Meclizine Hydrochloride Lozenges: Design, Development and Characterization

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***Abstract*- Background: Meclizine hydrochloride, an antihistamine is widely utilized to alleviate vertigo, nausea, and vomiting. However, patients may find its traditional tablet shape bothersome, especially if they have difficulty in swallowing it.**

Method: Meclizine hydrochloride lozenges were developed with a blend of excipients, such as binding agents, flavourings, and sweeteners by heating and congealing method. A randomized 3^2 full factorial design with two components and three levels was used to optimize the formulation of the lozenges. Sucrose and HPMC-E5 were independent variables and hardness and disintegration time (minute) were response variables. Formulation was assessed for thickness, diameter, hardness, weight variation, cooling, drug content, in vitro dissolution, FTIR, PXRD, DSC and stability study.

Results: All developed lozenges were elongated, red in colour, and had good physical facets, encompassing a smooth surface. Hardness was found to be in the range of 7kg/cm^2 and 16 Kg/cm^2. There were no cracks, bubbles, or black specs in developed formulation. Rate of erosion of prepared lozenges ranged from 15 to 20 min. Weight variation was 1335.9 ± 0.002 mg to 2332 ± 0.001mg. Dissolution of developed lozenges (F1 -F9) was in range of 88 to 97%.

Conclusion: Lozenges of meclizine hydrochloride were satisfactorily developed and assessed as a novel oral delivery system that served as a substitute for traditional tablets that may avert ease in swallowing since they have their high release of drugs and acceptable physical attributes.

***Index Terms*- lozenges, meclizine hydrochloride, nausea, oral delivery system, patient compliance, vertigo. vomiting.**

I. INTRODUCTION

Motion sickness is the term used to describe a group of autonomic symptoms brought on by disparate sensory impressions while moving.[1][2] An alternative term for it is "kinetosis." Autonomic symptoms are a collection of symptoms that arise when an individual or their environment moves, causing a stress response.[3] The main symptoms of motion sickness are vomiting, sweating, nausea, hypersalivation, pallor, stomach awareness, etc. Compared to men of the same age, women are more prone to motion sickness due to the higher frequency and intensity of symptoms, particularly during menstruation.[4] For decades, antihistamines have been used either alone or in combination with other interventions to mitigate motion sickness. Antihistamines prevent motion sickness by blocking emetic H1-receptors. Several first-generation antihistamines, including promethazine, cinnarizine, dimenhydrinate, diphenhydramine, cyclizine, and meclizine, can be used to prevent and treat motion sickness.[5] They are likely effective because of their antihistamine action and, if applicable, their anticholinergic property. Histamine receptor blocking in the vomiting centre can lessen symptoms, and anticholinergic actions may help with the prevention effect.[6]

Central histamine system is engaged in several central nervous system procedures,[7] such as an increase stress-related hormones, the activation of the sympathetic nervous system, and motion sickness.[8] Activation of the vestibular system therefore initiates the histaminergic neural system, which in turn activates the histamine H1[9] receptors in the brainstems and induces vomiting with the beginning of motion sickness.[10] Major enzyme responsible for catalysing histamine production, histidine decarboxylase (HDC),[11] is inhibited by first-generation antihistamine medications. Alternatively, medications block histaminergic reactions mediated by the nervous system's H1 receptors.[12]

A medication combined with flavouring and sweetening agents is pivotal in lozenges, that are solid, flavoured medicated dosage forms that

dissolve or disintegrate gradually in mouth and are meant to be held in and sucked in throat or mouth.[13] They are utilised for drugs that are intended to be gradually released in order to either bathe the tissues of the throat in a drug solution or produce a steady level of drug in the oral cavity.[14] These are most frequently applied to oral cavity for localised effects. It optimises drug's local activity for systemic effects as well, provided that pharynx and buccal lining absorb it well.[15] They offer local drug delivery to throat, tongue, and mouth, among other areas. They entail different types of Active pharmaceutical ingredients (API) such as such as cough suppressants, decongestants, analgesics, vitamins, and local anaesthetics.[15] They can be made by compressing or moulding tablets made of sugar. While compressed lozenges are sometimes called troches, moulded lozenges are sometimes called pastilles. Lozenges were developed in 20th century and are currently being produced commercially.

