.36 ± 0.35%). The increased swelling in F9 was due to the higher concentration of hydrophilic polymers that absorb water and form a gel layer on the tablet surface.
**Mucoadhesive Strength:** Mucoadhesive strength was evaluated using sheep buccal mucosa. The strength increased with polymer concentration, especially with the presence of Carbopol 940 and guar gum. Formulation F9 exhibited the highest mucoadhesive strength (47.58 ± 0.28 g) due to its enhanced swelling and gel formation, which promotes better adhesion. In contrast, F1 had the lowest strength (9.4 ± 0.37 g), attributed to its lower polymer content and poor gel consistency.

**Table 7: Surface pH, Mucoadhesive Strength, and Swelling Index (8 hr)**

| Formulation | Surface pH ± SD | Mucoadhesive Strength (g) ± SD | Swelling Index at 8 hr (%) ± SD |
|---|---|---|---|
| **F1** | 6.06 ± 0.12 | 9.4 ± 0.375 | 379.36 ± 0.35 |
| **F2** | 6.18 ± 0.16 | 10.35 ± 0.410 | 397.65 ± 0.57 |
| **F3** | 6.04 ± 0.12 | 14.38 ± 0.520 | 412.73 ± 0.85 |
| **F4** | 5.97 ± 0.06 | 22.76 ± 0.583 | 387.51 ± 0.72 |
| **F5** | 6.16 ± 0.12 | 23.91 ± 0.635 | 413.02 ± 0.30 |
| **F6** | 6.07 ± 0.12 | 28.02 ± 0.162 | 429.16 ± 0.48 |
| **F7** | 6.08 ± 0.06 | 36.57 ± 0.537 | 423.45 ± 0.31 |
| **F8** | 6.13 ± 0.06 | 39.88 ± 0.577 | 450.79 ± 0.94 |
| **F9** | 6.30 ± 0.08 | 47.58 ± 0.283 | 448.76 ± 0.49 |

Values are the mean of three determinations (n = 3) ± Standard Deviation.

**In-vitro Release Profile Studies**
The in-vitro drug release profile of formulations F1, F2, and F3 was studied using a USP type-II (paddle) dissolution apparatus in phosphate buffer (pH 6.8) over a period of 9 hours. All three formulations exhibited a gradual and sustained drug release. F1 showed a cumulative drug release of 86.70% by the end of 9 hours, while F2 exhibited a slightly higher release of 88.30%. Among all, F3 demonstrated the highest cumulative drug release of 92.34%, indicating a better release performance. The release data confirm the effect of polymer concentration on drug release and establish F3 as the most efficient formulation in sustaining drug delivery.

