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Promethazine Chewing Gum Formulations for Preventing Motion Sickness: Design, Development, And Characterization

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Abstract

Chewing gums are mobile drug delivery systems, with a potential for administering drugs either for local or systemic absorption via buccal route. It can be administered discreetly without water. Medicated Chewing Gums contains gum base along with antiemetic agent which is intended to chew not to be swallowed. These formulations contain Promethazine, Polyvinyl alcohol, Carboxymethyl agorase, Peppermint oil, Polyethylene glycol (PEG-400), Calcium carbonate, Synthetic gum base, Propyl paraben, and Ascorbic acid. The medicated chewing gums were prepared by the direct compression method. The prepared formulations were evaluated for various pre-compression and post-compression parameters. The in-vitro drug release of Formulation F7 showed satisfactory drug release within 30 min at various chewing conditions. From the results, it is concluded that the chewing gum containing Promethazine HCl will be the potential dosage form for the treatment of chemotherapy induced nausea and vomiting.

Keywords: Promethazine, Medicated Chewing gum, Formulation, Development, Characterization, Stability

INTRODUCTION

A drug's concentration in the body must be maintained over an appropriate time period, therefore new dosing schedules and modified release dosage forms are always being researched and produced. Compared to traditional dosage forms, modified release dosage forms have been greatly improved upon in terms of formulation development and product design, making them much more acceptable. The use of modified dosage forms is increasingly accepted and is drawing the attention of academics throughout the globe. Newer technologies are being developed to change standard, ordinary tablets in order to boost bioavailability and increase acceptance. Oral disintegrating pills, lozenges, medicated chewing gums, effervescent tablets, sublingual and buccal tablets, extended-release tablets, etc., fall within the category of modified-release dosage forms. Gum may be utilized to deliver drugs in an innovative and practical way. These days, medicated gum is just as safe and effective as pills, and it can even be designed to have a variety of drug release patterns and therefore be used with certain populations in mind.

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Mankind has been chewing gum since prehistoric times. At now, it is one of the most widely utilized dosage forms for administering a wide variety of therapeutic agents [1].

Medicated gums have a gum base infused with one or more medications, which are dispersed into the body after being chewed for a certain amount of time and then discarded. Some of the medication was ingested for gastrointestinal absorption after being broken down into saliva during chewing, while the rest was absorbed via the oral mucosa. After the medication had been expelled, the residual bulk was spat out. Chewing gum with active ingredients may be used locally to treat oral problems or taken by mouth to work throughout the body. The recently licensed drug delivery technique of medicated chewing gum has applications in the pharmaceutical, over-the-counter medication, and dietary supplement industries [2].

"State of Maine Pure spruce gum" was the first American chewing gum to be on sale to the general public in 1948. In 1869, Dr. W. F. Semple was granted the first patent. Dentifrice versions of this gum were made but never sold. Aspergum, the first medicinal gum, was introduced to the market in 1928. Aspirin, the primary medicine in this gum, is still widely accessible. Dimenhydrinate is also used commercially as chewing gum for the treatment of motion sickness. However, it was not until the introduction of nicotine chewing gum in 1978 that gum was widely recognized as a practical drug delivery mechanism. With the advancements in science and medicine that have occurred in recent decades, it is possible that humans may one day create medicated gum with the desired qualities. As a new and practical drug delivery technology, gum may accommodate a wide variety of active ingredients. In 1991, the European Council's commission unanimously voted to recognize gum as a pharmaceutical dosage form. Medicated gums are described as solid, single-dose formulations having a base of gum that is meant to be chewed but not ingested, in accordance with the European Pharmacopoeia and related standards [3].

The present study focuses on development and characterization of Promethazine containing chewing gum formulations for preventing vomiting and motion sickness.

MATERIALS AND METHODS

Materials

Promethazine HCl was purchased from Shreya Scientific and Chemical Wholesale, Bilaspur. Gum base, Carboxy methyl agorase, Polyvinyl alcohol, Ascorbic acid, Propyl paraben, Calcium

carbonate, PEG 400, Sucrose, and Peppermint oil were procured from the central store of School of Pharmacy, Chouksey Engineering College, Bilaspur. Double distilled water was obtained from Borosil® water system. Other analytical grade solvents, reagents, and chemicals were purchased from Himedia Ltd., Mumbai.

Instrumentations

Spectroscopic analysis was carried out using double-beam Shimadzu® Ultraviolet-Visible Spectrophotometer (Model UV-1800, Kyoto, Japan) connected to a computer having a spectral bandwidth of 1 nm and wavelength accuracy of ±0.3 nm with a pair of 10 mm path length matched quartz cells was used. All weighing were performed using Shimadzu® electronic balance (Model AUW220D, Kyoto, Japan). FT-IR was performed using Shimadzu® IRAffinity-1S instrument employing KBr disc. Vernier caliper (Indian caliper, Ambala, India), Roche friabilator (Electrolab, India), Chewing gum dissolution test apparatus (Erweka, Germany), Pfizer hardness tester (Pfizer, Spacelabs, India) were employed for evaluation of chewing gums. Stability chamber (Bio-Technics, India) was employed for accelerated stability studies.

