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Original Article

# To study the effect of HPMC and Carbopol in mucoadhesive buccal tablets of Meclizine hydrochloride using Central Composite Design: In-vitro Characterization

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**Abstract**

For the study, mucoadhesive buccal tablets containing Meclizine Hydrochloride (MCZ HCL) were designed to avoid first-pass metabolism and enhance its bioavailability while reducing the dose administration frequency. As a result, this work aimed to design, evaluate, and determine the optimum conditions for the bioadhesion and drug release. MCZ HCL mucoadhesive buccal tablets were prepared using multiple grades of HPMC, including HPMC 15 cps, 50 cps, 100 cps, and HPMC K4M, by the direct compression method. Ethyl cellulose was employed as a backing layer to facilitate the unidirectional flow of medication in the buccal region of the mouth. Using the central composite design (CCD), the drug delivery formulations undergo a thorough optimization process. The response surface and contour plots were generated, and grid searches and feasibility analyses were conducted to select the most effective formulations. The developed formulations underwent various tests to determine their physiochemical characteristics and *in-vitro* drug release. Optimized formulation containing HPMC 15 cps 24.63 mg and Carbopol 934P 4.17 mg showed $t_{50}$ in 5.6 h. Additionally, the optimized formulation's mucoadhesive strength was 7.04 ± 0.41, and its swelling index was 99.82% after 8 h. Furthermore, studies conducted with FTIR spectroscopy revealed no interactions between the drug and the excipient. According to short-term stability experiments performed on the promising formulation, there were no significant changes in the amount of drug present.

**Keywords:** Meclizine hydrochloride; central composite design; mucoadhesive buccal tablets; HPMC; Carbopol

## Introduction

Because of its many advantages over other methods of drug delivery, including simple consumption, self-medication, precise dosage, an adjustable and regulated dosing schedule, and high patient compliance with little risk of administration difficulty, the oral route of administration is the most prevalent and recommended method of drug delivery [1]. This method has several significant drawbacks, including the first-pass effect, enzymatic breakdown in the digestive tract, and a delayed commencement of action [2]. Alternatives such as sublingual dosing or mucoadhesive drug administration may be more suitable for avoiding these drawbacks [3].

For optimal therapeutic effect, mucoadhesive dose forms are designed to stick to the mucosal surface, where they will be retained for longer [4]. Mucoadhesive drug delivery systems include, but are not limited to, patches, gels, pills, films, discs, etc. [5]. The mucosal layer is a protective lining that lines many body parts, including the gastrointestinal tract (GIT), urogenital tract, ear, nasal passage, and airways. The GIT, the bronchi, and the intestines all have single-layered epithelium. At the same

time, the esophagus, the vagina, and the cornea all have multilayered stratified epithelium, and each of these is a possible target for mucoadhesive drug delivery systems [6,7].

Among these mucosal sites, the buccal mucosa has a high degree of vascularization that allows blood to drain directly into the jugular vein, preventing medicines from potentially being metabolized by the liver and GIT [8]. Therefore, the absorption of the medication through the mucosal lining of the buccal cavity is implied by the term "buccal delivery." The drug delivery system offers several notable benefits, including simpler drug administration, the ability to promptly terminate treatment in the event of unexpected adverse effects or crises, and the potential to incorporate enzyme inhibitors and penetration enhancers [9,10].

Patients and doctors alike favor the oral route as the most convenient and effective mode of drug administration. Patients typically accept oral self-medication due to its accessibility and convenience [11]. The buccal surface of the mouth cavity is considered to provide a feasible route for drug delivery with the goal of efficient systemic administration by bypassing first-pass drug metabolism related to the GIT and liver. The mucosal layer lining the mouth cavity receives adequate blood flow and is relatively permeable [12]. Increasing the bioavailability of drugs with poor oral bioavailability by administering them via the buccal route is a good strategy, and the buccal route is preferable to the oral route of dosing since it avoids the problems associated with the oral route [13]. Drugs with both local and systemic effects can be administered with this method. The mucosal site-specific release is achieved when the drug is employed for local activity, while systemic action necessitates drug absorption through the mucosal barrier and into the systemic circulation [14]. Buccal tablets are tiny and designed to be grasped in the mouth between the gum and cheek or in a cheek pouch, where they can be absorbed directly through the oral mucosa [15]. Buccal drug delivery is a secure and practical method of drug use since absorption can be rapidly prevented in the event of toxicity by withdrawing the drug from the buccal cavity. It's an alternative route of drug delivery for those who can't take their medication orally. Buccal administration is therefore recommended for mucosal adhesive dose forms such as adhesive tablets, sticky gels, and adhesive patches. This is why it's recommended to use mucosal adhesive dose forms for buccal administration, such as adhesive tablets, sticky gels, and adhesive patches.

Natural, semi-synthetic, and synthetic mucoadhesive polymers are all suitable for this delivery system since they become adhesive upon hydration [16]. Initiating deep contact with the mucosal layer, mucoadhesive materials (polymers) are activated by moisture, and medication release occurs gradually. When the mucoadhesive product comes into contact with the mucosal membrane, it expands and spreads, initiating deep contact with the mucosal layer [17]. Bioadhesive polymers like hydroxypropyl methylcellulose (HPMC) are semi-synthetic and non-toxic. HPMC is listed as GRAS (generally considered safe) in the FDA's database of inactive substances and is used to manufacture many different types of commercially available dosage forms. The viscosity of HPMC ranges from 3 to 100,000 mPa. HPMC is an ideal excipient for making buccal discs because of its biocompatibility, biodegradability, bioadhesion, and release rate retarding qualities [18].

The application of quality through Design is common in industry and research settings, and the Design of export (DOE) is widely utilized. It is a tool that helps formulate and design optimization problems by making it feasible to analyze several dependent and independent variables simultaneously. Box and Wilson were the ones who came up with the idea of a central composite design (CCD), which refers to a factorial or fractional factorial design that includes center points [19]. This research was conducted to develop and improve mucoadhesive buccal tablets of MCZ HCL by utilizing a variety of grades of HPMCs in various amounts and different ratios. Oral MCZ HCL has been utilized clinically for a significant amount of time. Tablets, capsules, and chewable tablet forms are the three distinct delivery methods that are at your disposal to purchase.

MCZ HCL is an antihistamine of the piperazine class and belongs to the first generation of antihistamines [20]. It has a molecular weight of 481.9 gm/mol. It is characterized as a biopharmaceutical classification system (BCS) class II, attributed to low solubility and high permeability. In addition to depressing effects on the central nervous system and local anesthetic, MCZ HCL is an antagonist at H1-

receptors. MCZ HCL decreases both the vestibular system's stimulation and the labyrinth's excitability. This approach might help relieve some of the acute symptoms of vertigo, such as nausea and a sensation of the room whirling around you.