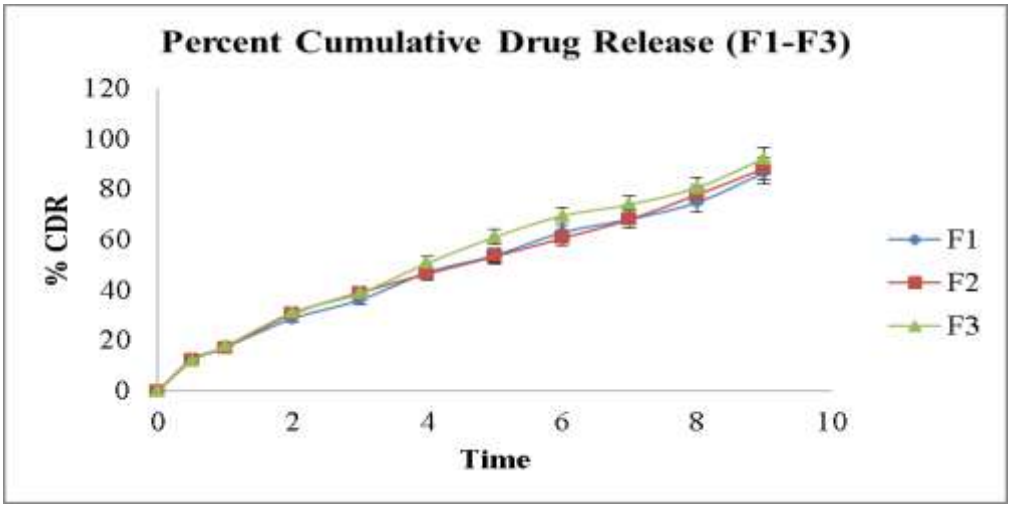


**Figure 6: Percent Cumulative Drug Release F1-F3**

The formulation batch F1, F2 and F3 contain same quantity of Carbopol 940 and variable quantity of guar gum i.e. (7.5%, 15% and 22.5%) respectively. The in vitro release profile was obtained 74.83%, 77.84% and 80.75% for F1, F2 and F3 respectively. This clearly indicates that on increasing the amount of guar gum (7.5%, 15%, and 22.5%) by keeping the constant amount of Carbopol 940 (12.5%), the release profiles is also increases.
The in-vitro drug release studies for formulation batches F4, F5, and F6 revealed a progressive increase in drug release with higher concentrations of guar gum, while keeping Carbopol 940 constant at 18.75%. Formulation F4 with 7.5% guar gum showed a release of 81.94%, F5 with 15% released 84.58%, and F6 with 22.5% released 87.69% over 8 hours. This trend clearly indicates that increasing the concentration of guar gum enhances the drug release rate due to improved swelling and hydration capacity, contributing to more efficient matrix erosion and diffusion.

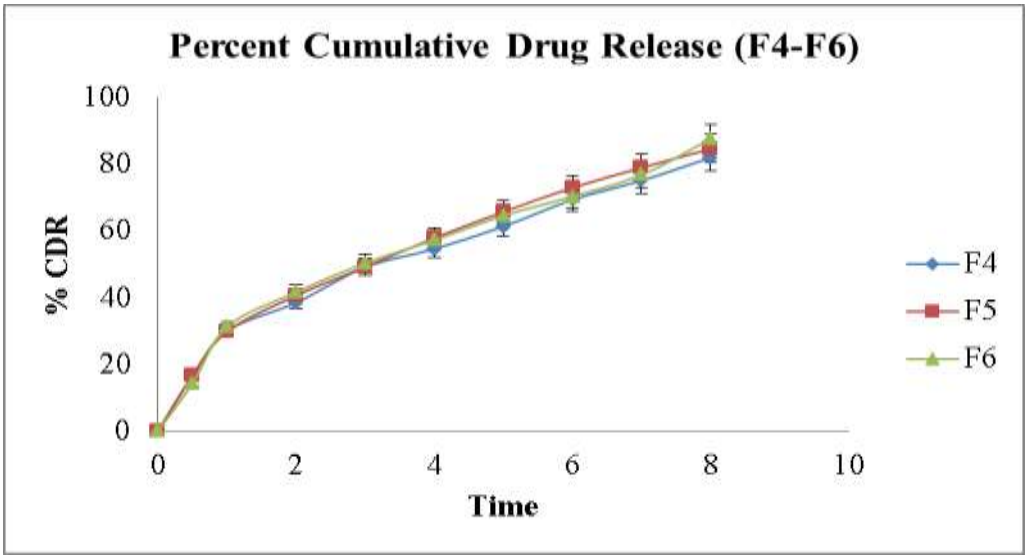


**Figure 7: Percent Cumulative Drug Release F4-F6**

Similarly, formulations F7, F8, and F9, all containing a constant 25% of Carbopol 940 and varying guar gum concentrations (7.5%, 15%, and 22.5% respectively), demonstrated increasing drug release profiles. F7 released 90.80%, F8 achieved 94.35%, and F9 recorded the highest release at 100.41%. This consistent rise in drug release across all three formulations further confirms the positive influence of higher guar gum content on drug diffusion and matrix dissolution, validating its role as a release-modifying polymer in buccal tablet formulations.