Drug-excipient interactions

The interaction of Promethazine with the excipient (carboxymethyl agorase) was determined by Fourier transformed infrared (FT-IR) spectroscopy [4] and Differential Scanning Calorimetry (DSC) [5] to examine the compatibility in the formulation. In order to verify any type of interaction(s); FT-IR spectra and DSC thermogram of pure drug and physical mixture were taken.

Gum Base

Determination of color

The color of gum was observed visually and reported [6].

Determination of softening point of gum base

The sufficient quantity of gum base was taken in porceline dish and heat at the lowest temperature on heating mantle. Softening point (temperature at which gum was started to soft be measured) was determined by thermometer [7].

Determination of solubility of gum base

For determination of solubility of gum base, 1 g of gum base was dissolved in 10 mL of different solvents like diethyl ether, ethanol, chloroform, acetone, pH 6.4 buffer solution, and water. Each

solvent containing gum base kept in sonicator for 24 hrs. After 24 hrs, the solvent was filtered and determine the solubility [8].

Preparation of chewing gum formulations

Each ingredient was weight accurately as per mentioned in **Table 1**. The synthetic gum base was molten slowly with constant stirring in porcelain crucible at 50-55°C, then physical mixture of drug and sucrose was added to it with constant stirring until even distribution of mixture. After calcium carbonate was added as diluents the mixture was allowed to cool at room temperature. After cooling the mixture it was triturated in the mortar and pastel along with other ingredients (ascorbic acid, peppermint oil, etc.). The mixture was triturated until the solid mass was formed. Thin and wide ribbon were made out of this mass and cut in the desired size [9].

Table 1: *Formulation chart for Promethazine chewing gum.*

Ingredients	B1	B2	B3	B4	B5	B6	B7	B8
Promethazine HCl	2	2	2	2	2	2	2	2
Polyvinyl alcohol	-	-	-	1.5	2	2.5	-	-
Carboxymethyl agorase	2	2.5	3	-	-	-	-	-
Polyvinyl alcohol + carboxymethyl agorase	-	-	-	-	-	-	2.2	-
Polyvinyl alcohol + carboxymethyl agorase	-	-	-	-	-	-	-	1.5:2
Peppermint oil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Polyethylene glycol (PEG-400)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Calcium carbonate	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Synthetic gum base	2	2	2	2	2	2	2	2
Propyl paraben	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Ascorbic acid	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20

Pre-compression study

Granules were evaluated suitably for their characteristic parameters such as angle of repose, Hausner's ratio, bulk density, tapped density and Carr's index. Angle of repose was determined by funnel method. Bulk density and Tapped density was determined by cylinder method. Carr's index (C_I) and Hausner's ratio (H_R) was calculated [10].

Post-compression study

Based on reported standards/procedures, compressed content were characterized for their properties such as hardness, friability, thickness, content uniformity and weight variation. The hardness of chewing gum formulations was determined by using Monsanto hardness tester. Friability was determined using Roche friability testing apparatus. Likewise, the thickness was determined using Vernier Calipers. The weight variation testing was carried out according to the guidelines mentioned in USP Pharmacopoeia. Content uniformity was determined by individually weighing 20 units and extracting the powdered material (270 mg) in water. The solution was filtered through 0.45 μm membrane and absorbance was measured at 248 nm after suitable dilution [11].

Evaluation parameter

The optimized formulation was comprehensively evaluated for physical appearance, content uniformity, mass uniformity, dissolution test, organoleptic properties, taste, tensile strength, and pH as per the methods/protocols.

Physical appearance

The physical appearance of the medicated chewing gum formulation was determined in terms of surface smoothness, continuous film, degree of uniformity, and amount of roughness [12].

Content uniformity

10 medicated chewing gum formulations was selected randomly, then their contents was measured, if every single content will lie in between 85% and 115% of the average content, then only it will comply with the test, but if one single preparation was out of this range, then the preparation will not comply with the test [13].

Mass uniformity

20 medicated chewing gum formulations was selected randomly and weighed, not more than 2 single masses should vary the average mass [14].

Dissolution test

Mastication devices are designed to simulate human chewing behavior. To mimic a drug release in these devices or machines, the following test was specified. During each chewing cycle, apparatus speed and pistons' movements should be controlled not to interfere with each other's work. Actually, horizontal and vertical pistons are, respectively, instead of teeth and tongue. A defined volume of dissolution medium was shed into the mastication chamber, the acidity of the

medium reaches pH 6.4 by phosphate buffer and the temperature should be 37°C ± 0.5°C, the piston speed is 60 rpm. The usual number of chews per minute of a normal person was 60 strokes/min, then a part of MCG or the whole gum was placed into the chamber and the apparatus was set and the procedure was started. The machine was stopped at a determined time, the remaining part of the gum was then removed and a sample of dissolution medium was prepared, the content of active agent(s) was determined by a suitable method, after each sampling, dissolution medium could have been replaced by a new and fresh medium so that the dilution factor should be calculated. The content of active agent(s) in the gum residue could be determined too. This test was carried out on three medicated chewing gums for three times [15].

Organoleptic properties

The organoleptic properties of the medicated chewing gum formulation were determined in terms of color, odor, and taste [16].

