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Formulation Development and Evaluation of Promethazine As A Lozenge

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ABSTRACT

Motion sickness is a complex syndrome representing symptoms nausea and vomiting. Anti-motion sickness drugs can build up the rate of adaptation without symptoms being evoked. The present study aimed to formulate and evaluate Promethazine hydrochloride as a lozenge to combat flaws in regard to conventional dosage form. The sucking and swallowing process is a simple method for relieving symptoms, the mechanism being development of increased saliva, swallowing and this process equals the Eustachian tubes. Promethazine hydrochloride is a BCS class I, phenothiazine derivative showing antihistamine, sedative and antiemetic effect being a H1 receptor blocking agent, it also acts by blocking the action of acetylcholine and is indefinitely metabolized by the liver. Lozenges were prepared by heating and congealing method with isomalt and sucrose as a base and HPMC E5 in varying concentrations. Preformulation demonstrated compatibility of drugs and excipients coordinated using FT-IR and DSC. Post-compression parameters were studied which included general appearance, thickness, hardness, friability, cooling check, drug content, moisture content and *in vitro* dissolution as well as microbial test. Factorial design 3^2 was opted to optimize the formulation. Formulation F3 was considered an engineered medicated confection that met all the requirements showing adequate hardness and disintegration of 10 kg/cm^2 and 13.60 seconds respectively with a strong drug release rate of 98.22%. The microbial test showed large inhibition zone which concluded it showed quite good resistance and hence was considered as a promising candidate.

Keywords: Motion sickness, Lozenges, Heating, congealing, Zone of inhibition.

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INTRODUCTION

Motion sickness is a complex syndrome inclusive of many aspects besides just nausea and vomiting. The other established terms for motion sickness are air sickness, travel sickness, sea sickness. Motion sickness is a result of prevalent disturbance of the inner ear, eyes, skin pressure receptors, the muscle and joint sensory receptor. The linchpin being velocity integration, also inclusive of other symptoms such as pallor, sweating, short breath, dizziness, vomiting and nausea[1]. The sopite syndrome may also be one of the reasons for its occurrence. It's observed that subjects with normal vestibular function, blind individuals and congenitally blind subjects are susceptible whereas individuals with the loss of labyrinthine functions are less susceptibility. It can be attenuated by bypassing the exposure to provocative situations completely or by dispensable functioning labyrinth. Gradual exposure, cumulating the intensities of stimulation over multiple exposures is considered a competent method for its prevention. Anti-motion sickness drugs such as Promethazine hydrochloridecan build up the rate of adaptation without symptoms being evoked. The process of sucking and swallowing is a simple method for relieving mild motion sickness, the mechanism being production of increased saliva and swallowing which makes the "ear pops" as the process equalizes the Eustachian tubes. Oral route for drug administration are commonly acknowledged for conventional and novel drug delivery [2]. Lozenges are solid dosage forms derived from the French word lozenge, intended to be held and sucked in the mouth or pharynx wherein medicaments are contained in a sweetened base [3]. These are either prepared by molding or compression and depending upon the method used they are called as pastilles or troches respectively [4].

Promethazine hydrochloride is freely water soluble, phenothiazine derivative shows antihistamine, sedative and antiemetic effect by blocking H1 receptors. It also acts by blocking the action of acetylcholine, hence was considered for the treatment of motion sickness.

Its absorption window is from gastrointestinal tract showing clinical effects within 20 minutes upon oral administration and is indefinitely metabolized by the liver [5].

Oral delivery of the Promethazine hydrochloride in lozenges form is multidirectional or by mucosal surface thus increasing its bioavailability, hence reducing first pass metabolism, and more over easy to prepare and store, compact with high patient compliance. This dosage form is widely appreciated by pediatrics and geriatrics subjects [6]. Molding technique which is widely used in the production of confectionaries is done by heat and congealing method, the resultant known as hard candy lozenges [7].

Hard candy lozenges are a combination of sugar and carbohydrates either in amorphous or glassy state which is also designated as 'solid syrups of sugar'. Heat labile ingredients are to be considered as the temperature required for the formulation is high [8].