In the same way, people who have been experiencing acute vertigo symptoms for more than five days should not be given this medication. The reflex that causes vomiting is centrally controlled, and it activates centers responsible for the chemoreceptor trigger zone. MCZ HCL is the medication of choice for the symptomatic treatment of vertigo and the prevention and treatment of nausea, vomiting, and dizziness associated with numerous disorders, including motion sickness. It is also the medicine of choice for the treatment of vertigo itself. It takes approximately an hour for MCZ to begin acting, and its effect might last anywhere from 8 h to 24 h. The plasma elimination half-life of MCZ HCL is 5-6 h. Take 25 to 50 mg MCZ HCL 1 hour before traveling to treat motion sickness. Take up to 100 mg of MCZ HCL each day in divided doses to treat vertigo and vestibular disorders. When treating children aged 2 to 6 years for motion sickness, a dose of 6.25 mg is administered, while a single dose of 12.5 mg is given to children aged 6 to 12 years. Oral formulations produce many drugs; nevertheless, making these medications could be challenging if the active ingredient has a low bioavailability [21]. MCZ HCL is not commercially available as a buccal mucoadhesive tablet. Therefore, it will be a different composition than the products available. This new formulation aims to prevent first-pass metabolism and improve bioavailability by reducing dosing frequency. This study was designed to formulate the different batches of mucoadhesive buccal tablets of MCZ HCL by using different polymers like HPMC and carbopol 934P, with various ratios to study the impact on *in-vitro* drug release along with their quality control evaluation.

**Materials and Methods**

Active ingredient (MCZ HCL) was provided ex-gratis by M/s Symed Labs Ltd. (Hyderabad). Ethylcellulose was received as a gift sample from M/s Loba Chemie Pvt. Ltd., Mumbai. Carbopol 934P was provided as a gift by Alkem Labs Pvt Ltd., Mumbai. All other materials employed during the studies were of analytical grade and were used as obtained.

*Pre-optimization studies*

The current research work involved the preparation of preliminary trial formulations of MCZ HCL buccal tablets employing synthetic polymers of various grades of HPMC (HPMC 15 cps, HPMC 50 cps, HPMC 100 cps, and HPMC K4M) in varying ratios. The direct compression method was adopted to formulate these formulations. A total of 20 batches of pre-optimized formulations were prepared, the composition of which is shown in Table 1.

The batch formulations correctly weighed all the components, including the active ingredient, the polymer, and the excipients. The mannitol and the drug of choice are thoroughly combined with the aid of a spatula made of stainless steel and some parchment paper. All ingredients, except the lubricant, were combined in an ascending sequence of weight in a polyethylene bag that had been inflated, and the mixture was blended for 10 min. After the materials had been properly combined, the lubricant was added and thoroughly mixed for another 2 min after the ingredients had been thoroughly mixed. The prepared mix of each formulation was pre-compressed on a 10-station rotating tablet-piercing machine (Clit, Ahmedabad) at a pressure of 0.5 tonnes and a turret speed of 2 rpm to form single-sided flat-faced tablets with an 8mm diameter layer. The final compression was carried out at a pressure of 3.5 tonnes and a turret speed of 2 rpm to manufacture Meclizine HCl buccal tablets. In this step, 50 mg of ethylcellulose powder was added to the mixture.

*Formulation characterization of Pre-optimization studies*

Formulated tablets were examined for a wide range of characteristics, including their friability, weight variation, hardness, homogeneity of the drug content, swelling index, surface pH, ex vivo mucoadhesive strength, in-vitro drug release, short-term stability (IR spectroscopy), and drug-excipient interaction.

**Table 1.** The Constituents of Pre-optimized formulations of MCZ HCL Buccal Tablets.

| Ingredients* (mg/tablet) | Formulation code | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AH 0 | AH 1 | AH 2 | AH 3 | AH 4 | BH 0 | BH 1 | BH 2 | BH 3 | BH 4 | CH 0 | CH 1 | CH 2 | CH 3 | CH 4 | DH 0 | DH 1 | DH 2 | DH 3 | DH 4 |
| **MCZ HCL** | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| **Carbopol 934 P** | --- | 2 | 4 | 6 | 8 | --- | 2 | 4 | 6 | 8 | --- | 2 | 4 | 6 | 8 | --- | 2 | 4 | 6 | 8 |
| **HPMC 15 cps** | 10 | 15 | 20 | 25 | 30 | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **HPMC 50 cps** | --- | --- | --- | --- | --- | 10 | 15 | 20 | 25 | 30 | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **HPMC 100 cps** | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | 10 | 15 | 20 | 25 | 30 | --- | --- | --- | --- | --- |
| **HPMC K4M** | --- | --- | --- | -- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | 10 | 15 | 20 | 25 | 30 |
| **Mannitol** | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| **Aspartame** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **SSF** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Flavour** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **MCC** | 43 | 36 | 29 | 22 | 15 | 43 | 36 | 29 | 22 | 15 | 43 | 36 | 29 | 22 | 15 | 43 | 36 | 29 | 22 | 15 |
| **Ethyl cellulose** | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| **Total weight** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** | **150** |

*Tabular amounts are given in milligrams
AH- HPMC 15 cps polymer-based formulation BH-HPMC polymer (50 cps) formulation.
CH-formulation with HPMC 100 cps polymer DH-HPMC K4M polymer-based formulation

*Hardness test*

It is an important quality control test to indicate tablet strength. During handling and transportation, the tablet should be resistant to mechanical stress. The crushing strength of tablets ($kg/cm^2$) was determined using a Monsanto hardness tester [22-25].

*Friability test*

Weighing 20 dust-free tablets and putting them in friabilator, the measurement procedure involved rotating the plastic cylinder vertically at 25 rpm for 4 min. After dusting, the weight of the remaining tablets was calculated, along with their percentage of friability (% weight loss).

*Thickness*

Three tablets were taken from each formulation batch, and a vernier caliper was used to determine the thickness of each tablet. The typical thickness was determined [22,23,25,26].

*Weight variation*

Twenty tablets were chosen randomly. Each of the 20 tablets was dusted before being placed on an electronic balance to ascertain its weight (in milligrams). Table weight data was evaluated to calculate the sample mean and percent deviation from the mean.