Taste

A Latin-square design was carried out using a taste panel of some trained and healthy volunteers and then was asked to score to their points of view according to a series of scales like the Likert scale. To finally diagnose the best and most desirable flavor among volunteers; a further taste panel test was performed [17].

Tensile strength

Simply that is a test in which the chewing gum specimens are subjected to tension until such time as failure occurs. The load required for elongation before fracture is recorded by the computer. The tensile testing machine is set for the determination of force-elongation properties. Engineering stress and strain are obtained as described below [18]:

$$\textbf{Stress} = \sigma = P/Ao \text{ (Load/Initial cross-sectional area)}$$

$$\textbf{Strain} = e = \Delta l/lo \text{ (Elongation/Initial gage length)}$$

pH

The medicated chewing gum formulation pH measurement was carried out in triplicate using a pH meter. The equipment was calibrated with buffer solutions and pH values were measured by inserting the electrode directly into the sample at 25°C [19].

Oral mucosal compatibility study

The optimized formulation batch (F7) without drug was made to chew for 15 min by human volunteers (both male and female) and signs for irritation, redness,and erythema were observed after 24 hrs, 48 hrs, and 72 hrs [20].

Accelerated stability studies

The optimized batch of the chewing gum was studied under the accelerated conditions of temperature (40°C±2°C) and moisture (75%±5% RH). The protocol involved weighing the gum unit, wrapping in the aluminum foil, and packing it inside a black PVC bottle for the duration of 90 days. After the termination of the specified period, the content was withdrawn and evaluated suitably for physical appearance, hardness, thickness, and friability [21].

Similarity Factors

The similarity factor (*f*2) is an important parameter in fabricating a new formulation. CDER, FDA and EMEA define it as the 'logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products. The similarity factor (*f*2) involves calculation performed in comparison with reference or with the innovator product to know the possible similarities employing Pair-wise model-independent approach. It was calculated using PCP Disso v2.08 software [22].

Similarity Factor = $$50\log\left\{\left[1+1/n\sum_{t=1}^{n}(Rt-Tt)^2\right]^{-0.5}\times 100\right\}$$

Statistical analysis

The data was displayed in Mean ± SD format. Using Sigmastat® software, data was analyzed using one-way ANOVA and Dunnett's multiple comparison tests. When the p-value is < 0.05, the group means are deemed substantially significant.

RESULTS AND DISCUSSION

Drug-excipient interactions

FT-IR

The drug-polymer interaction study highlighted no as such interaction of carboxymethyl agorase or polyvinyl alcohol with Promethazine. The pure drug demonstrated characteristic peaks at 3522.13 (-OH stretching), 3441.12 (-NH_2 stretching), 1691.63 (-C=O stretching), 1631.83 (-C=N stretching), 1219.05 (C-O), and 1182.40 (C-N) (**Figure 1A**). The polymers; carboxymethyl

agorase (**Figure 1B**) and polyvinyl alcohol (**Figure 1C**) demonstrated characteristics peaks. In the physical mixture, same characteristic peaks were seen (**Figure 1D**), which demonstrated that there was no drug polymer interaction and are compatible with each other.

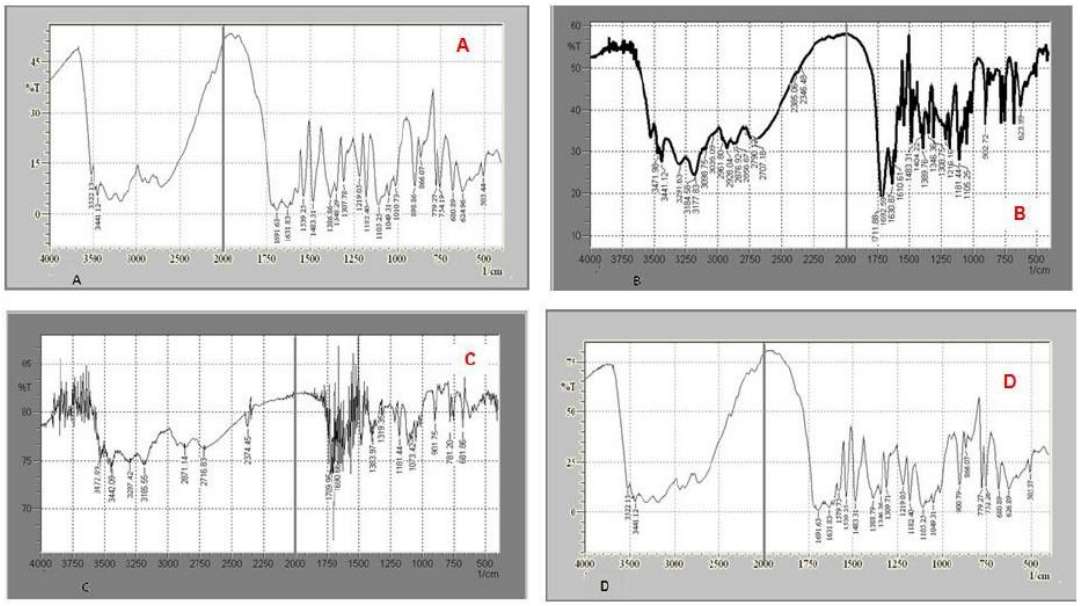

Fig. 1: *Drug-excipients interaction: (A) Promethazine (B) carboxymethyl agorase (C) polyvinyl alcohol (D) physical mixture.*