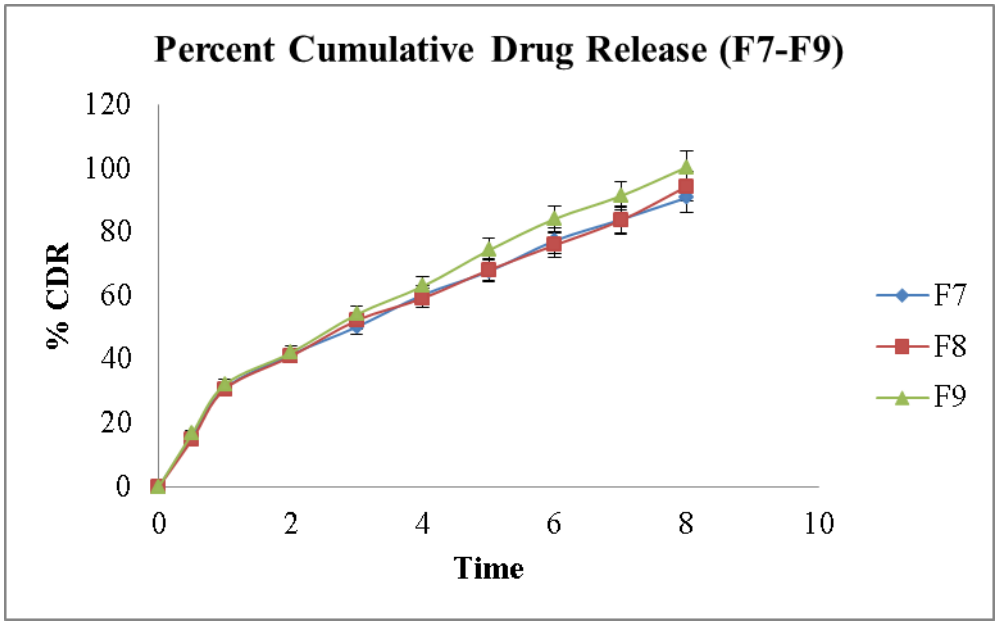


**Figure 8: Percent Cumulative Drug Release F7-F9**

**Permeation Study**

The permeation of Metoclopramide Hydrochloride through sheep buccal mucosa was studied to assess drug transport from buccoadhesive tablets. The mucosa was selected due to its pH similarity with human saliva. The flux values for various formulations ranged from 0.437 to 0.579 mg/cm²/h, with F8 showing the highest flux. The corresponding diffusivity values ranged from 0.0221 to 0.0331 cm²/h. The results indicate effective permeation of the drug, likely involving both ionized and unionized forms, supporting the suitability of the buccal route for sustained delivery.

**Drug Release Kinetics**

Drug release kinetics were evaluated using the Korsemeyer-Peppas model, which showed good linearity with high $r^2$ values across all formulations. The release exponent 'n' values ranged between 0.518 and 0.671, indicating non-Fickian (anomalous) diffusion, governed by a combination of polymer swelling, diffusion, and erosion mechanisms. Both Carbopol 940 and guar gum formed hydrating gel layers upon contact with the dissolution medium, modulating the drug release rate. These findings confirm that drug release is controlled by the physical properties of the polymer matrix and the tablet geometry.

**Data Analysis Using Design Expert Software**

A $3^2$ full factorial design was employed to study the combined effects of Carbopol 940 (X1) and guar gum (X2) on mucoadhesive strength (ʃ) and drug release at 8 hours (Rel8h). Traditional trial-and-error methods were replaced with statistical optimization using Design Expert® 8.0.7.1 software, enabling a more efficient and robust formulation approach. The experimental design revealed that increasing both polymers significantly enhanced ʃ and Rel8h values, confirmed by high regression coefficients ($R^2 = 0.9980$ for ʃ and 0.9968 for Rel8h). ANOVA results ($p < 0.05$) validated the statistical significance of the models. Polynomial equations and response surface plots clearly depicted the positive influence of polymer concentration on formulation performance, demonstrating the utility of factorial design in optimizing buccal tablet characteristics.