Because of its ease of use, affordability, non-invasiveness, and convenience, the oral route is still the most popular and widely accepted way to administer drugs. Among the different oral dosage forms, lozenges offer a special and beneficial platform for drug delivery through the buccal cavity, both locally and systemically. Pharmaceutical preparations known as lozenges are solid, flavoured, and meant to dissolve or disintegrate gradually in the mouth. They are frequently employed for the Although they can also be used as vehicles for systemic drug delivery through buccal absorption, they are frequently used to treat localised conditions in the oral cavity and throat, such as sore throat, mouth ulcers, or dental pain. Retention time in the oral cavity, provide an excellent opportunity to utilize this route effectively. Lozenges, also known as troches or pastilles. They are commonly used for treating throat irritation, cough, and minor mouth infections and have expanded to deliver medications such as antifungals, analgesics, and even vitamins. Lozenges offer advantages such as prolonged contact with the mucosa, ease of administration. Lozenges are promising alternative to conventional tablets for patients with swallowing difficulties thus current research aims at design, develop, and assess meclizine hydrochloride lozenges as a novel oral delivery with the goal of strengthening compliance among patients and offering prompt symptom alleviation.

II. MATERIALS AND METHODS

Meclizine hydrochloride was generous gift from D. K. Pharmachem Pvt. Ltd Badlapur Thane; sucrose, citric acid, rose oil, amaranth were purchased from Research Labs, Mumbai: Mannitol and stevia sugar were purchased from Mohini organics Pvt limited Mumbai; HPMC-E5 was from Research Labs fine industries Mumbai.

2.1 Preparation of lozenges

Lozenges were made using heating and congealing technique. The necessary amount of sugar syrup was made by combining sugar and water, dissolving mannitol and stevia sugar in a small amount of water, and warming the blend to 110 °C until the mannitol and stevia sugar completely dissolve and create a transparent, viscous syrup. Then, mannitol stevia solution was added to the sugar syrup and heated to 160 °C until it turns golden yellow. [16]Temperature was then lowered to 90 °C. Meclizine hydrochloride was dissolved in small amount of water, followed by polymer in drug solution with other ingredients. Drug solution was then thoroughly mixed with sugar and mannitol stevia solution, and mixture was poured into mould.[17][18] Table 1 and 2 presents translation of values (coded) in the actual unit for 3^2 factorial design and 3^2 Full factorial design with independent variables and composition respectively.

Table 1 Translation of values (coded) in the actual unit for 3^2 factorial design

Variable levels	Low (-1)	Medium (0)	High (+1)
X_1= Conc. of sucrose (mg)	500	1000	1500
X_2= Conc. of HPMC-E5 (mg)	30	45	60

Table 2 3^2 Full factorial design with independent variables and composition

STD	Run	HPMC-E5 Factor 1	Sucrose Factor 2
4	1	60	1500
6	2	30	1000
9	3	45	1000
8	4	45	1500
1	5	30	500
3	6	30	1500
2	7	60	500
5	8	45	500
7	9	60	1000

2.2 Experimental design

Sucrose and HPMC-E5 were held constant during formulation development. To optimize hardness and disintegration time (mouth dissolving time test), a full factorial 3^2 design was utilized, with hardness and disintegration time as response variables. Table 3 gives formulation chart for lozenges as per 3^2factorial design.

Table 3 Formulation chart for lozenges as per 3^2factorial design

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	25	25	25	25	25	25	25	25	25
Mannitol	800	800	800	800	800	800	800	800	800
HPMC-E5	60	30	45	45	30	30	60	45	60
Sucrose	1500	1000	1000	1500	500	1500	500	500	1000
Citric acid	15	15	15	15	15	15	15	15	15
Stevia	15	15	15	15	15	15	15	15	15
Rose oil	15	15	15	15	15	15	15	15	15
Amaranth	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45

2.4 Characterization of Lozenges

2.4.1 Organoleptic features

Developed lozenges were inspected for organoleptic features.