DSC

The pure drug showed a very pointed endothermic peak at 174.17°C with peak onset at 169.26°C, which corresponds to its melting point (**Figure 2A**). The sharp endothermic peak of drug confirms crystallinity in the structure. In contrast, carboxymethyl agorase (**Figure 2B**) and polyvinyl alcohol (**Figure 2C**) exhibit no such endothermic peak over the entire scanning range of 30 - 300 °C, suggesting its polymeric nature. The physical mixture highlighted the appearance of same drug peak with no difference, suggesting that there is no cross-reactivity between the drug and the polymer (**Figure 2D**).

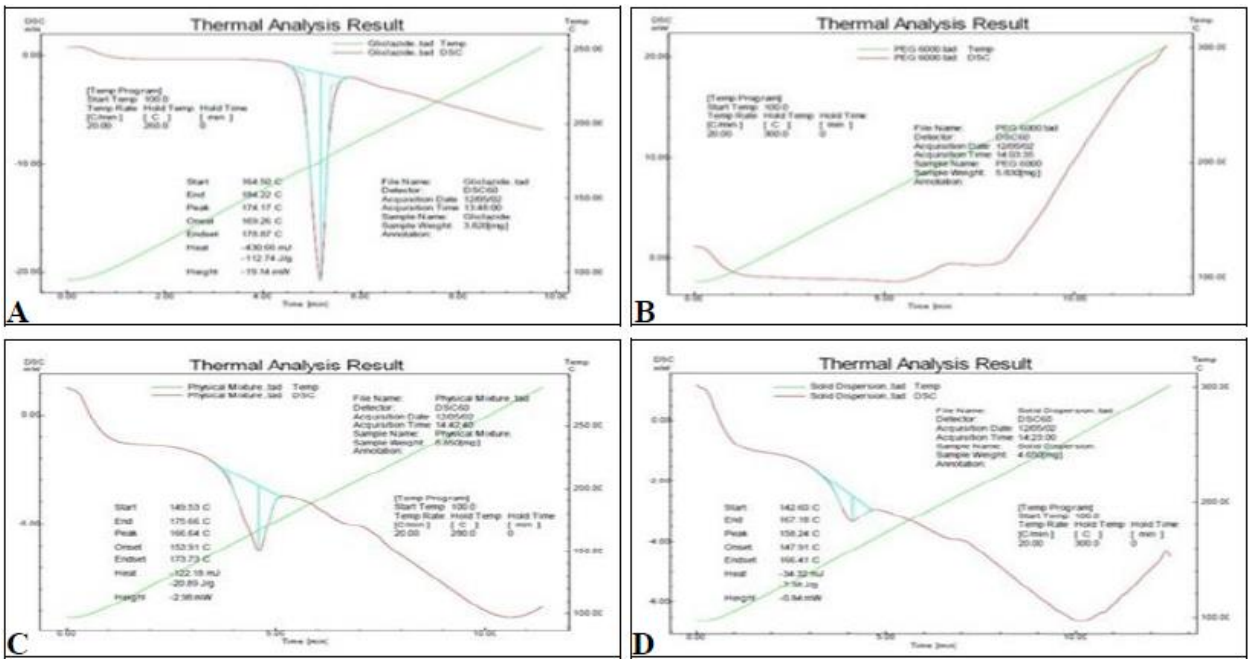

Fig. 2: *Drug-excipients interaction: (A) Promethazine (B) carboxymethyl agorase (C) polyvinyl alcohol (D) physical mixture.*

Gum Base

Color

The color of gum was observed to be pink.

Softening point

The softening point for gum was found 50°C-55°C.

Solubility profile

The solubility of gum demonstrated that the gum was soluble in chloroform and methanol whereas it is insoluble in distilled water and buffer pH 6.4 (**Table 2**).

Table 2: *Solubility profile of gum base.*

S. No.	SOLVENT	SOLUBILITY PROFILE	INTERPRETATION
1.	Methanol	+++	Soluble
2.	Chloroform	+++	Soluble
3.	Distilled water	+	Sparingly soluble
4.	Buffer pH 6.4	+	Sparingly soluble

Pre-compression parameters

The assessed granules were found to be within acceptable bounds. The bulk and tapped densities, which range from 0.853 to 0.874 g/cm^3 and 0.946 to 0.959 g/cm^3, respectively, show good granule packing. For the batches, the angle of repose was observed to be between 29° and 31°, indicating flow characteristics that were generally adequate. The computed Hausner's ratio and Carr's index were in the range of 1.11–1.15; this indicates that packing ability is rather excellent. In essence, the blend showed reasonable micromeritic qualities necessary for demonstrating sustained release properties (**Table 3**).