**Table 8: Design Summary**

| Factor | Name | Unit | Type | Coded Level | | | Actual Level | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Low | Medium | High | Low | Medium | High |
| $X_1$ | CP | Mg | Numerical | -1 | 0 | +1 | 10 | 15 | 20 |
| $X_2$ | Guar Gum | Mg | Numerical | -1 | 0 | +1 | 6 | 12 | 18 |

**Table 9: The responses of all formulations**

| Formulations | $X_1$ | $X_2$ | ʃ(g) | $Rel_{8h}$(%) |
|---|---|---|---|---|
| **F1** | -1 | -1 | 9.4 | 74.83 |
| **F2** | -1 | 0 | 10.35 | 77.84 |
| **F3** | -1 | +1 | 14.42 | 80.75 |
| **F4** | 0 | -1 | 22.76 | 81.94 |
| **F5** | 0 | 0 | 23.91 | 84.58 |
| **F6** | 0 | +1 | 28.02 | 87.69 |
| **F7** | +1 | -1 | 36.57 | 90.80 |
| **F8** | +1 | 0 | 39.70 | 94.35 |
| **F9** | +1 | +1 | 47.58 | 100.41 |

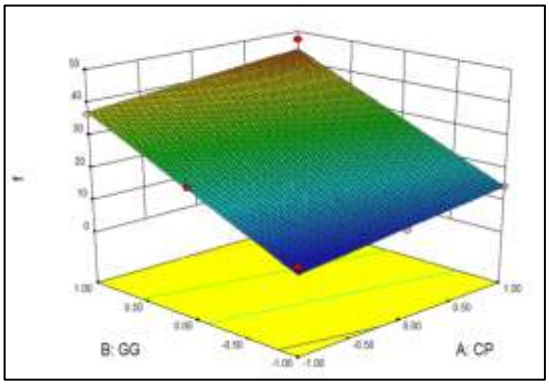


**Figure 9: Response Surface Plot for f**

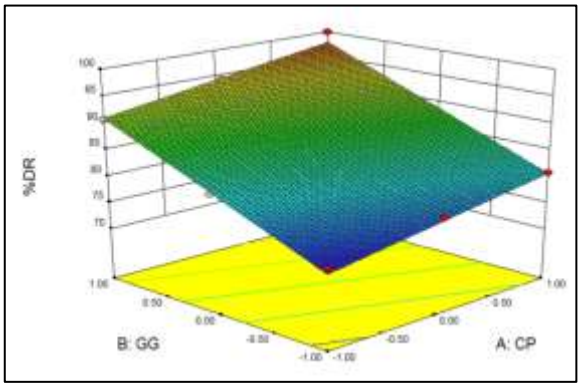


**Figure 10: Response Surface Plot for $rel_{8h}$**

**Stability Studies**

Stability studies of the optimized buccoadhesive tablet formulation were conducted under accelerated conditions (40 °C ± 2 °C / 75% RH ± 5%) and refrigeration, with evaluations at 10, 20, and 30 days. Parameters such as appearance, weight variation, friability, thickness, hardness, drug content, surface pH, and in vitro drug release were monitored. Results indicated no significant changes in any of the tested parameters throughout the study period, confirming the formulation's stability and consistent drug release profile over time.

**In vivo Pharmacological study:** [58-64]

**Experimental Animals**

**Animal Selection and Housing Conditions**

New Zealand White rabbits were selected as the experimental animal model owing to their well-developed buccal mucosal surface, ease of handling, and established relevance in buccal drug delivery and pharmacokinetic studies. A total of fourteen (14) healthy rabbits of either sex, weighing between 2.0 and 2.5 kg, were employed in the present investigation.The animals were housed individually in clean, well-vetilated standard polypropylene cages under controlled laboratory conditions. Environmental parameters were maintained at a temperature of 22 ± 2 °C, relative humidity of 55 ± 10%, and a 12-hour light/dark cycle throughout the study period. Animals were provided with a standard laboratory pellet diet and potable water ad libitum. All housing and husbandry practices were in accordance with CPCSEA recommendations.\

**Procurement, Acclimatization, and Ethical Approval**

The experimental animals were procured from a CPCSEA-registered breeding facility. Upon arrival, all rabbits were acclimatized to laboratory conditions for a minimum period of seven days prior to the commencement of the study. During this acclimatization period, animals were handled daily to familiarize them with human contact and to minimize stress during experimental procedures.