2.4.2 Thickness and diameter

A vernier calliper was used to assess lozenges thickness and diameter. Lozenges were placed between jaw; jaw was closed. Reading of thickness displayed on scale was noted. Same procedure was carried for diameter. Thickness and diameter were measured triplicate in millimetres; the average was calculated and controlled within ±5% variability.

2.4.3 Weight variation

20 lozenges were chosen at random from lots, and their individual weight was recorded and average weight was calculated. Weight variation was calculated by subtracting the average weight from individual weight. For each lozenge, % deviation from average weight was calculated.% deviation was compared with acceptable limits, (Set by Pharmacopeial standards). Typically, weight variation should be within ±5% of average weight for consistent quality.

$$Percent\ deviation = \frac{(Individual\ weight - Average\ weight)}{Average\ weight} \times 100$$

2.4.4 Hardness

A Monsanto hardness tester was employed to assess hardness. Lozenges were placed in the centre of the anvil, gentle pressure was applied and held for some time (30 seconds), and then the pressure was released. The hardness of the lozenges was measured in kg/cm² and expressed as mean and standard deviations.

2.4.5 Cooling test

Visual examinations were carried out to look for any signs of cracks, air bubbles, or black specs.

2.4.6 Moisture analysis

The range of the moisture content was 0.595 ± 0.002. and 0.789 ± 0.002, which concluded that the values were within the Pharmacopoeial limits (0.5-1%).

2.4.7 Drug content

100ml volumetric flask of pH 6.8 phosphate buffer was used to dissolve 25mg of powdered lozenges, from which 1ml was diluted in a 50ml volumetric flask and filtered through filter paper. The corresponding blank was used to measure the absorbance at 223 nm. The drug content was measured using a calibration curve, and the procedure was carried out in triplicate.

2.4.8 FTIR

Samples were analyzed by KBr pellet method using IR spectrophotometer (Alpha II Bruker) in the 4000 to 400 cm^{-1} regions. FTIR analysis was executed for pure drug, and lozenges. FTIR of pure drug, and lozenges are shown in Figure 1.

2.4.9 DSC

DSC was performed for pure drug and formulation to check compatibility, insights of the thermal and physical properties of lozenges. Samples were taken in aluminum pans and standard procedure was followed by using DSC (Mettler Toledo, DSC 821e). 5 mg samples were heated in hermetically sealed aluminum pan under nitrogen atmosphere at heating rate of 10 °C /min DSC thermogram of propolis extract and formulation are shown in Figure 2.

2.4.10 XRD

PXRD has been used to study interaction and to obtain the changes in the crystallinity of drug developed formulation, PXRD study was executed using X-ray diffractometer (X RD-Burker - D8 ADV) For this the samples of pure drug, developed formulation were irradiated with CuKα radiation and analysed between from 5° to 60° (2θ). PXRD Diffractograms of pure drug, lozenges (hard candy) are shown in Figure 3.

2.4.11 In vitro disintegration time (Mouth dissolving time test)

USP disintegration apparatus was used to calculate the mouth dissolving time of each formulation. Lozenges were placed in each tube of the apparatus, and time it took for the lozenges to completely erode was recorded using Phosphate buffer solution (PBS) pH 6.8 at 37 °C. Three duplicates of the study were conducted.

2.4.12 In vitro dissolution

In vitro release studies were conducted using paddle-type USP-II dissolution equipment, 250 ml of PBS 6.8 at 37±0.5 °C was employed as the dissolution media, with 50 rpm. Samples were taken every five minutes, and the absorbance at 223 nm was measured spectrophotometrically (Shimadzu UV spectrophotometer 1900i). Figure 4 presents dissolution profile.