Table 3: *Evaluation of pre-compression parameters for chewing gum formulations.*

Formulation	Angle of repose (°)	Bulk density (in g/mL)	Tapped density (in g/mL)	Compressibility Index (in %)	Hausner ratio
F1	30.28±0.53	0.853±0.026	0.959±0.085	11.31±1.81	1.15±0.025
F2	31.19±0.55	0.867±0.043	0.976±0.073	10.67±1.37	1.12±0.017
F3	29.13±0.49	0.874±0.024	0.946±0.054	9.76±1.68	1.11±0.019
F4	29.48±0.58	0.856±0.028	0.967±0.038	11.07±1.61	1.13±0.034
F5	30.59±0.37	0.869±0.062	0.970±0.019	10.52±1.76	1.11±0.029
F6	29.96±0.43	0.859±0.038	0.953±0.092	10.91±1.49	1.14±0.023
F7	30.11±0.66	0.862±0.043	0.961±0.047	10.74±1.82	1.12±0.048
F8	29.55±0.84	0.870±0.056	0.958±0.083	10.42±1.91	1.14±0.063

Post-compression parameters

Organoleptic properties

All formulations were pink in color, no characteristic odor, sweet in taste in inner layer, characteristic taste in outer layer, non-sticky in nature, oval shaped, length in the range of 10.62 mm to 10.74 mm, breadth in the range of 8.14 mm to 8.54 mm, and thickness in the range 5.42 mm to 5.79 mm (**Table 4**).

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Table 4: *Organoleptic characterization of chewing gum formulations.*

FORMULATION	COLOR	ODOUR	LENGTH (mm)*	BREADTH (mm)*	THICKNESS (mm)*	STICKINESS
F1	Pink	Odourless	10.67 ± 0.39	8.19 ± 0.74	5.42 ± 0.81	Non-sticky
F2	Pink	Odourless	10.62 ± 0.49	8.31 ± 0.66	5.61 ± 0.28	Non-sticky
F3	Pink	Odourless	10.74 ± 0.43	8.54 ± 0.53	5.79 ± 0.77	Non-sticky
F4	Pink	Odourless	10.70 ± 0.27	8.28 ± 0.34	5.58 ± 0.42	Non-sticky
F5	Pink	Odourless	10.71 ± 0.71	8.14 ± 0.46	5.49 ± 0.58	Non-sticky
F6	Pink	Odourless	10.66 ± 0.27	8.36 ± 0.57	5.59 ± 0.49	Non-sticky
F7	Pink	Odourless	10.69 ± 0.33	8.41 ± 0.67	5.52 ± 0.43	Non-sticky
F8	Pink	Odourless	10.73 ± 0.46	8.29 ± 0.31	5.66 ± 0.38	Non-sticky

*n = 3

pH

The pH of the formulations (F1-F8) was found to be in the range of 6.6-6.9 which indicated that the product pH falls in the close proximity with the physiological or buccal pH.

Drug content

High drug content of the formulations (F1-F8) was found in the range of 94.7% to 99.6%, which indicated the presence of desired amount of drug.

Hardness

The hardness of the formulations (F1-F8) was found to be much optimized in the range of 4.1 Kg/cm^2 to 4.8 Kg/cm^2. A high hardness would definitely prevent friability characteristics but it could be difficult to chew and release the drug properly.

Weight uniformity

The weight uniformity of the formulations (F1-F8) was found to be sufficiently high and proper in the range 1037 mm to 1177 mm. The weight difference of not more than 2 formulations falls within the 5% limit as prescribed in the pharmacopoeia.

Friability

The friability of the formulations (F1-F8) was found to be less than 0.1% which was within the prescribed pharmacopoeia limit. A low friability indicated that the formulation would be stable during transportation and will bear wear and tear during the travel (**Table 5**).

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Table 5: *Physical characterization of chewing gum formulations.*

FORMULATION	WEIGHT UNIFORMITY (mg)*	DRUG CONTENT (%)	pH*	FRIABILITY (%)*	HARDNESS (Kg/cm^2)*
F1	1037 ± 2.17	99.6 ± 1.67	6.6 ± 0.1	0.032 ± 0.006	4.2 ± 0.57
F2	1105 ± 2.13	96.8 ± 1.38	6.8 ± 0.2	0.023 ± 0.008	4.3 ± 0.99
F3	1177 ± 1.91	98.3 ± 1.42	6.9 ± 0.1	0.011 ± 0.003	4.8 ± 0.37
F4	1093 ± 2.29	95.4 ± 1.97	6.7 ± 0.1	0.028 ± 0.007	4.6 ± 0.72
F5	1064 ± 2.23	94.7 ± 1.83	6.8 ± 0.2	0.019 ± 0.004	4.1 ± 0.44
F6	1066 ± 1.88	95.1 ± 1.83	6.6 ± 0.1	0.021 ± 0.006	4.4 ± 0.62
F7	1101 ± 2.09	96.9 ± 1.83	6.7 ± 0.1	0.013 ± 0.005	4.3 ± 0.77
F8	1099 ± 2.11	97.4 ± 1.83	6.7 ± 0.2	0.017 ± 0.003	4.5 ± 0.36

*n = 3

In-Vitro Dissolution test

The in-vitro drug release profile of a chewing gum containing promethazine over a period of 6 hours is as follows: F1: 86.44±0.25%, F2: 88.34±0.36%, F3: 84.35±0.52%, F4: 86.12±0.36%, F5: 89.33±0.35%, F6: 87.73±0.42%, F7: 90.62±0.26% & F8: 93.53±0.35%. Thesevalue represent the percentage of promethazine released from the chewing gum formulation at different time points within the 6-hour duration. The release profile indicates the amount of drug that becomes available for absorption over time. The values are expressed as means with the standard deviation (±) provided. F8 shows a better drug release 93.53%±0.35% from chewing gum in compared to other formulation. On average, 93.53% of the promethazine is released from the F8 chewing gum formulation within 6 hours, with a relatively low degree of variability.