*Uniformity of drug content*

Equivalent to 1 mg of the drug was taken and put in a Stoppard 100 ml conical flask after five pills were weighed and finely ground in a glass mortar and pestle. After extracting the drug with 25 ml of methanol and vigorously swirling it on a mechanical gyratory shaker (100 rpm) for two hours, the absorbance at 232 nm is measured against a solvent blank. The medication is then filtered into a 50 ml volumetric flask using Whatman No.1 filter paper (mean pore diameter 1.5 µm) [25-28].

*Surface pH*

The tablets' surface pH was measured to learn more about the adverse effects in vivo. We aimed for a near-neutral surface pH because extremes in either direction can irritate the buccal mucosa. The tablets were immersed in 1 ml of distilled water for 2 h in glass test tubes. The pH was recorded after bringing a glass microelectrode near the tablet's surface and letting it equilibrate for 1 min [29-31].

*Swelling index*

Buccal tablets of MCZ HCL that had been individually produced and weighed were randomly selected from each formulation (W1). When measuring the rate buccal tablets swell, a phosphate buffer

with a pH of 6.8 is utilized. A measurement is taken to obtain the tablet's initial weight (W1). Afterward, the Petri dish containing the tablets and the phosphate buffer with a pH of 6.8 and a total volume of 6 ml was placed in an incubator adjusted to 37 ± 1º C. The tablets are taken out of the apparatus at various time intervals (0.0, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h) and wiped with filter paper, and then reweighed (w2) [32-34].

The formula below is used to compute the swelling index:

$$\text{Swelling index} = 100\ (w2-w1) / w1$$

*Mucoadhesive strength*

The bioadhesion testing apparatus was assembled in the laboratory. Using the bovine cheek pouch as a model mucosal membrane, the bioadhesive strength of the buccal tablets was determined using the "Modified Physical Balance Method." The method uses a buccal membrane from sheep as a model of the mucosal membrane [35-38]. A double-beam physical balancing determined it. The pan on the left was taken off. A thick thread of the appropriate length was used to hang from the left arm of a balance. The bottom side of the thread was used to knot a glass stopper with a consistent surface. Below the hanging glass stopper, a glass mortar that had been cleaned was placed. In this, the mortar was placed on top of a clean glass beaker that had a capacity of 500 ml, and inside of that, another glass beaker with a capacity of 50 ml was placed in an upside-down position and weighed with 50 gm to prevent floating. The pan control system involves placing a thermometer into a beaker with a capacity of 500 ml and periodically pouring hot water into an outer mortar that is filled with water. The weight on the right-hand side was exactly 5 gm higher than that on the left after the balance was corrected.

A weight of 5 gm was placed on the right-hand side of the balance, which allowed the two sides to be equalized. Within two hours of the sheep being slaughtered, fresh buccal mucosa from the sheep was collected from a local abattoir and used. After separating the mucosal membrane by removing the underlying fat and loose tissues, the membrane was rinsed with distilled water and then treated with phosphate buffer at a pH of 6.8 and 37 ºC.

After being cut into pieces and rinsed with phosphate buffer pH 6.8, the fresh buccal mucosa from sheep was used in the experiment. A portion of buccal mucosa was threaded over the protrusion in the Teflon block and then knotted with the mucosal side facing upwards using the thread. After that, the block was dropped into the glass beaker, which was then filled with phosphate buffer pH 6.8 maintained at 37 ± 1 ºC in order to keep the mucosal membrane moist. After that, this was kept under the left-hand setup of the balance. The tablet that would be evaluated for its mucoadhesion was then affixed to the cylinder hanging on the left side using a small amount of moisture. The beam used to maintain equilibrium was raised. The weight of 5 gm lying on the right pan was taken away. Because of this, the Teflon cylinder containing the tablet was brought down against the mucosa with a force of 5 gm.

After leaving the balance in this position for three minutes, the weights were gradually increased on the right pan until the tablet detached from the mucosal surface. The force necessary to remove the tablet from the mucosa equals the excess weight on the pan or the total weight minus 5 gm. Three trials of each tablet formulation were carried out as part of this investigation.

In-vitro drug release study

The study was conducted in USP type XXIII tablet dissolution test apparatus-II (Electrolab TDT-06N). Phosphate buffer with a pH of 6.8 makes up 900 ml of the dissolution medium and is performed at a temperature of 37 ± 0.5 ºC with a rotational speed of 50 rpm. Using cyanoacrylate adhesive, the backing layer of the buccal tablet was adhered to the glass disc. The disk was then positioned at the lowest possible point in the dissolution vessel. 5 ml of the sample was taken out of the dissolution medium at predetermined intervals and Filtered through a membrane filter disc with a pore size of 0.25 µm. Concentrations of the released drug were determined by UV spectrophotometrically at 272 nm [39-45].

*Preparation of buccal tablets as per experimental design*

Based on the outcome of pre-optimized studies, polymers such as HPMC 15 cps and Carbopol 934P were chosen and finally selected as the two critical influential factors. A central composite design (CCD) was employed, where the amounts of HPMC 15 cps (X1) and Carbopol 934P (X2) were studied at three levels each. Overall, 11 experimental runs were analyzed, each per the experimental design matrix in Table 2. CCD with two factors and three levels with three center points were applied to optimize the formulations. The response variables considered for the current Design of Expert (DoE) optimization studies encompassed mucoadhesive strength (gm) (Y1) and $t_{50}$% (time taken for 50% of drug release) (Y2). This experimental design generated a polynomial Equation. The regression coefficients of factors and their interactions were enumerated from the observed experimental results. The design of Expert data was analyzed mathematically, and the results pointed toward a first-order polynomial equation being a good fit.

**Table 2.** Central composite experimental design with measured responses of mucoadhesive buccal tablets of MCZ HCl.

| Run | HPMC 15cps mg (X1) | Carbopol 934 mg (X2) |
|---|---|---|
| 1 | 1 | -1 |
| 2 | 0 | 0 |
| 3 | 0 | 1 |
| 4 | -1 | 1 |
| 5 | 1 | 0 |
| 6 | -1 | 0 |
| 7 | 0 | -1 |
| 8 | 0 | 0 |
| 9 | 1 | 1 |
| 10 | -1 | -1 |
| 11 | 0 | 0 |

**Formulation characterization of optimization studies**

Buccal tablets were formulated as per the experimental design and evaluated for friability, weight variation, hardness, homogeneity of the drug content, swelling index, surface pH, mucoadhesive strength, and in-vitro drug release, as the procedure explained above.