The purpose of the present study is to prepare Promethazine hydrochloride lozenges by heating and congealing method to avoid hepatic metabolism and improve the bioavailability for faster onset of action.

MATERIALS AND METHOD [2,3,4,7]

Materials

Promethazine Hydrochloride was obtained as gift sample from Cadila Health care Ltd. (MORAIYA), Sucrose and Stevia was obtained from Merck Life Science Pvt. Ltd, Mumbai and Zero Enthalpy Labs Pvt. Ltd, Mumbai respectively. Citric Acid, HPMC E5 and quinoline yellow from HIMEDIA Laboratories Pvt. Ltd. Ginger samples were obtained from Kings Dehydrated Foods Pvt. Ltd, Bhavnagar.

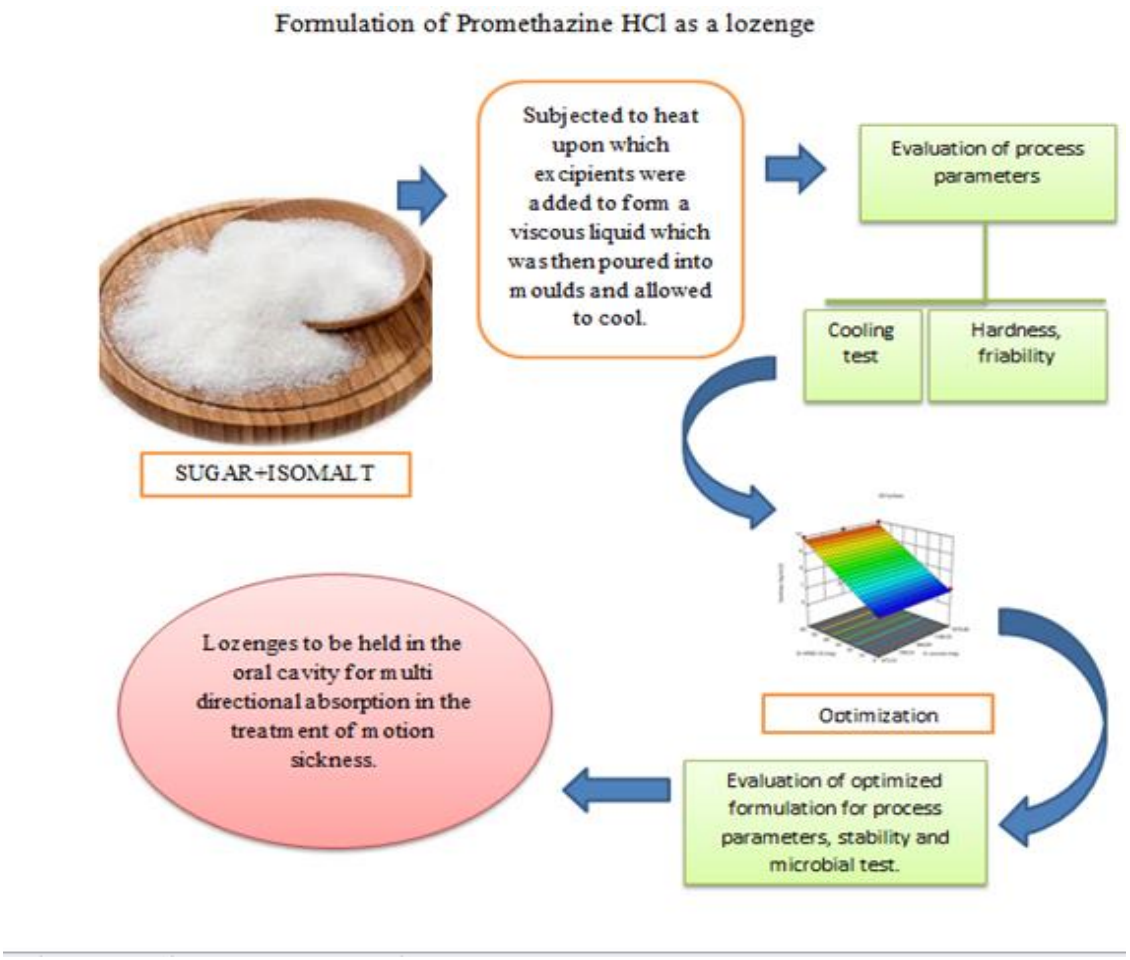
Methods

Formulation of Promethazine hydrochloride lozenges

Hard candy lozenges were prepared by heating and congealing technique. Wherein the required quantity of isomalt and water was allowed to dissolve, when heated upto 300°C. Once completely dissolved the required quantity of sucrose and citric acid was added to form a clear viscous syrup, the temperature is then brought down to less than 90°C and then the drug, binder, flavouring agent, colouring agent and sweetener is mixed with the consistency being maintained. The prepared solution or mixture was poured into the mould and were allowed to harden upon cooling at room temperature and then the prepared lozenges were wrapped up in aluminium foils and stored. (Table 1.)

Table 1. Composition of the Promethazine lozenges batches (F1 to F9)

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	25	25	25	25	25	25	25	25	25
Isomalt	800	800	800	800	800	800	800	800	800
HPMC E5	-	-	-	30	30	30	60	60	60
Sucrose	472.22	944.44	1416.66	472.22	944.44	1416.66	472.22	944.4	1416.6
Citric acid	15	15	15	15	15	15	15	15	15
Stevia	15	15	15	15	15	15	15	15	15
Ginger	15	15	15	15	15	15	15	15	15
Colouring Agent	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
Total weight	1342.67	1814.89	2287.05	1372.67	1844.89	2317.05	1402.67	1874.89	2347.05



Optimization by factorial design

Full factorial two level designs were set up using Design expert version 12 was utilized for the design of experimentation. Independent factors included sucrose (X1) and HPMC E5 (X2) and dependent factors were hardness (Y1) and disintegration (Y2). These factors were used to evaluate the relationship between factors that influence a process and its performance.

Evaluation of promethazine hydrochloride lozenge

General appearance:

The presence or absence of odour, texture of the surface and colour was determined organoleptically.