Table 6: *In-vitro Drug Release Profile of Formulation*

Time (hrs.)	% Drug Release ± S. D.							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
1.	12.33±0.55	11.23±0.21	9.42±0.21	14.42±0.29	13.41±0.29	10.52±0.31	13.72±0.29	15.91±0.39
2.	28.22±0.83	25.37±0.26	27.18±0.22	27.72±0.43	24.40±0.39	27.68±0.12	26.72±0.33	30.20±0.19
3.	44.95±0.29	46.26±0.34	43.72±0.53	48.14±0.26	44.93±0.25	47.76±0.13	47.23±0.36	51.63±0.35
4.	68.35±0.36	67.18±0.46	66.63±0.29	65.45±0.39	69.52±0.38	63.32±0.19	64.35±0.39	71.16±0.38
5.	79.32±0.12	75.83±0.49	77.32±0.34	74.93±0.35	78.45±0.31	78.42±0.34	75.43±0.45	81.45±0.32
6.	86.44±0.25	88.34±0.36	84.35±0.52	86.12±0.36	89.33±0.35	87.73±0.42	90.62±0.26	93.53±0.35

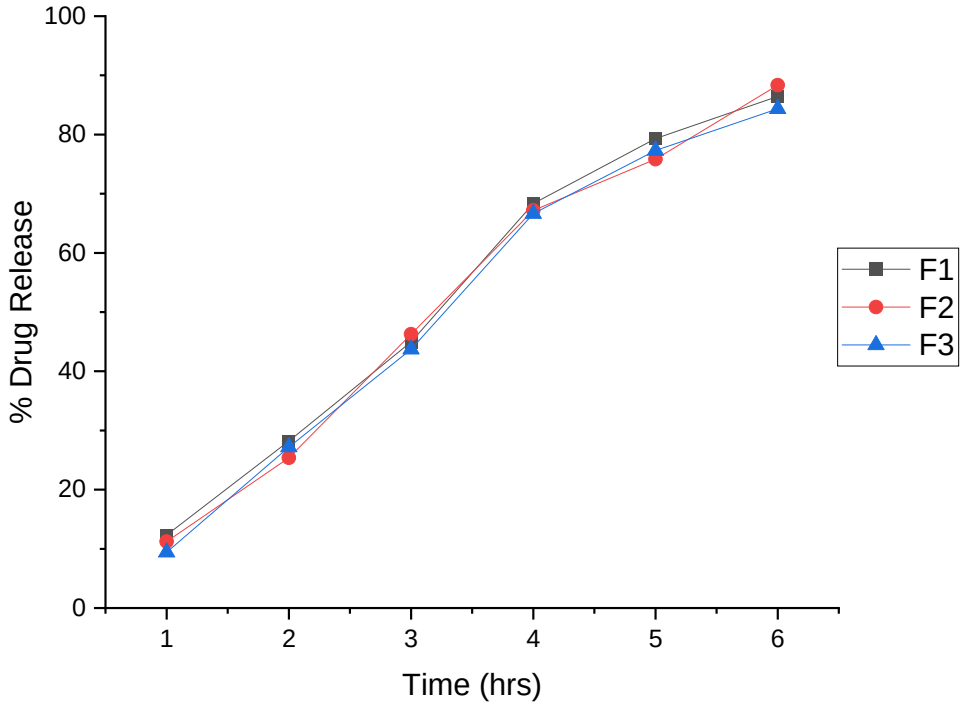

Fig. 3: *Dissolution profile of Promethazine-loaded chewing gum formulations f1, f2 &f3.*