*Data analysis and validation of experimental design*

The resulting response values for all factorial lots were entered into the Design Expert software (version 12, Stat-Ease Inc). Contour plots and three-dimensional (3D) response surface plots were constructed to understand the relationship of variables and their interactions. The compositions were optimized using the Design Expert software, keeping the independent factors within the selected range while the responses were set at the desired level. The desirability function was used to optimize the formulation, while checkpoint analysis performed design validation. Central Composite Design (CCD) analysis revealed that a two-factor, three-level approach yielded the best results for optimizing drug-loaded mucoadhesive buccal tablets. To determine the optimum concentrations of the two independent variables viz., HPMC 15 cps and Carbopol 934P that would have a significant impact on the two dependent variables such as mucoadhesive strength (gm) and $t_{50}$ (time taken for 50% drug release) at three different points in the experiment. Overall, 11 experimental batches were predicted by the Design expert software.

*Fourier transform infrared (FTIR)*

FTIR spectra of the pure drug (MCZ HCL), physical mixture (drug with Carbopol 934P and HPMC 15 cps), and optimized formulation were obtained with Bruker FTIR-Tensor 27 spectrophotometer, using the potassium bromide (KBr) pellet disk technique (about 10 mg of sample for 100 mg of dry KBr) to conclude the drug excipient interaction. The disc was placed in an IR spectrophotometer using a sample holder, and the spectrum was recorded from 4000 to 400 $cm^{-1}$.

*Statistical analysis*

Mean values and their standard errors were used to summarize the data collected in the study. ANOVA was used to analyze mucoadhesive strength and $t_{50}$ of different batches. p-value of less than 0.05 was considered statistically significant.

*Stability studies*

The tablets were covered in aluminium foil and kept at 40 ± 2 °C / 75 ± 5 % RH for three months as part of stability testing on the optimized formulation. The wrapped samples were removed after three months and subjected to physical parameters, hardness, thickness, friability, drug content, and surface pH examinations. The formulation did not undergo any significant alterations. As a result, it was discovered that the manufactured mucoadhesive buccal tablets were stable and not particularly impacted by humidity or temperature.

**Results**

As the drug is sparingly soluble in water, methanol is substituted with a pH of 6.8 for dissolution investigations. The standard calibration curve of MCZ HCL was carried out in methanol at λ max 232 nm and for pH 6.8 phosphate buffer at λ max 272 nm. It showed a linear line. The result indicates that the drug obeys Beer's Lambert's law in the concentration range of 2 - 10 mcg/ml, and the 'r²' value was found to be 0.999.

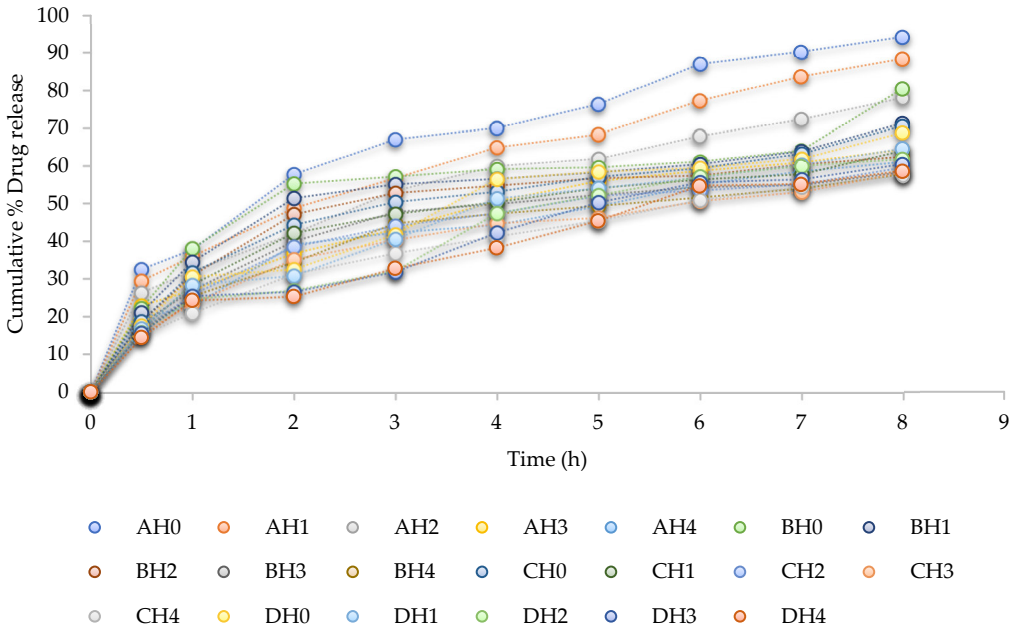


**Figure 1.** In-vitro release profile of Meclizine HCl buccal tablets in pH 6.8 phosphate buffer saline (PBS). The data points shown are mean ± standard deviation (SD) (n = 3).

*Pre-optimization studies*

The hardness of prepared buccal tablets of MCZ HCL ranged from 3.35 ± 0.09 to 5.23 ± 0.11 kg/cm²; hardness increases with Carbopol 934P concentration in the formulation. The thickness prepared buccal tablets ranged from 2.86 ± 0.13 to 3.32 ± 0.10 mm and weight variation from 148.80 ± 0.57 to 150.57 ± 0.11 mg. Friability values less than 1% indicate good mechanical strength to withstand the rigors of handling and transportation. The average drug content of formulated buccal tablets ranged from 94.95 ± 1.40 to 104.47 ± 1.82%, and the low values of standard deviation indicate that the drug was distributed uniformly within the prepared buccal tablets. Too acidic or alkaline pH may irritate buccal mucosa; the surface pH was measured to evaluate the probability of secondary effects occurring in the oral cavity. All the formulations were found to have a surface pH that fell in the range of 6.35 ± 0.08 to 8.15 ± 0.24. Because of this, it is generally accepted that the oral cavity will not experience any irritation of these

formulations. Furthermore, all the different formulations have a swelling index ranging from 28.10 ± 1.56 to 92.36 ± 4.51%. The mucoadhesive strength of every buccal tablet was evaluated, and the results showed that the mucoadhesive strength of buccal tablets was found to be approximately in the range of 3.84 ± 0.06 to 7.11 ± 0.11%.

*In-vitro dissolution studies*

The *in-vitro* drug release study was carried out for all the formulations prepared in pre-optimization studies using the abovementioned method. All the formulations tended to release in the range of 58.62 % to 94.14 % of the drug within 8 h, as demonstrated in Figure 1. Based on the data acquired from the pre-optimization studies, the best polymer HPMC 15 cps along with Carbopol 934P was selected for optimization studies using a central composite design and evaluated for hardness, thickness, friability, weight variation, drug content, surface pH, swelling index, and mucoadhesive strength.