The entire experimental protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of HSBPVT's Faculty of Pharmacy, Kashti, Ahilyanagar – 414701, Maharashtra. The study was conducted in strict accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines.

- Project Proposal Number: 1697/PO/Re/S/13/CPCSEA/2025/02
- IAEC Approval Date: 25th August 2025

**General Observations and Animal Tolerability**

The optimized buccal tablet formulation (F9) was well tolerated by all experimental animals throughout the study period. No signs of distress, abnormal behavior, changes in food or water consumption, or significant body weight variations were observed. Visual examination of the buccal mucosa revealed no evidence of erythema, ulceration, edema, or

inflammation, indicating excellent mucosal compatibility of the formulation. Similarly, animals receiving the placebo tablet showed no adverse physiological responses, confirming the safety of the buccal dosage form.

**Experimental Design**

**Grouping and Treatment Plan**

The acclimatized animals were randomly divided into three experimental groups to evaluate the in vivo performance of the optimized buccal formulation (F9) in comparison with a marketed oral formulation.

- Group G1 (n = 2): Placebo buccal tablet (control group)
- Group G2 (n = 6): Optimized buccal tablet (F9) of Metoclopramide Hydrochloride
- Group G3 (n = 6): Marketed oral tablet of Metoclopramide Hydrochloride

Group G1 served as the control to assess any physiological or behavioral effects associated with the buccal dosage form in the absence of the active drug. Groups G2 and G3 were used to evaluate buccal and oral pharmacokinetic profiles, respectively, enabling comparative assessment of drug absorption and bioavailability.

**Table 10: Experimental Design and Grouping of Animals**

| Group | Treatment Administered | Route of Administration | Purpose of study | No. of Rabbits (n) |
|---|---|---|---|---|
| G1 | Placebo buccal tablet | Buccal | Control group to assess physiological and behavioral effects of buccal dosage form | 2 |
| G2 | Optimized buccal tablet (F9) of Metoclopramide HCl | Buccal | Evaluation of buccal residence time, absorption, and pharmacokinetic profile | 6 |
| G3 | Marketed oral tablet of Metoclopramide HCl | Oral | Comparative pharmacokinetic and bioavailability assessment with buccal formulation | 6 |

**Buccal Residence Time**

The in vivo mucoadhesive performance of the optimized buccal tablet was evaluated by determining its residence time in the buccal cavity. Formulation F9 exhibited a significantly prolonged residence time (6.42 ± 0.58 h) compared with the placebo tablet (1.18 ± 0.22 h) ($p < 0.001$). The enhanced retention of F9 can be attributed to the synergistic mucoadhesive properties of Carbopol 940 and Guar Gum, which undergo hydration and swelling upon contact with saliva, promoting intimate contact with the buccal mucosa. Prolonged retention is essential for sustained drug release and efficient transmucosal absorption, thereby improving therapeutic performance.

**Table 10: Buccal Residence Time of Buccal Tablets**

| **Group** | **Treatment** | **Buccal Residence Time (h)** |
|---|---|---|
| G1 | G1 – Placebo buccal tablet | 1.18 ± 0.22 |
| G2 | G2 – Optimized buccal tablet (F9) | 6.42 ± 0.58*** |
| G3 | G3 – Marketed oral tablet | NA |

**NA =** Not applicable (oral formulation is not retained in the buccal cavity)

**$p < 0.001$ compared with placebo buccal tablet (G1)

**Blood Withdrawal Protocol**

To minimize animal stress and adhere strictly to CPCSEA/IAEC guidelines, a staggered blood sampling design was adopted. Each rabbit was subjected to blood withdrawal at only two time points, ensuring animal welfare while allowing complete pharmacokinetic profiling when data from all animals were combined.