Thickness and Diameter:

The thickness and diameter of the prepared lozenges were measured in triplicates with a vernier caliper in mm, the average of which was determined and regulated within ±5% variability.

Hardness test:

The prepared lozenges were tested for hardness using a monsanto hardness tester which is expressed in kg/cm2 and measured further was mean and standard deviations.

Friability:

The friability test was carried out by considering twenty lozenges which had been put in the rochefriabilator and permitted 100 revolutions to be made. The lozenges were reweighed and dedusted. The weight loss percentage was calculated using formulae,

$$\text{Percentage friability} = \frac{w1-w2}{w1} \times 100$$

Where,

W1= Initial weight of 20 lozenges.

W2= Final weight of 20 lozenges.

Weight Variation test:

Twenty lozenges randomly selected from lots were considered, the average weight of which was determined and compared with the individual weight.

Cooling Tests:

Visual inspections were conducted to check if cracks, air bubbles or black specs were present. Upon which they were accepted and rejected.

Drug Content:

Lozenges were powdered equivalent to 25mg and dissolved in pH 6.8 Phosphate buffer 100ml volumetric flask from which 1ml was diluted in 50ml volumetric flask and filtered using filter paper. The absorbance was measured at 249nm using corresponding blank. It was performed in triplicates and the calibration curve used to measure the drug content.

Moisture content analysis:

The samples were weighed and crushed in mortar and pestle and were placed in desiccator for 24 hours. After 24 hours the sample were weighed and was determined by using the formulae.

$$\% \text{ Moisture Content} = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

Disintegration Test (*In vitro* mouth dissolving time):

The mouth dissolving time of each formulation was calculated by the use of USP Disintegration apparatus, in which lozenges were put in each tube of the apparatus and the time taken to fully erode the lozenges was taken into account with the aid of Phosphate buffer pH 6.8 at 37°C. The study was performed in triplicates which were measured and presented on average.

***In Vitro* Dissolution studies:**

In Vitro release studies were carried out using paddle type USP-II dissolution apparatus considering 250ml of Phosphate buffer pH 6.8 at 37±0.5°C was taken as dissolution media where in 50rpm was considered and samples were withdrawn every 5 minutes whose absorbance was recorded at 249nm.