*Response surface analysis*

The mucoadhesive tablets were optimized by using a two-factor, three-level Central Composite Design (CCD). To optimize the formulation uses two factors (independent variables) viz., HPMC 15 cps concentration and Carbopol 934P concentration on two responses (dependent variables) viz., mucoadhesive strength (gms) and $t_{50}$ (time taken for 50% drug release) with three center point.

All 11 formulations were evaluated for various tests. The results of hardness ranged from 3.91 ± 1.22 to 4.84 ± 0.83 kg/cm$^2$, thickness 2.81 ± 0.96 to 3.38 ± 0.81 mm, and weight ranged from 147.94 ± 0.25 to 151.57 ± 0.63 mg. Friability values less than 1%, and average drug content range of 96.23 ± 2.11 to 106.11 ± 0.96%. All 11 formulations were found to have a surface pH in the range of from6.68 ± 0.87 to 8.23 ± 0.52, with a swelling index ranging from 56.14 ± 1.22 to 88.64 ± 2.14 %. The mucoadhesive strength was found in the range of 3.96 ± 0.81 to 7.44 ± 0.59 %, and $t_{50}$ ranges from 1.6 h to 5.6 h.

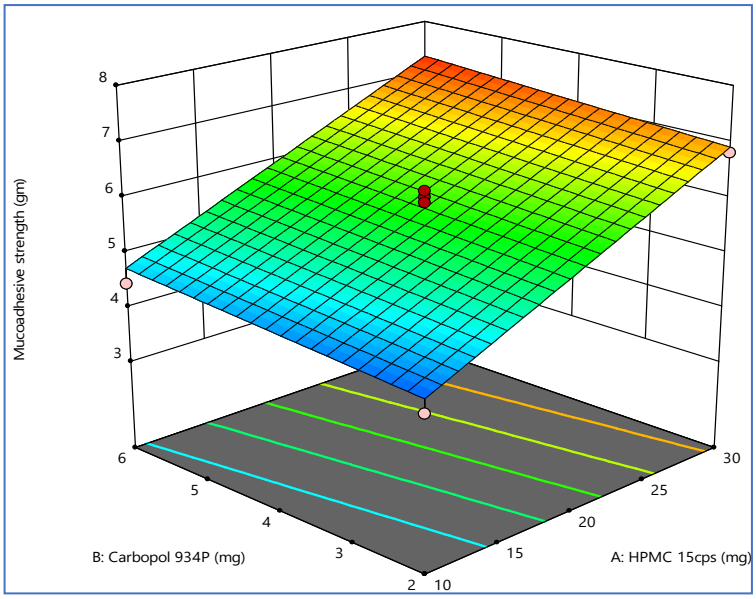


**Figure 2.** 3D response surface plots showing the effect of HPMC 15 cps and Carbopol 934P on Mucoadhesive strength (response Y1).

*Effect of process variable on mucoadhesive strength (Y1)*

Significant model terms $P < 0.05$. The lack of fit F-value of 7.09 implies no significance relative to pure error, with only a 12.88 % chance that a Lack of fit F-value large could occur due to noise and is good for model fitting. Here, A is a significant model term, predicted $R^2$ of 0.9319 is in reasonable agreement with the Adjusted $R^2$ of 0.9571 (the difference is < 0.2), adequate precision measures the signal-to-noise ratio, a ratio greater than 4 is desirable, where 28.386 indicates an adequate signal, and model can be used to navigate the design space. The model proposes an order linear polynomial equation for mucoadhesive strength, as given below:

*Polynomial equation:*

Mucoadhesive strengthY1 (Response) = 5.83+1.30 *A + 0.1979 * B

$t_{50}Y_2$ (Response) = 2.73 + 1.44 * A + 0.278 * B + 0.300 *AB +0.4708 * A2 + 0.0208 B2

Where A- HPMV 15 cps; B- Carbopol 934P

Figure 2 shows response surface analysis 3D surface plots. The 3D surface plots showed a linear relation between HPMC 15 cps and Carbopol 934P concentration on mucoadhesion strength, which was further justified by the first-order linear equation suggested by ANOVA studies ($p < 0.05$). An increase in HPMC 15 cps and Carbopol 934P concentration results in an increase in the mucoadhesion property. The Run 5 shows the highest mucoadhesive strength (7.44 gm) with high HPMC 15 cps and median Carbopol 934P concentration. The predicted vs. actual plot, as in Figure 3, shows color points by the value of mucoadhesive strength (trial run response) situated nearer to the predicted response. The results suggest a significant correlation between the predicted and actual values.

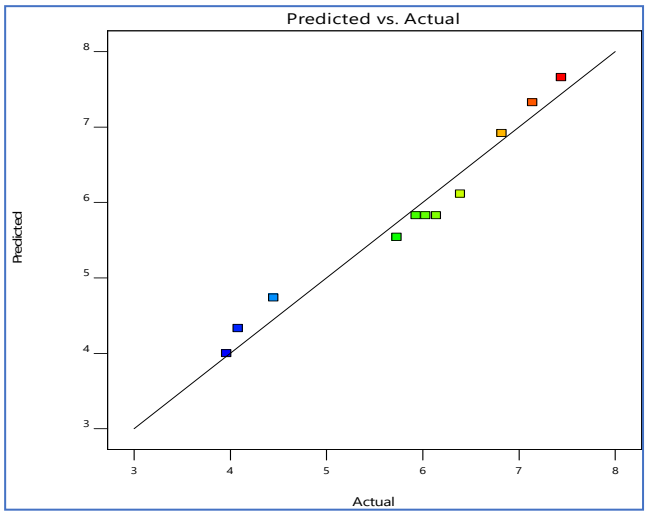


**Figure 3.** Predicted vs Actual plot.

*Effect of process variable on $t_{50}$ (Y2)*

Significant model terms ($P<0.05$). Here, A, B, and $A^2$ are significant model terms. The Lack of Fit F-value of 5.58 implies the Lack of Fit is not significant relative to the pure error, with only a 15.56% chance that a Lack of Fit F-value this large could occur due to noise and is good for the model to fit. The Predicted $R^2$ of 0.8504 is in reasonable agreement with the Adjusted $R^2$ of 0.9547; i.e., the difference is less than 0.2. Adeq Precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable. The ratio here, 18.634, indicates an adequate signal. This model can be used to navigate the design space.