Approximately 0.5 mL of blood per sample was collected from the marginal ear vein using sterile techniques. The total blood volume withdrawn from any animal did not exceed 3.5–4.0 mL within 24 hours, which is well below the permissible limit of 10% of total circulating blood volume. After each collection, gentle pressure was applied with sterile gauze to prevent hematoma formation. Animals were closely monitored for signs of discomfort, bleeding, or stress following sampling.

**Table 11: Blood Sampling Schedule**

| Rabbit Number | Sampling Time Points (Hours) | | | | | |
|---|---|---|---|---|---|---|
| Rabbit 1 | 0.5 | 2 | 4 | 8 | 12 | 24 |
| Rabbit 2 | ✓ | | | ✓ | | |
| Rabbit 3 | ✓ | | | ✓ | | |
| Rabbit 4 | | ✓ | | | ✓ | |
| Rabbit 5 | | ✓ | | | ✓ | |
| Rabbit 6 | | | ✓ | | | ✓ |

**Plasma Drug Concentration–Time Profile**

The plasma concentration–time profile demonstrated effective absorption of Metoclopramide Hydrochloride following buccal administration of formulation F9. Detectable plasma drug levels were observed within 0.5 h, confirming rapid onset of absorption through the buccal mucosa. Plasma concentrations gradually increased and reached a maximum level at 8 h, indicating controlled drug release and sustained absorption. In contrast, the marketed oral formulation produced higher initial plasma concentrations but showed a rapid decline at later time points. The buccal formulation maintained significantly higher plasma drug levels at 8 h and 24 h, suggesting prolonged systemic availability and effective avoidance of hepatic first-pass metabolism.

**Table 12: Plasma Drug Concentration (ng/mL) After Buccal and Oral Administration**

| Time (h) | G1 – Placebo | G2 – Buccal F9 | G3 – Oral |
|---|---|---|---|
| 0.5 | ND | 48.6 ± 5.2* | 62.4 ± 6.1 |
| 2 | ND | 96.3 ± 8.4* | 118.7 ± 9.5 |
| 8 | ND | 168.4 ± 12.1** | 109.2 ± 9.8 |
| 24 | ND | 118.9 ± 9.7*** | 41.3 ± 5.4 |

**ND = Not detected (absence of active drug in placebo group)** *p < 0.05, **p < 0.01, **p < 0.001 (comparison between G2 and G3)

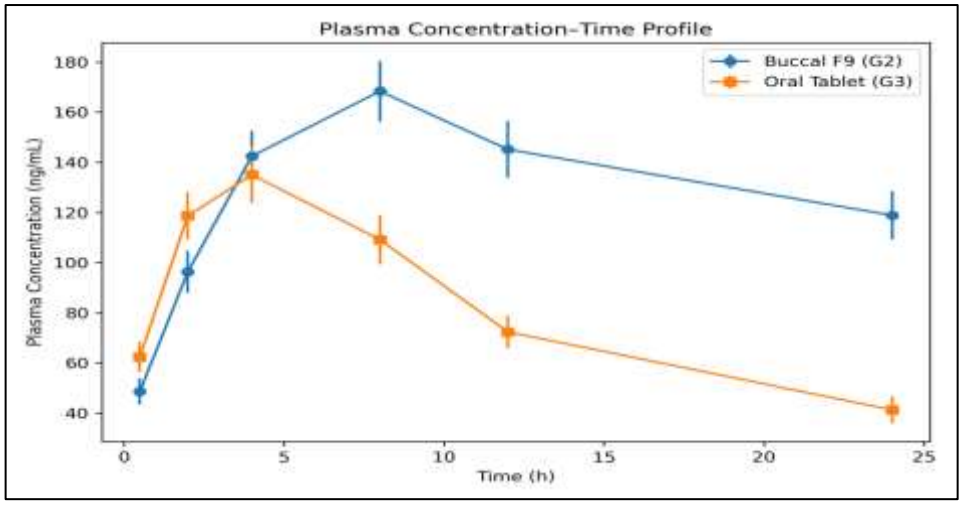


**Figure 11: Plasma concentration–time profiles of Metoclopramide Hydrochloride following administration of optimized buccal tablet F9 (G2) and marketed oral tablet (G3) in rabbits**