Microbial check:

Microbial check was carried out for the optimized formulation wherein the presence of any bacterial, mold, or spore contamination was observed here it was carried out in the presence of *Staphylococcus aureus*.

Stability Test:

Stability testing was carried out as per ICH guidelines at room temperature and at accelerated temperature.

RESULTS AND DISCUSSION

The present study involves both pre-formulation and post-molded test.

Description:

A white to off white crystalline powder as per IP. The obtained drug was found to be white in colour.

Melting Point:

The melting point of Promethazine Hydrochloride was found to be 234°C. The study was conducted using Thiele's tube apparatus. The results obtained were within the range of 222.0°C - 236.5°C thus indicating the purity of the drug sample.

Solubility Analysis:

According to literature Promethazine is freely soluble in water, alcohol, chloroform and is practically insoluble in ether and acetone. The solubility studies of drug were carried out in two different pH (pH 6.3 and pH 6.8). The solubility of Promethazine hydrochloride in pH 6.3 and pH 6.8 was found to be 9.83±0.032 mg/ml and 9.15±0.024 mg/ml respectively.

Scanning of Promethazine Hydrochloride (spectrum-λ max):

Drug analysis of Promethazine Hydrochloride pure drug was undertaken with absorption spectrum scanned over the 800nm-200nm range to determine its λ max. Solutions of concentration 10µg/ml were prepared in methanol and water mixture. The pure drug showed only one peak of absorption spectrum at 249.60nm in methanol and water mixture giving the maximum absorption (λ max) of drug.

Standard calibration curve of Promethazine Hydrochloride:

Promethazine Hydrochloride standard calibration curve was obtained using UV absorption (SHIMADZU-1900). Sample of varying concentrations were prepared in methanol and distilled water mixture. Sample were analyzed at λ max of 249.60nm and their absorbance was noted the equation observed was y=0.0731x+0.0158.

The standard calibration curve was found to be accurate and precise with slope value of 0.0158 and R^2 (Regression coefficient) of 0.998 and the curve was found to be linear in the concentration range of 2-10 µg/ml (Beer's range) at 249.60 nm.

FTIR spectroscopy:

FT-IR spectra of pure drug sample, mixture of various lozenges formulation were analyzed and their results showed similar peaks at their respective wavelengths with no major difference, all the important functional group frequencies Promethazine hydrochloride were present in the spectral peaks of the drug and polymer mixture indicating compatibility of drug with polymers.

Differential scanning calorimetry (DSC) Analysis:

Compatibility studies of pure drug along with all polymers were conducted and assessed by DSC curve (Thermographs). The DSC thermographs of Promethazine Hydrochloride pure drug and physical mixture containing drug, is malt, HPMC E5, sucrose, citric acid, stevia, flavouring agent (Ginger), colouring agent (Quinoline yellow).Promethazine hydrochloride showed an endothermic peak at 234.24^{0}C corresponding to its melting point. The melting endotherm of Promethazine hydrochloride was found to be retained within the limits in the thermographs of physical mixtures incorporated with drug and excipients used.

PROCESS PARAMETERS OF PROMETHAZINE HYDROCHLORIDE AS LOZENGES:

General appearance:

All the developed lozenges were orange colored and had good physical characteristics with a smooth surface, and were round and elongated.

Thickness:

The thicknesses of the formulated lozenges were found to be within the range 11.00±0.0235mm and 14.35±0.0047mm as reported in Table 2.