2.4.13 Statistical analysis (Surface response study and statistical optimization)

Effect of factors on response variables was evaluated statistically by one-way ANOVA level employing Design-Expert® version 8 (Stat-Ease Inc). [19] To investigate response surface curvature, evaluation of design was carried out for a suitable model by equation.[20]

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2 \quad \text{..... Equation (1)}$$

2.4.14 Stability study

Stability study for lozenges was carried out by using of stability chamber (Remi SC-19 Plus) by storing lozenges in an ambered colored screw-capped glass bottles at room temperature for a period of 60 days. Mechanical strength, drug content, and % drug release of lozenges were assessed at the end of study period. [40-41]

III. RESULT AND DISCUSSION

3.1.1 Organoleptic features

All of the developed lozenges were elongated, red in colour, and had good physical characteristics, including a smooth surface.

3.1.2 Thickness and diameter

A vernier calliper was used to assess lozenges thickness and diameter. Thickness was in the range of 8.00 ± 0.015 to 9.46 ± 0.123. Diameter for batches F1

to F9 was 15 ± 0.2 mm. Table 4 presents results for thickness and diameter.

3.1.3 Weight variation

All lozenge formulations had to have an average percentage deviation that was within the acceptable range., thus all formulations met the weight uniformity test according to official specifications, ranging 1335.9 ± 0.002 mg to 2332 ± 0.001mg. Table 4 presents results for weight variation.

3.1.4 Hardness

A Monsanto hardness tester was employed to assess hardness. Hardness was found to be in the range of 7-16 Kg/cm^2. Table 4 presents hardness of the all batches.

Table 4 Thickness, Hardness, Disintegration time, Weight variation of lozenges

Batch	Thickness	Hardness (kg/cm^2)	Disintegration Time	Weight Variation
F1	8.02±0.002	16.00±0.012	15.25±0.001	1335.9±0.002
F2	8.00±0.015	12.00±0.013	16.12±0.121	1813.9±0.010
F3	8.05±0.012	14.00±0.002	17.23±0.021	2269.8±0.023
F4	8.31±0.010	15.00±0.121	16.20±0.002	1356.8±0.012
F5	8.56±0.021	07.00±0.002	16.40±0.001	1845.2±0.002
F6	8.89±0.012	13.00±0.213	17.11±0.121	2332.2±0.001
F7	9.21±0.020	11.00±0.001	17.22±0.021	1440.2±0.0121
F8	9.46±0.123	09.00±0.002	18.02±0.002	1856.7±0.002
F9	9.42±0.002	15.00±0.121	20.01±0.001	2332.8±0.001

3.1.5 Cooling test

There were no cracks, bubbles, or black specs in the formulation that was created.

3.1.6 Moisture analysis

The range of the moisture content was 0.595 ± 0.002. and 0.789 ± 0.002 which concluded that the values were within the Pharmacopoeial limits (0.5-1%). Table 5 presents moisture analysis.

3.1.7 Drug content

The average drug content was recorded in triplicates and was found to be between 95 to 98 %. Table 5 presents drug content values.

Table 5 Moisture content, drug content, drug release

Batch	Moisture content	Drug content	Drug Release
F1	0.595±0.002	96.00±0.012	93.00±0.001
F2	0.543±0.012	97.00±0.031	91.00±0.023
F3	0.548±0.001	96.00±0.002	89.00±0.001
F4	0.569±0.012	96.00±0.001	96.00±0.002
F5	0.632±0.002	98.00±0.002	95.00±0.003
F6	0.712±0.012	96.00±0.002	92.00±0.003
F7	0.765±0.001	95.00±0.121	88.00±0.121
F8	0.743±0.002	98.00±0.001	90.00±0.002
F9	0.789±0.002	95.00±0.001	91.00±0.001

3.1.8 FTIR

Interaction between meclizine hydrochloride and other adjuvants in lozenges formulation was revealed by FTIR (Figure1). For meclizine hydrochloride, peaks were found nearby ~3330 cm^{-1} (N-H or O-H stretching), ~2940 cm^{-1} (C-H aliphatic stretching), ~1600–1650 cm^{-1} (C=N or aromatic C=C), ~1250–1030 cm^{-1} (C-N and C-O stretching), ~700–900 cm^{-1} (aromatic C-H bending). All these principle characteristic peaks were retained and did not shift in lozenges. As the results, it is concluded that meclizine hydrochloride is compatible with other excipients in formulation**.** Figure 1 illustrate FTIR spectra of meclizine hydrochloride and developed lozenges.