**Comparative Pharmacokinetic Evaluation**

Pharmacokinetic analysis revealed notable differences between buccal and oral administration. The optimized buccal tablet exhibited a Cmax of 172.6 ± 12.8 ng/mL, which was comparable to that of the marketed oral formulation (185.4 ± 14.2 ng/mL). However, the buccal formulation showed a significantly delayed Tmax (8.0 ± 0.6 h) compared to the oral tablet (2.1 ± 0.4 h), reflecting its sustained-release characteristics. Furthermore, the buccal formulation produced a significantly higher $AUC_{0–24}$ value (2946 ± 185 ng·h/mL) than the oral formulation (2018 ± 164 ng·h/mL) ($p < 0.001$), indicating enhanced systemic exposure and improved bioavailability.

**Table 13: Pharmacokinetic Parameters of Metoclopramide Hydrochloride**

| Parameter | G1 – Placebo | G2 – Buccal F9 | G3 – Oral |
|---|---|---|---|
| **Cmax (ng/mL)** | ND | 172.6 ± 12.8 | 185.4 ± 14.2 |
| **Tmax (h)** | NA | 8.0 ± 0.6*** | 2.1 ± 0.4 |
| **$AUC_{0–24}$ (ng·h/mL)** | NA | 2946 ± 185*** | 2018 ± 164 |

ND = Not detected; NA = Not applicable, **p < 0.001 (comparison between G2 and G3)

**Maximum Plasma Concentration (Cmax)**

Both formulations achieved therapeutically relevant plasma concentrations. Although the oral tablet exhibited a slightly higher peak concentration, the difference was not substantial. The buccal formulation achieved comparable systemic exposure while avoiding rapid plasma fluctuations, which may contribute to improved therapeutic consistency and reduced incidence of concentration-related adverse effects.