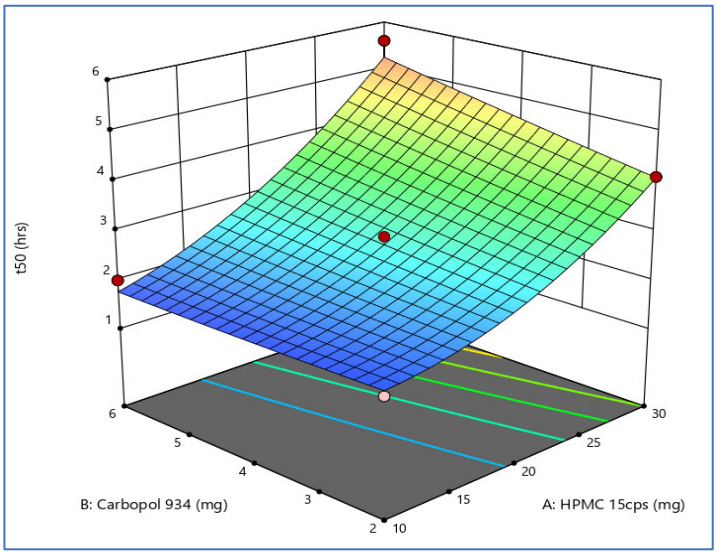


**Figure 4.** 3D response surface plots showing the effect of HPMC 15 cps and Carbopol 934P on $t_{50}$ (response Y2).

Figure 4 shows 3D surface analysis plots of the $t_{50}$ response. 3D surface plots showed a linear relation between HPMC 15 cps and Carbopol 934P concentration on t50, which was further justified by the second-order quadratic polynomial equation suggested by ANOVA studies ($p<0.05$). An increase in HPMC 15 cps and Carbopol 934P concentration results in an increase in the mucoadhesion property. Run 5 shows the highest $t_{50}$ (5.5 h) with high HPMC 15 cps and median Carbopol 934P concentration. The predicted vs. actual plot, as in Figure 5, shows color points by the value of mucoadhesive strength (trial run response) situated nearer to the predicted response. The results suggest a significant correlation between the predicted and actual values.

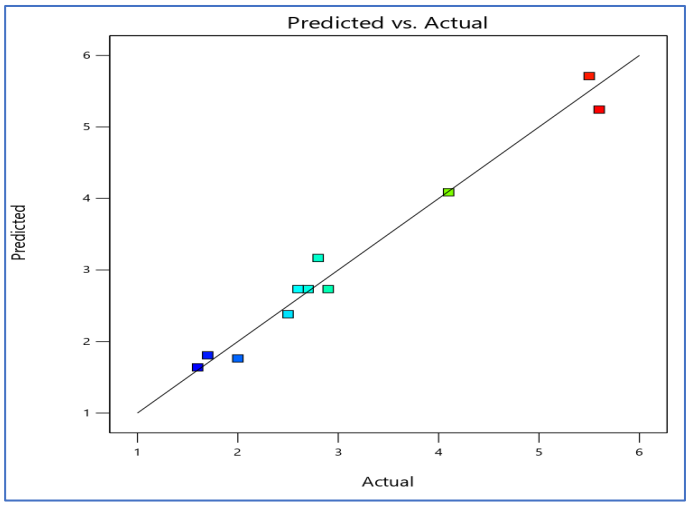


**Figure 5.** Predicted vs Actual plot.

The point prediction method confirms the HPMC 15 cps, Carbopol 934P concentration as 24.63 gm and 4.17 gm, respectively. After all the data proposed by central composite design, the formulation of optimized buccal tablets was described in Table 3.

**Table 3.** Composition of Optimized Buccal Tablets of MCZ HCL.

| Ingredients* (mg/tablet) | Formulation code |
|---|---|
| | Optimized Formulation |
| MCZ HCL | 25 |
| Carbopol 934 P | 4.17 |
| HPMC 15 cps | 24.63 |
| Mannitol | 15 |
| Aspartame | 3 |
| Sodium stearyl fumarate (SSF) | 2 |
| Flavour | 2 |
| MCC | 24.20 |
| Ethyl cellulose | 50 |
| Total weight (mg) | 150 |

*Evaluation of optimized formulation of mucoadhesive buccal tablets*

The mean evaluation parameters of optimized mucoadhesive buccal tablets of MCZ HCL are as follows. Hardness, Thickness, Weight variation, Friability, Drug content, Surface pH, swelling index and Mucoadhesive strength was found to be 3.98 ± 0.29 kg/cm$^2$, 3.46 ± 0.081 mm, 150.49 ± 0.86 mg, 0.88± 0.19%, 99.14 ± 0.53%, 6.73 ± 0.28, 99.82 ± 3.19% and 7.04 ± 0.41 gm, respectively.

*An in-vitro* drug release study of optimized mucoadhesive buccal tablets has been carried out using phosphate buffer pH 6.8. According to the optimized formula, HPMC 15 cps and Carbopol 934P were used as polymers in the preparation of buccal tablets based on the excellent swelling and adherent characteristics of the mucosal surface. The optimized formulation showed $t_{50}$ (50%) drug release in 5.6 h, as shown in Figure 6.

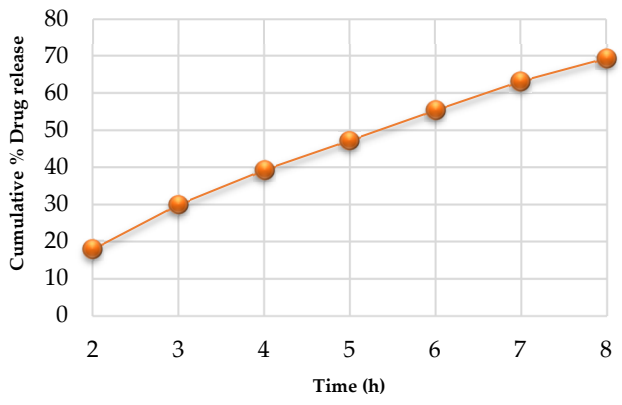


**Figure 6.** In-Vitro release profile of optimized buccal formulation tablets in pH 6.8 phosphate buffer saline (PBS). The data points shown are mean ± standard deviation (SD) (n = 3).