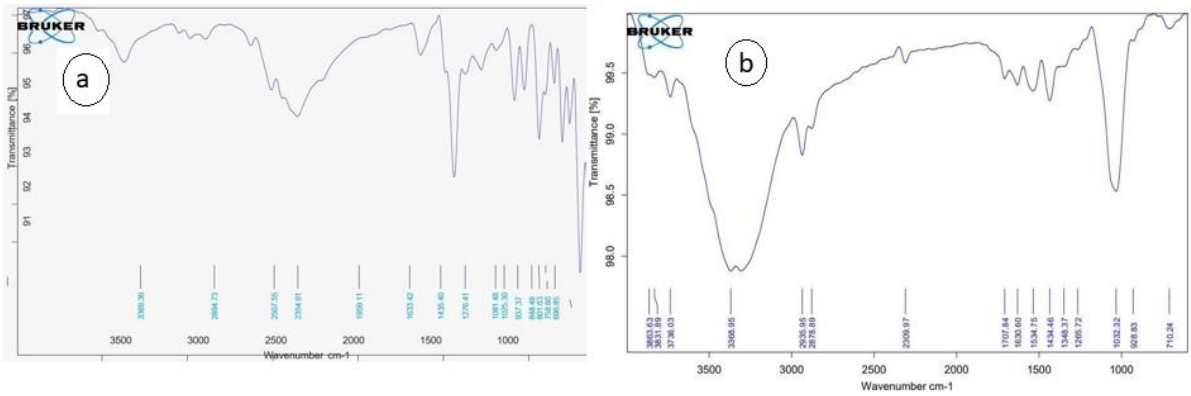

Figure 1 FTIR spectra of a) meclizine hydrochloride b) developed lozenges

3.1.9 DSC

DSC analyses were performed to know thermal interaction between meclizine hydrochloride, and other excipients. Figure 2 illustrates DSC thermograms of meclizine hydrochloride and developed lozenges. DSC thermogram of pure drug exhibited a sharp endothermic peak around the melting point of meclizine HCI (typically ~217-220°C), indicating high crystallinity, well-defined melting behaviour. This sharp peak confirmed the purity and crystalline nature of API. DSC thermogram of lozenges exhibited suggested that sharp melting peak was reduced, broadened indicating a shift in melting point or a broad hump, indicating a change in physical state. These changes are indicative of reduced crystallinity or amorphous dispersion and absence of degradation peaks indicated no incompatibility. Thus, it was concluded that drug in lozenges is likely amorphous or molecularly dispersed, which is expected and favourable in many formulations to enhance solubility. The absence or shift of the pure drug's melting peak indicated successful formulation and compatibility.