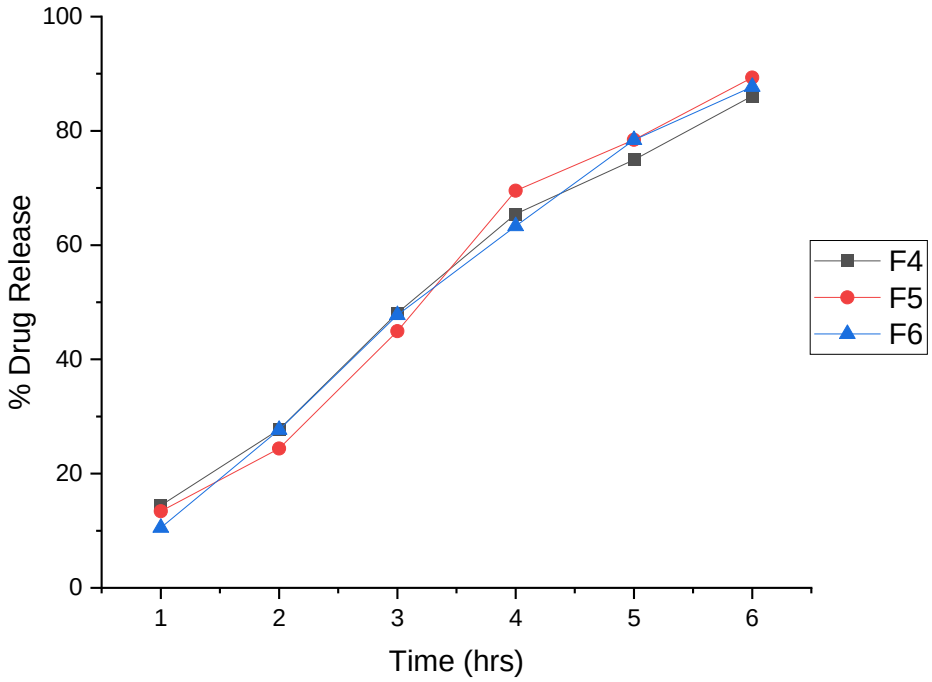

Fig. 4: *Dissolution profile of Promethazine-loaded chewing gum formulations f4, f5 &f6.*

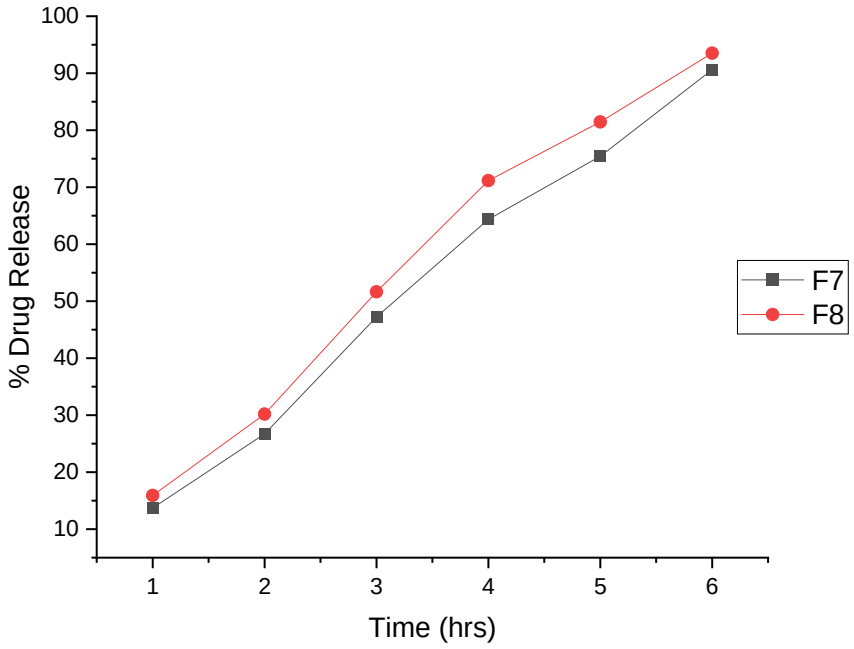

Fig. 5: *Dissolution profile of Promethazine-loaded chewing gum formulations f7&f8.*

Oral mucosal compatibility study

In both male and female volunteers, no oral irritation and associated symptoms such as irritation, redness,and erythema were observed after 24 hrs, 48 hrs, and 72 hrs of applications of optimized formulation without drug (**Table 6**).

Table 7: *Oral mucosal compatibility study.*

Batch Code	Volunteers	Before application			After 24 hrs application			After 48 hrs application			After 72 hrs application		
F7		**I**	**R**	**E**	**I**	**R**	**E**	**I**	**R**	**E**	**I**	**R**	**E**
	Male	X	X	X	X	X	X	X	X	X	X	X	X
	Female	X	X	X	X	X	X	X	X	X	X	X	X

I = Irritation; R = Redness; E = Erythema

Accelerated stability studies

The accelerated stability study (40°C±2°C and 75%±5% RH for 90 days) of the chewing gum displayed no noticeable alterations in terms of physical appearance, hardness, drug content, thickness, and friability of batch F7 formulation. No remarkable dissimilarity was observed in terms of physical appearance, hardness, thickness, and friability (**Table 7**). Although, a small change in drug content (0.11 %) was identified. In summary, it might be concluded that the prepared chewing gum formulation was stable under accelerated conditions and will remain stable under storage conditions.

Table 8: *Accelerated stability study.*

PARAMETERS	0 DAY	90 DAYS
Physical appearance	Pink, odorless, non-sticky	Pink, odorless, non-sticky
Hardness (Kg/cm^2)	4.3 ± 0.77	4.2 ± 0.34
Drug content (%)	96.9 ± 1.83	96.1 ± 1.17
Thickness (mm)	1101 ± 2.09	1100 ± 1.36
Friability	0.013 ± 0.005	0.011 ± 0.003

Section A-Research Paper
ISSN 2063-5346

Similarity factor

The similarity factor calculated by comparing the *in vitro* release profile of optimized formulation with that of marketed product stated a very closely similarity. Similarity factor (*f*2) of the prepared batches was observed to be in between the range 33–73. The optimized formulation F7 displayed the highest similarity factor of 73 reflecting the highest *in vitro* release similarity with that of marketed product. This result also supports the bio-equivalency in relation to the innovator brand and the IVIVC may be predicted on the basis of *in vitro* drug release and the similarity factor under bio-waiver conditions. The prepared formulations have peer perspectives to be marketed as generic medicine.