PROCESS PARAMETERS OF PROMETHAZINE HYDROCHLORIDE AS LOZENGES:

Table 2. Physicochemical parameter of prepared lozenges (F1-F9)

Batches	Thickness (mm) Mean±S.D	Diameter (mm) Mean±S.D	Weight variation (%) Mean±S.D	Hardness (Kg/cm^2) Mean±S.D	Friability (%) Mean±S.D	Disintegration (min) Mean±S.D
F1	11.00±0.0235	12±0	1337.9±0.006	7±0.4714	0.133±0.0008	10.05±0.0707
F2	12.05±0.0047	12±0	1814.9±0.025	8±0.4714	0.136±0.0012	11.6±0.4714
F3	14.10±0.0081	12±0	2275.9±0.020	10±0.4714	0.125±0.0004	13.6±0.4714
F4	11.55±0.0408	12±0	1359.7±0.011	7±0.4714	0.132±0.0008	11.25±0.2041
F5	12.50±0.0047	12±0	1846.2±0.002	8±0.4714	0.137±0.0012	11.78±0.3065
F6	14.35±0.0047	12±0	2324.2±0.006	10±0.4714	0.122±0.0012	13.83±0.4478
F7	12.00±0.8164	12±0	1443.0±0.098	7±0.4714	0.138±0.0016	11.52±0.0648
F8	13.56±0.0094	12±0	1864.0±0.014	8±0.4714	0.138±0.0017	12.06±0.0942
F9	14.00±0.0047	12±0	2332.9±0.003	10±0.4714	0.140±0.0012	20.00±0.4714

Diameter:

The diameters of all the formulations were constant due to the mold and were found to be 12±00.0000mm.

Hardness:

Hardness was found to be in the range of 7±0.4714 and 10±0.4714 Kg/cm^2 as tabulated in Table 2. The results obtained showed that the lozenges have good hardness and these were carried out in triplicates.

Friability test:

Friability for all the formulations (F1-F9) was found to be within the range of 0.122±0.0012 and 0.140±0.0012 as shown in Table 2.The results obtained indicated that the lozenges developed conformed to the I.P specifications (<1%) and had good mechanical strength.

Weight variation test:

The average percentage deviation of all lozenges formulations was to be within the mark, and thus all formulations met the weight uniformity test according to official specifications, ranging from 1337.9±0.006 mg to 2332.9±0.003 mg. As shown in Table 2.

Cooling test:

Visual inspection was conducted during the formulation process to examine any stress crack due to rapid cooling, the creation of air bubbles, surface cracking and black specs. The formulations produced were free of cracking, bubble forming and black specs when examined.

***In vitro* disintegration test:**

The rate of erosion of prepared lozenges ranged from 10.05±0.0707 seconds and 20.00±0.4714 seconds. As tabulated in Table 2.

Moisture analysis:

The moisture content ranged between0.530±0.0012 and 0.851±0.0008, which concluded that the values were within the pharmacopoeial limits (0.5-1%). As shown in Table 3.

Table 3. Moisture, drug content and drug release values

Batches	Moisture content (%) Mean±S.D	Drug content (%) Mean±S.D	Drug release (%) Mean±S.D
F1	0.596±0.0026	96.2± 0.28	96.71± 0.55
F2	0.549±0.0012	97± 0.81	97.44± 0.84
F3	0.530±0.0012	96.6± 0.08	98.22± 0.48
F4	0.729±0.0008	96.4± 0.08	99.55± 0.63
F5	0.759±0.0016	96± 0.55	99± 0.81
F6	0.604±0.0012	97.8± 0.66	97.28± 0.88
F7	0.714±0.0017	95.2± 0.16	96.26± 0.62
F8	0.800±0.0012	97± 0.47	95.25±0.71

F9	0.851±0.0008	97.2± 0.54	99.30±0.75

Drug content:

The mean drug content was registered in triplicates and was found to be between 95.2± 0.16 % and 97.8± 0.66 %. As represented in Table3.

***In vitro* dissolution test:**

The invitro dissolution study for all formulations was conducted using phosphate buffer pH 6.8 using a USP type II device in which the predetermined samples were removed for 30-40 minutes at 5 minutes intervals, and then analyzed for 249.60nm. The cumulative release of respective lozenges was calculated on the basis of the mean amount of Promethazine hydrochloride present. The dissolution studies for lozenges developed (F1 -F9) were in the range of 95.25% to 99.55% as tabulated in Table 3. respectively.

Microbial test:

The presence of sugar content makes lozenges susceptible to microbial growth and hence microbial assessment is seemingly important. The activity was assessed in the presence of *S.aureus* for the optimized formulation F3 it was observed that there was a growth inhibition zone of 13mm. Figure 1. showing the zone of inhibition.