*Fourier transform infrared spectroscopy study*

The IR spectrum of pure drug MCZ HCL shows characteristic peaks at 3385.60 $cm^{-1}$, 1493.92 $cm^{-1}$, 3005.53 $cm^{-1}$, and 698.90 $cm^{-1}$ due to Aromatic C-H stretching, Aliphatic C-C stretching, N-H stretching and C-CL stretching respectively. Drug with Carbopol and HPMC 15 cps were displayed characteristic peaks at 3321.38 $cm^{-1}$, 3319.57 $cm^{-1}$, 3319.54 $cm^{-1}$, 3320.75 $cm^{-1}$ for the Aromatic C-H stretching, 1384.24 $cm^{-1}$, 1384.31 $cm^{-1}$, 1384.27 $cm^{-1}$, 1384.20 $cm^{-1}$ peaks for Aliphatic C-C stretching, 2949.28 $cm^{-1}$, 2974.20 $cm^{-1}$, 2937.68 $cm^{-1}$, 2937.44 $cm^{-1}$ for N-H stretching and 681.72 $cm^{-1}$, 683.51 $cm^{-1}$, 682.99 $cm^{-1}$, 681.23 $cm^{-1}$ for C-CL stretching, respectively. This confirms the undistributed structure with the excipients. Hence, there are no drug-excipient interactions were found. IR spectra of MCZ HCL (pure drug) along with Carbopol 934P and HPMC 15 cps are shown in Figure 7&8.

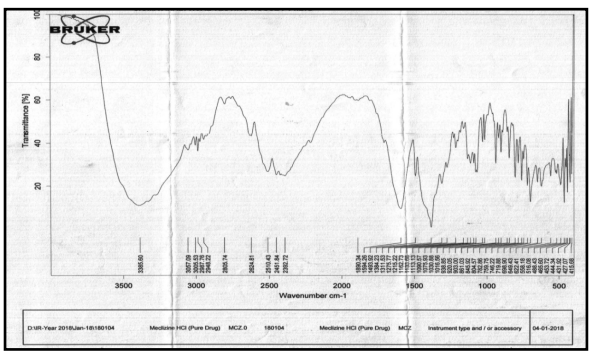


**Figure 7.** IR spectrum of MCZ HCL (Pure Drug).

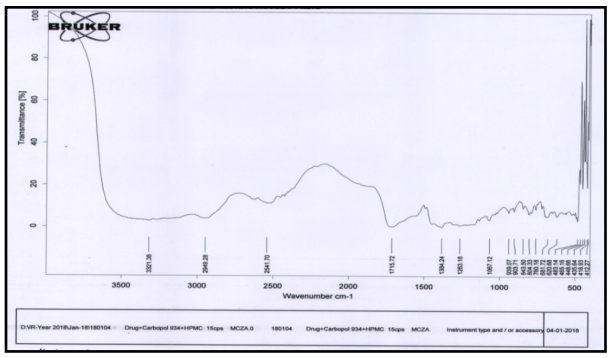


**Figure 8.** Physical mixture.

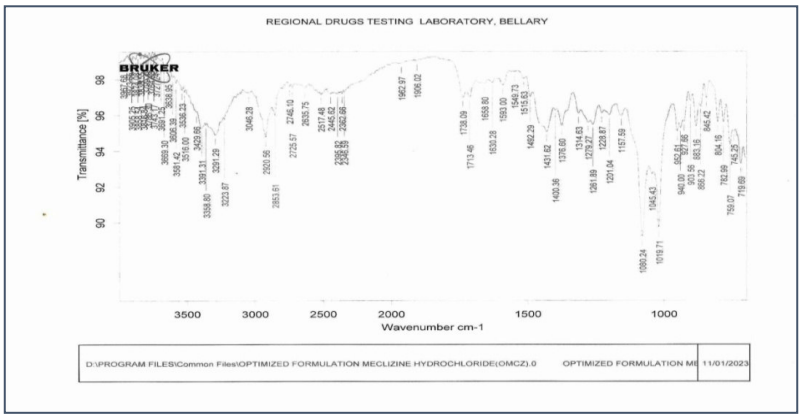


**Figure 9.** IR Spectrum of Optimized formulation.

It was determined, based on the examination of the FTIR spectra of the optimized formulation of mucoadhesive buccal tablets of MCZ HCL and its interpretation data, that there is interaction between the drug and the polymer, as seen in Figure 9.

## Discussion

One of the alternate methods of medication administration that avoids first-pass metabolism and provides regulated drug release is the development of mucoadhesive buccal tablets. The perfect mucoadhesive tablet would have both a quick and sustained drug release, producing a pharmacological impact that would be felt immediately but would last for a longer period of time, and it would also have adequate oral residence time [46]. MCZ HCL mucoadhesive buccal tablets have been designed and evaluated for a variety of physicochemical qualities in order to fulfill these requirements.

There were twenty batches of each of the four polymers (HPMC 15 cps, HPMC 50 cps, HPMC 100 cps, and HPMC K4M) that were employed in the formulation of the buccal tablets that were produced. In most cases, HPMC is a material that is not poisonous and does not irritate the skin. It can be utilized as a protective colloid that functions as a thickening agent, coating agent, film forming, stabilizer, suspending agent, tablet binder, and viscosity builder. These are only a few of its many applications. In

oral controlled delivery systems, HPMC is a preferred choice for the matrix material. Matrix materials made from HPMC show a continuous release pattern due to two different mechanisms, namely diffusion and erosion of the gel layer. When an aqueous solution comes into contact with a matrix, the wetting process begins at the surface and then travels deeper into the matrix through the small pore spaces. Additionally, the matrix's excipients absorb water, hydrate, and expand, which blocks up any existing pores. Furthermore, the matrix's contents dissolve, which results in a more porous, structured gel generated by a viscous solution. This gel either gives rise to a positive pressure that prevents liquid entrance or causes the matrix to disintegrate. The release of both hydrophilic and hydrophobic drugs can be controlled by using HPMC as a matrix. This is possible because of HPMC's unique chemical structure. It is currently being included in buccal adhesive tablet formulations [47].

In this study, mucoadhesive bilayer buccal tablets of MCZ HCL were made utilizing mannitol and SSF. These tablets were intended for buccal administration. Mannitol is a channeling agent that gives the product a pleasant mouth feel. SSF is an inert hydrophilic lubricant.

All prepared tablets were smooth, biconvex, milky white in color, and circular with no visible cracks. The hardness, thickness, friability, and weight variations of the entire batch were within the pharmacopeial limits, which ensured the standard quality of the prepared tablets. It was reported that hardness increased with the increase in the proportion of Carbopol 934P. Buccal tablets of MCZ HCL were tested and found to have a hardness between 3.41 ± 0.09 to 5.16 ± 0.11 kg/cm$^2$. Standard deviation values for both thickness and weight were found to be quite small, indicating a high degree of consistency. Buccal tablets made to these specifications measured between 2.94 ± 0.09 to 3.44 ± 0.21 mm in thickness and weighed between 148.28 ± 0.64 mg to 151.33 ± 0.43 mg. Less than 1% friability was obtained. All formulations were found to have a surface pH between 6.16 ± 0.25 and 8.44 ± 0.41.