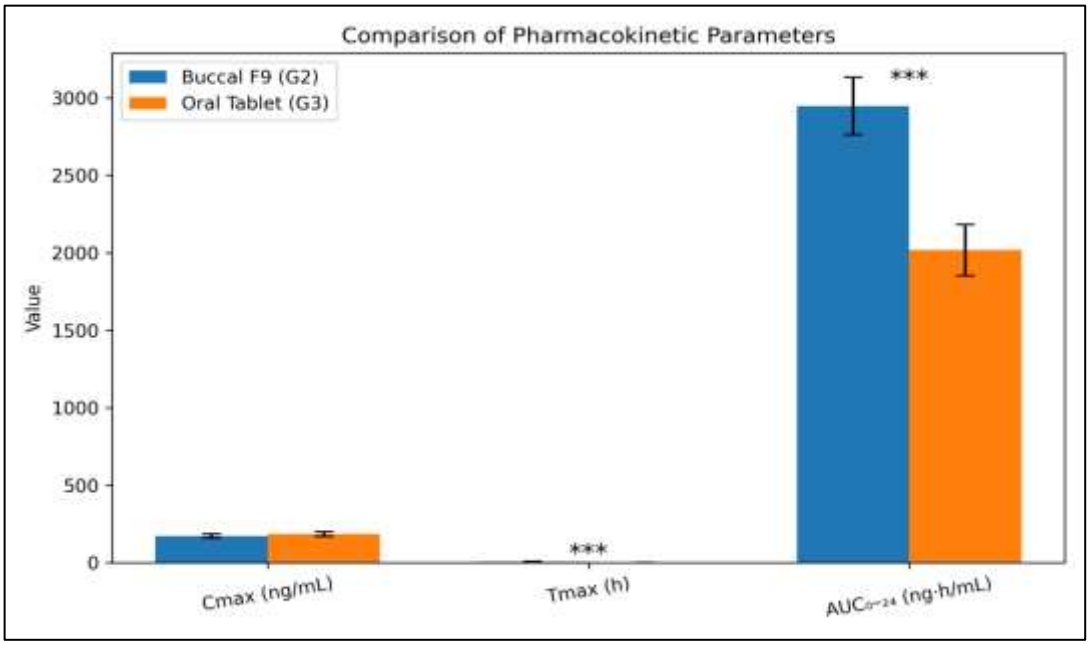


**Figure 12: Comparison of peak plasma concentration (Cmax), Tmax values and $AUC_{0–24}$ values of Metoclopramide Hydrochloride following buccal (G2) and oral (G3) administration**

**Time to Reach Maximum Plasma Concentration (Tmax)**

The significantly prolonged Tmax observed with formulation F9 confirms its controlled-release behavior and gradual transmucosal drug absorption. In contrast, the marketed oral formulation displayed rapid gastrointestinal absorption and early attainment of peak plasma concentration. The delayed Tmax of the buccal formulation is advantageous for maintaining prolonged antiemetic activity and reducing dosing frequency.

**Area Under the Curve ($AUC_{0–24}$)**

The significantly higher $AUC_{0–24}$ obtained with the optimized buccal tablet demonstrates superior overall drug exposure compared with the oral formulation. This enhancement in bioavailability can be attributed to prolonged buccal residence, sustained drug release, and direct absorption into systemic circulation, thereby bypassing hepatic first-pass metabolism. The findings confirm the effectiveness of buccal drug delivery in improving the pharmacokinetic performance of Metoclopramide Hydrochloride.

The in vivo findings clearly demonstrate the superiority of the optimized buccal tablet formulation (F9) over conventional oral administration. The formulation exhibited prolonged buccal retention, sustained plasma drug concentrations, delayed Tmax, and significantly enhanced bioavailability. These improvements can be attributed to the combined mucoadhesive and controlled-release properties of Carbopol 940 and Guar Gum, which facilitated prolonged contact with the absorption site and continuous drug permeation across the buccal mucosa. Overall, the optimized buccal tablet represents a promising alternative delivery system for Metoclopramide Hydrochloride, offering improved pharmacokinetic performance and potential therapeutic advantages in long-term antiemetic therapy.

**CONCLUSION**

The present investigation successfully developed and optimized mucoadhesive buccal tablets of Metoclopramide Hydrochloride using Carbopol 940 and Guar Gum as mucoadhesive polymers through a $3^2$ full factorial design approach. All formulations demonstrated acceptable physicochemical properties, including hardness, friability, weight variation, drug content uniformity, surface pH, swelling behavior, and mucoadhesive strength. The optimized formulation (F9) exhibited superior performance with desirable swelling characteristics, strong mucoadhesion, and controlled drug release. Drug release followed the Korsmeyer–Peppas model, indicating a non-Fickian diffusion mechanism. FTIR studies

confirmed the absence of significant drug–excipient interactions, while accelerated stability studies established the stability of the optimized formulation under storage conditions. In vivo studies in New Zealand White rabbits further validated the effectiveness of the optimized formulation. Formulation F9 demonstrated prolonged buccal residence time, excellent mucosal compatibility, and sustained systemic drug absorption. Pharmacokinetic evaluation revealed a significantly delayed Tmax and enhanced $AUC_{0–24}$ compared with the marketed oral formulation, indicating prolonged drug release, improved bioavailability, and effective avoidance of hepatic first-pass metabolism. Sustained plasma drug concentrations were maintained for up to 24 h, confirming the ability of the formulation to provide extended therapeutic coverage. Overall, the optimized mucoadhesive buccal tablet formulation of Metoclopramide Hydrochloride offers a safe, stable, and effective alternative to conventional oral therapy. The combination of prolonged buccal retention, controlled drug release, and enhanced systemic availability highlights its potential as a promising platform for sustained antiemetic therapy and improved patient compliance.

**CONCFILCT OF INTREST:** The authors declare that there is no conflict of interest.

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