Figure 1: Microbial test conducted using *S. aureus* representing zone of inhibition of formulation F3

Stability studies:

Stability studies at room temperature (25±2°C and 60±5%RH) and at accelerated temperature (40±2°C and 75±5%RH) for 30 days were performed for optimized formulation (F3). Lozenges were examined at the end of 30 day for strength, drug content, and drug release percentage. Stability testes of F3 formulation showed no significant change in hardness, drug content, % drug release and other parameters. From the results obtained it was inferred that F3 was stable and retained its original properties but was found to be more stable at room temperature.

DISCUSSION

Promethazine hydrochloride as a white crystalline powder existed in pure state without odour but had a bitter taste. The melting point is an important factor in order to identify the component and its purity and was found to be 234^0C which is within the range. Promethazine hydrochloride's solubility in both buffers was sufficiently high, but pH 6.8 (phosphate buffer) in un-stimulated saliva was moderately effective due to its maximum buffering capacity. Wavelength at which the absorption of the drug is maximum or the photon absorption is maximum is considered as λmax which was found to be 249.60nm in a mixture of methanol and water. The results upon conducting FT-IR and DSC showed that there were no incompatibilities between drug and excipients and that all the excipients used would not cause any concern in the process as it also indicates that the mixture was stable. Sucrose and isomalt was used as base in the preparation where in these components helped in crystallization of the sugar, in glass transition and to produce adequate hardness also reduced graining tendencies. Stevia the naturally occurring sweetener that was incorporated to block the bitter taste and provide health benefits such as prevention of cancer and blood pressure regulation. HPMC E5 was used as a binder when compared with formulations in its absence didn't show much of a difference in process parameters. Ginger which was included not just helps in blocking the bitter taste but also helps in handling motion sickness to quite an extent. The ratios of sucrose, corn syrup and dextrose used resulted in softening, stickiness and increased moisture content incorporation in larger amounts may lead to graining tendencies and recrystallization of the sugar. All formulations produced, suggested a good physical appearance. Thickness and diameter play a very important role because size helps to generalize the erosion rate. The friability must be < 1% according to IP requirements and the findings obtained have helped to infer that the lozenges had sufficient mechanical power. The weight of all the lozenges prepared didn't vary much and complied with the requirement. Visual observation revealed that the bubbles did not occur which indicated that there was no excessive mixing, during the heating cycle there was no charring nor did caramelization occur and that the lozenges did not crack upon rapid cooling process. The lozenges eroded within 5-15 minutes (F1-F8), the formulation F-9 resulted in 20 minute disintegration due to the increased lozenge weight with an increase in binder. Analysis of the moisture in the prepared formulations was found to be less than 2% due to the reduced capacity of the ingredients to absorb water and hence requires pressurized package to prevent it from stickiness. *In vitro* dissolution studies showed relatively good drug release (95.25%-99.55%) due to greater drug solubility being a component of BCS Class I. Formulations

F1-F3 did not contain binder, F4-F6 contained binder (30mg), F7-F9 contained binder (60mg) irrespective of its presence there was no significant difference in drug release profile.

The microbial growth was tested with *S.aureus* and the zone of inhibition was clearly observed and passed the test. Larger the zone of inhibition greater the antimicrobial activity and moreover the presence of ginger also helps in regulating microbial growth due to the presence of the active constituent gingerol. Stability studies were carried out for F3 formulation at room temperature and accelerated temperatures and it was seen that there were slight changes in hardness and moisture content 8±0 and 0.803±0.0013 respectively. The optimal formulation was achieved by imposing constraints on dependent response and independent variables. The constraints for the response, hardness and disintegration, were set between 7%-10% and 5-15 minutes respectively. The recommended concentration of the independent variables was calculated from the plots using the Design-Expert software with the highest desirability close to 1. The optimal region for getting the desired response value was obtained throughout the X1 ranging between the 472.22 to 1416.66mg, X2 ranging between 0-60mg.Formulation F3 was considered optimized as the parameters didn't show much of difference in the presence of HPMC E5 owing to the component isomalt which just not acts as a base but also as a binder.