The mucoadhesive strength of a formulation denotes the degree of adhesion that exists between the epithelial surface and either mucus or a polymeric substance that is included in the formulation. In the process of mucoadhesion, the wetting of the polymer, the interpenetration of the polymer, and the mechanical interaction between the polymer and the mucus are the three most important stages. Mucoadhesive strength is significantly dependent on the amount of time the polymer spends in contact with mucus, the sort of biological membrane that is utilized, the swelling behavior of the polymer, the average molecular weight of the polymer, as well as the concentration and composition of the polymer that is utilized [48-50]. According to the results of our research, the mucoadhesive strength of every medication formulation was satisfactory, ranging from 3.96 ± 0.013 to 7.44 ± 0.28%.

The swelling property plays a major role in achieving sustained and uniform drug release from the mucoadhesive system [51]. The swelling index of the tablets was shown to increase in direct correlation with the amount of Carbopol 934P, and HPMC used in the formulation. The formulas range from an expansion index of 30.241 ± 0.88 to 96.11 ± 4.89%.

Twenty different formulations (AH0-DH4) were investigated for drug release in a phosphate buffer at a pH of 6.8 in in-vitro research. The prepared buccal tablets used polymers in varying proportions. The primary polymer in all twenty batches was Carbopol 934P, chosen for its superior swelling and mucosal adhesion properties. The secondary polymer in each batch was HPMC. The rate of drug release slowed as the amount of secondary polymer added to the formulation increased. The therapeutic effect of a medicine can be extended by using HPMC to extend the time it takes for the drug to be released. Because it is essential for the drug to be released in a controlled manner in a buccal formulation, the dosage form must remain intact while it moves through the GIT, which is a region where chemical and mechanical obstacles have the ability to break apart the dosage form.

The batch AH0 showed a maximum drug release of 88.43 ± 1.73%. This batch was containing less polymer (Carbopol 934P 2mg and HPMC 15cps 15 mg). Minimum drug release was seen with formulation DH4, which showed 58.62 ± 0.93% drug release, which contains (Carbopol 934P 8 mg and HPMC K4M 30 mg). The amount of carbopol 934P and HPMC was reduced, and this resulted in an increase in the drug release rate. It's possible that this is because of the hydrophilic and swellable characteristics of Carbopol 934P and HPMC, both of which are capable of forming a viscous gel layer.

Because this gel layer limits the drug release via diffusion, the rate at which the medication is released is slowed down significantly [52]. Furthermore, the inclusion of Carbopol 934P affects the pace of drug dissolution. This is because the presence of carboxyl groups at buccal pH causes carboxyl groups to dissociate, which in turn results in slower diffusion of the drug through the matrix due to the creation of swelling gel. On the other hand, as a result of the non-ionic nature of HPMC, the viscosity of the gel layer is unaffected by the buccal pH. Based on the results of the swelling index of 92.36 ± 4.51%, mucoadhesive strength of 6.16 ± 0.08 gm, and in-vitro drug release of 88.43 ± 1.73% in 8 h, the formulation AH1 emerged as the most promising formulation among the twenty experimental formulations.

The best polymer screened was used for the final optimization. Pharmaceutical formulations are developed by changing one variable at a time, but this approach does not provide insight into the interaction between variables and makes it difficult to develop an optimized formulation. The formulations were optimized using two factors at three levels by Central Composite Design using Design expert 12 software. Hence, a central composite experimental design with two factors, three levels, and 11 runs was selected, as depicted in Table 2, for the optimization study. This Design consists of 4 full factorial design points, four axial points, and three center points. HPMC 15cps (X1) and Carbopol 934P (X2) were studied at three levels each. The response variables considered for the current Design of expert optimization studies encompassed mucoadhesive strength (gm) (Y1) and $t_{50}$% (time taken for 50% of drug release) (Y2). This experimental Design generated a polynomial Equation.

The optimized formulation showed hardness 3.98 ± 0.29, thickness 3.46 ± 0.08, weight variation 150.49 ± 0.86, friability less than 1%, drug content 99.14±0.53, swelling index 99.82±3.19 and mucoadhesive strength of 7.04±0.41.

The range of in-vitro dissolution data for all the created formulations was between 57.83 ± 1.44% and 96.44 ± 1.69%. Findings indicate that out of twenty formulations tested, AH1 showed the most promise, with an in-vitro drug release rate of 88.43 ± 1.73% in 8 h, a swelling index of 92.36 ± 4.51%, and a mucoadhesive strength of 6.16 ± 0.08 gm. In the end, the optimization was based on the best formulation. To optimize the process, Central Composite Design used Design Expert® 12.

To determine the mechanism of drug release, in-vitro data for all buccal tablet formulations of MCZ HCL were subjected to a goodness-of-fit test using linear regression analysis based on zero-order, first-order kinetics, and Higuchi's and Peppa's equation. According to the results of an in-vitro drug release research, the optimal formulation containing HPMC 15cps 24.63 mg and 4.17 mg of Carbopol 934P has a $t_{50}$ drug release in 5.6 h. The formulation is stable over a three-month period, according to the stability data.

**Conclusion**

It was reported that the synthesis of mucoadhesive buccal tablets of MCZ HCL utilizing HPMC 15 cps and Carbopol 934P as mucoadhesive polymers by the direct compression method was easy and appropriate for laboratory scale production. The goal of this study was to develop and assess mucoadhesive buccal tablets of meclizine hydrochloride in order to improve patient compliance for the management of a variety of illnesses. AH1 had the most sustained and effective medication release, swelling index, and mucoadhesive strength among the 20 formulations analyzed. Carbopol plays a significant part in boosting the mucoadhesive strength of the mucus. HPMC has the potential to play an important part in regulating swelling behavior and the drug release rate. The polynomial equations and contour plots that were generated through the use of central composite design enabled the production of mucoadhesive buccal tablets that possessed the best possible attributes. The values that the design model predicted were very well matched by the attributes of the formulation that was prepared. In addition, the formulation of MCZ HCL mucoadhesive buccal tablets can be one of the alternate strategies to circumvent the significant hepatic first-pass metabolism and to boost the bioavailability of MCZ HCL across the mucosal barrier. In addition to this, it can improve patients' compliance with medication due to the intriguing extended release of the drug.

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