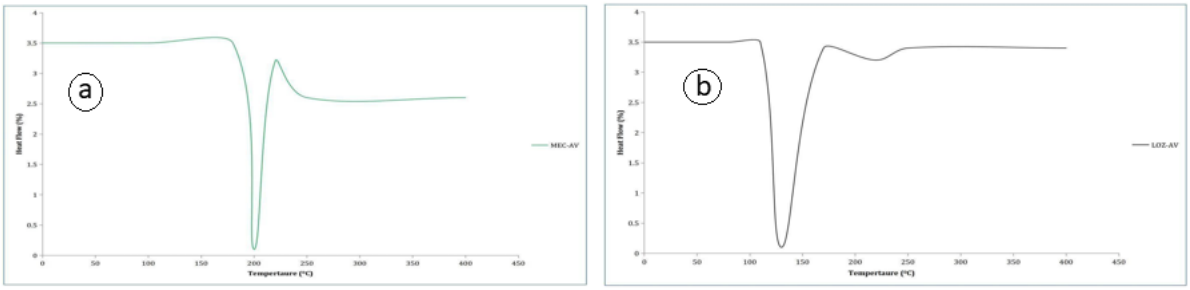

Figure 2 DSC thermograms of a) a) meclizine hydrochloride b) developed lozenges

3.1.10 XRD

PXRD patterns of meclizine HCI, lozenges are given in Figure 3. Powder X-ray diffraction spectroscopy was used to assess the degree of crystallinity of the given sample. PXRD spectra of pure drug revealed sharp, intense, well-defined peaks and indicated a highly crystalline nature of pure Meclizine HCI. Crystalline peaks suggest ordered molecular arrangement. PXRD spectra of lozenges revealed reduction in peak intensity, with many peaks becoming broader or flattened. Some sharp peaks of pure drug were reduced or missing. This suggested partial or complete amorphization or molecular dispersion in lozenge matrix.

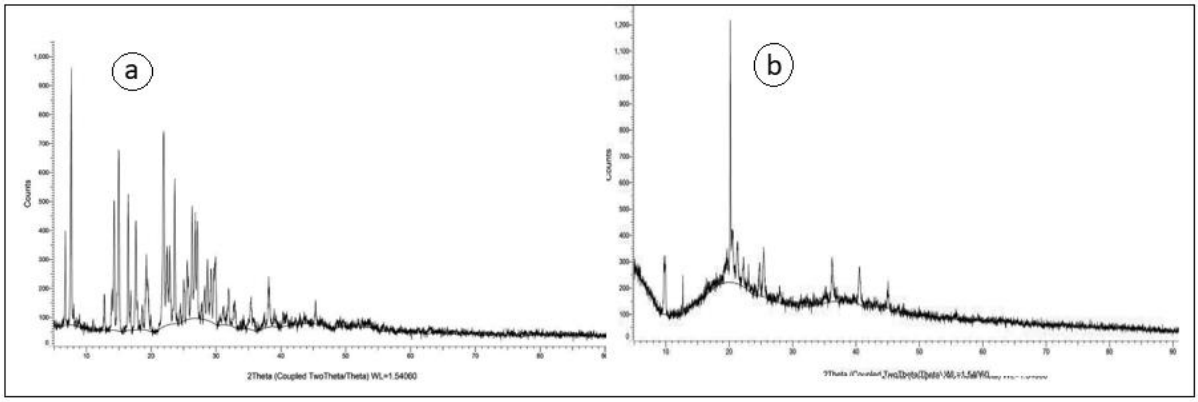

Figure 3 PXRD patterns of a) meclizine hydrochloride b) developed lozenges

3.1.11 In vitro disintegration

Mouth dissolving time test was employed to perform in vitro disintegration test and the rate of erosion of prepared lozenges ranged from 15 to 20 minutes.

3.1.12 In vitro dissolution

In vitro dissolution for all formulations was conducted using PBS 6.8 using USP type II device in which predetermined samples were removed for 20 minutes at 5 minutes intervals, and then analyzed for 223 nm. Cumulative release of respective lozenges was calculated on basis of mean amount of meclizine HCI present. Dissolution for developed lozenges (F1 -F9) was in the range of 88 to 97 %. Figure 4 demonstrates invitro dissolution and zero order release kinetics**.**

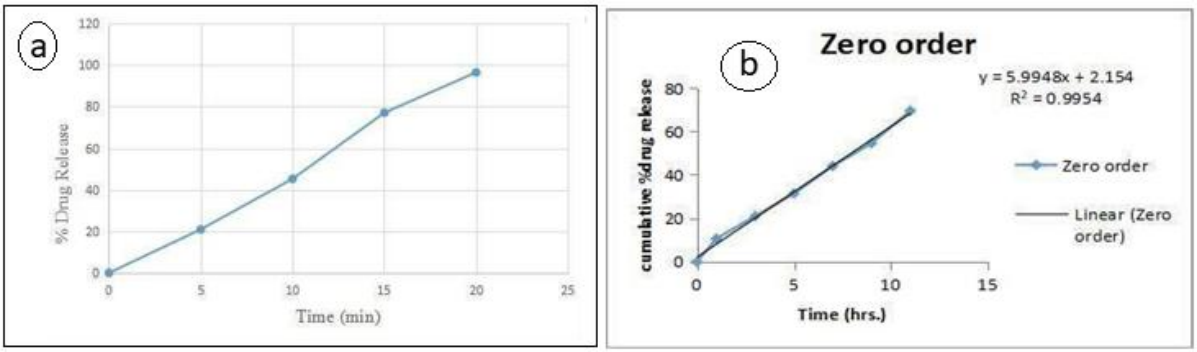

Figure 4 a) invitro dissolution b) zero order release kinetics

3.1.13 Surface response study and statistical optimization

a) Effect of formulation variables on hardness, (Y_1)