The use of factorial design was used to systematically investigate the factors affecting the formulation, and to optimize it in accordance with hardness and disintegration (Figure 2.).Sucrose (X1) and HPMC E5 (Y1) was considered as independent variables whereas hardness (Y1) and disintegration (Y2) were considered as dependent variables. Statistical analysis of response (Y1: hardness): The model F- value of 81.00 implies the model is significant. There is only 0.01% chance that an F value this large could occur due to noise. P- Value less than 0.0500 indicates that model terms are significant. Statistical analysis of response (Y2: disintegration): The model F-value of 6.73 implies the model is significant. There is only a 2.93% chance that an F-value this large could occur due to noise. P-value less than 0.0500 indicate model terms are significant. The regression analysis of model fit revealed that, hardness and disintegration are correlated with active factors X1 and X2. The software generated optimal formulation F3 containing 1416.66 mg of sucrose and without HPMC E5 showed experimental prominent hardness of 9.83 kg/cm^2 and disintegration of 13.9011 sec.

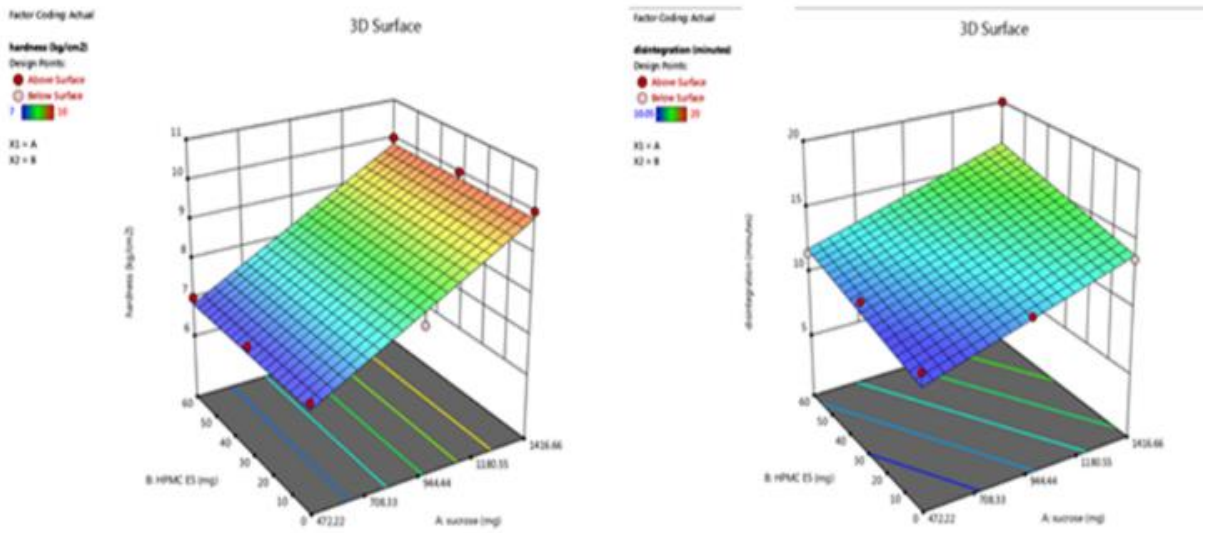


Figure 2. 3D Response graph showing effects of independent factors on hardness and disintegration

CONCLUSION

A successful attempt was made in this current study to formulate a local and systematic medicated confection. It's a simple formulating method and less time-consuming process which is accepted more organoleptically owing to the incorporation of sweetened base as well as sweetener. The formulation of this medicated confection centered not on the use of isomalt as a base but also as a medium to gradually dissolve in the mouth which may also reduce the ability to cause tooth decay. The sweetened base included sucrose and isomalt a tooth friendly component as it does not cause tooth decay and formation of plaque as the bacteria present in the oral cavity fail to convert sugar into acids responsible for decay. Formulation F3 was considered an engineered medicated confection that complied with all the requirements. Lozenges now has a significant role in pharmacy, and so anti-emetic medicated confection can help effectively fight movement sickness by offering a healthier and more efficient start to action.

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