A linear regression model was significant with a p value of 0.0003, below 0.05. Results of ANOVA revealed that hardness had a significant influence; the linear equation was as follows.

Y_1= +13.89+1.67 A +2.33 B -0.2500 AB -0.3333A_2 -1.83B^2 A ……. Equation 2

With F-value of 222.26, implied model is significant., indicating there's only a 0.05% chance that F Value this large occur due to noise. p-value below 0.0500 suggested that variables included in model have a meaningful impact and are statistically significant. The small gap between Adjusted R^2 (0.9928) and the Predicted R^2 (0.9690) being less than 0.2 showed a consistent and reliable performance of model. Adequate precision evaluated ratio of useful signal to background noise, with values above 4 being ideal. The model's score of 43.296 indicates a strong signal, confirming that it is well- suited for exploring design parameters. Figure 5 illustrates various surface response graphs for effect of factors on hardness with counter plot and 3D surface response plot and Table 6 presents formulation table of optimized batch.

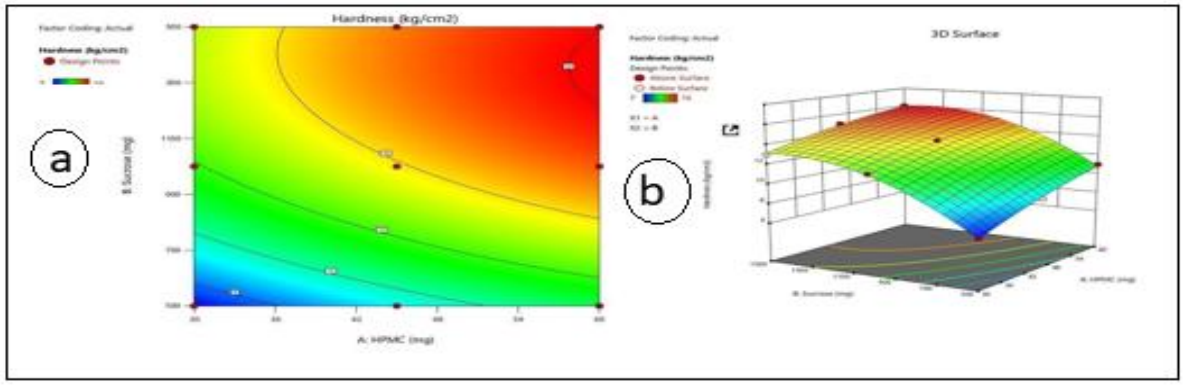

Figure 5 Various surface response graphs for effect of factors on hardness a) Counter plot b) 3D surface response plot

b) Effect of formulation variables on disintegration time, (Y_2)

A linear regression model was significant with a p value below 0.05. Results of ANOVA revealed that hardness had a significant influence; the linear equation was as follows.

$Y_2 = 17.06+0.9467\ A +1.11\ B$ ……. Equation 3

Model's F-statistic of 16.86 suggested it was highly significant, with only a 0.34 % chance that this result is due to random error, confirming model's strength. When the P-value is less than 0.0500, the model terms are considered significant. Predicted R^2 (0.6444) and Adjusted R^2 (0.7986) are close, and small negative difference between them implies that the model's prediction is consistent and dependable. Adequate precision, which measures how strong the signal is compared to background noise, showed value of 11.57. Since this exceeds the minimum acceptable value of 4. Figure 6 demonstrates various surface response graphs for effect of factors on disintegration time with counter plot and 3D surface response plot.

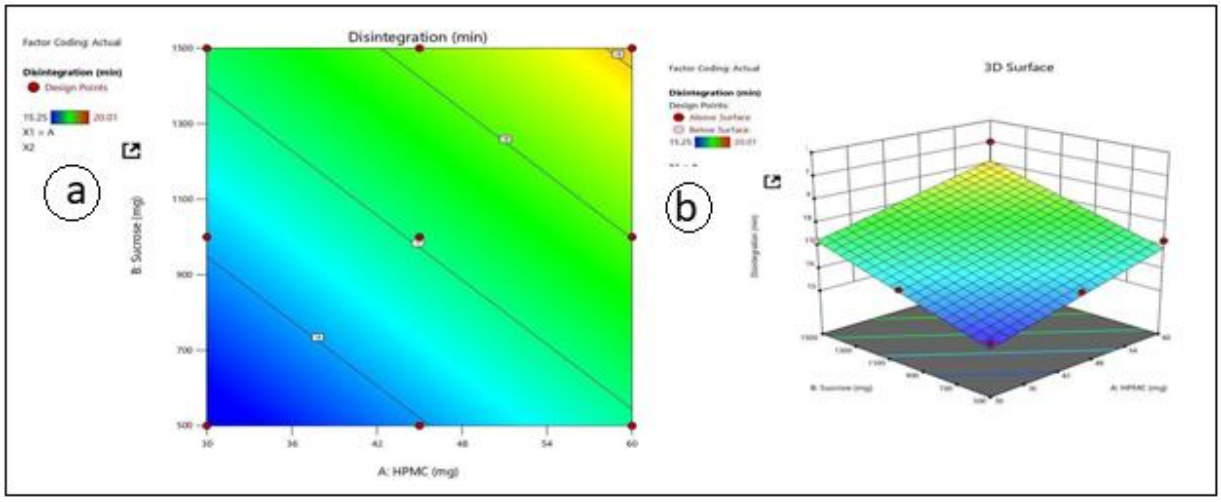

Figure 6 Various surface response graphs for effect of factors on disintegration time a) Counter plot b) 3D surface response plot

Table 6 Formulation table of optimized batch

Batch	X_1 (mg)	X_2 (mg)	Y_1	Y_2	Desirability
F5	30	500	7	15.25	0.944

3.1.13 Stability study

Optimised formulation (F5) was subjected to stability tests for 60 days at room temperature to determine any possible deterioration or variance in performance, lozenges' mechanical strength, drug content, and drug release percentage were assessed at the end of study period. F5 formulation's stability tests reveal no appreciable variations in hardness, disintegration time,

or drug content. It was concluded that F5 was stable based on the results.

IV. CONCLUSION

The current investigation comprised preparation of a Lozenges of meclizine HCl, drug for nausea, vomiting utilizing the heat and congealing method. FTIR analysis confirmed no chemical interactions between meclizine HCl and the selected excipients, thereby ensuring the stability of lozenges. Formulation was optimized employing 3^2 full factorial design, and F5 was optimized batch. This factorial design enabled systematic evaluation of effects of formulation variables on critical quality attributes such as hardness, disintegration time. F5 batch demonstrated satisfactory hardness, disintegration time, in vitro dissolution time, weight variation, moisture content, thickness. Emphasis was placed on optimizing drug release kinetics, ensuring uniform content, and maintaining desirable organoleptic attributes. The results demonstrated that the optimized lozenge formulations provided prolonged contact with the oral mucosa, improved patient compliance, and effective drug delivery. Additionally, lozenges were found to be particularly suitable for drugs requiring slow release and for patients who have difficulty swallowing conventional tablets or capsules. Thus, it was concluded that, the medicated hard candy lozenges developed in this study successfully met desired criteria for oral drug delivery systems. They offer several benefits, including ease of administration, avoidance of first-pass metabolism, and enhanced patient adherence.

Abbreviation	Meaning
API	Active pharmaceutical ingredients
DSC	Differential scanning calorimetry
FTIR	Fourier transform infra-red spectroscopy
PXRD	Powder X-ray Diffraction
Meclizine HCl	Meclizine hydrochloride

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