CONCLUSION

the study focused on the development and characterization of promethazine-containing chewing gum formulations for preventing vomiting and motion sickness. The formulations were prepared using various excipients and evaluated for their physical properties, drug content, in vitro dissolution, oral mucosal compatibility, accelerated stability, and similarity factor. The drug-excipient interaction studies using FT-IR and DSC indicated that there was no interaction between promethazine and the selected excipients, carboxymethyl agorase, and polyvinyl alcohol. The gum base used in the formulations had a pink color, a softening point between 50°C and 55°C, and demonstrated solubility in chloroform and methanol. The pre-compression and post-compression studies showed that the granules had good flow properties and the formulated chewing gum exhibited desirable physical characteristics such as color, odor, taste, hardness, and uniform weight. The pH of the chewing gum formulations was found to be within the physiological range. The in vitro dissolution test demonstrated the drug release profile of the chewing gum formulations over a 6-hour period. The percentage drug release ranged from 84.35% to 93.53%, with formulation F8 showing the highest drug release. This indicates that the chewing gum formulations can effectively release promethazine over time. The oral mucosal compatibility study showed no signs of irritation, redness, or erythema in male and female volunteers after 24, 48, and 72 hours of application of the optimized formulation without drug.

The accelerated stability study conducted at 40°C±2°C and 75%±5% RH for 90 days indicated that the chewing gum formulation remained stable with no significant changes in physical

appearance, hardness, drug content, thickness, and friability. The similarity factor analysis compared the in vitro drug release profile of the optimized formulation with a marketed product. The highest similarity factor of 73 was achieved by the optimized formulation (F7), indicating a close similarity in drug release to the reference product. Overall, the study successfully developed and characterized promethazine-containing chewing gum formulations with desirable physical properties, acceptable drug content, and controlled drug release profiles. These findings support the potential of medicated chewing gum as a practical and effective drug delivery system for promethazine and highlight its potential in the treatment of vomiting and motion sickness.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethics approval and consent to participate

Not applicable.

Human and animal rights

Not applicable.

Consent for publication

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Code availability

Not applicable.

REFERENCES

1. Al Hagbani T, Nazzal S. Medicated chewing gums (MCGs): composition, production, and mechanical testing. *AAPS PharmSciTech*. 2018; 19(7): 2908-20p.
2. Gururajbhat A, Kulyadi GP, Tippavajhala VK. A comprehensive review on formulation, preparation, evaluation and applications of Medicated Chewing Gum. *Res J Pharm Technol*. 2021; 14(3): 1760-6p.

3. Mohammadi N, Ehsani MR, Bakhoda H. Design and evaluation of the release characteristics of caffeine-loaded microcapsules in a medicated chewing gum formulation. *Food Biophys*. 2018; 13(3): 240-9p.

4. Trupti R. Evaluation Optimized Chewing Gum Formulations against Commercial Chlorpheniramine Maleate Tablet Formulation. *Int J Pharm Sci Clin Res*. 2021; 1(3): 51-9p.

5. Kumar K, Teotia D. Development and Evaluation of Medicated Chewing Gum Formulations of Promethazine. *J Drug Deliv Ther*. 2022; 12(1): 133-5p.

6. Al-Ghananeem AM, Leung KP, Faraj J, DeLuca PP. Development of a sustained antiplaque and antimicrobial chewing gum of a decapeptide. *AAPS PharmSciTech*. 2017; 18(6): 2240-7p.

7. McGowan BA, Padua GW, Lee SY. Formulation of corn zein chewing gum and evaluation of sensory properties by the time-intensity method. *J Food Sci*. 2005; 70(7): s475-81.

8. Kartal A, Hietala J, Laakso I, Kaihovaara P, Salaspuro V, Säkkinen M, Salaspuro M, Marvola M. Formulation and in-vivo evaluation of L-cysteine chewing gums for binding carcinogenic acetaldehyde in the saliva during smoking. *J Pharm Pharmacol*. 2007; 59(10): 1353-8p.

9. Boven L, Holmes SP, Latimer B, McMartin K, Ma X, Moore-Medlin T, Khandelwal AR, McLarty J, Nathan CA. Curcumin gum formulation for prevention of oral cavity head and neck squamous cell carcinoma. *Laryngoscope*. 2019; 129(7): 1597-603p.

10. Samiei N, Olyaie E, Saberi S, Zolfaghari ME. Development of a gum base formulation for nystatin; a new drug delivery approach for treatment of oral candidiasis. *J Drug Deliv Sci Tech*. 2018; 48: 59-65p.

11. Aslani A, Esfahani SK. Design, Formulation and Physicochemical Evaluation of Clotrimazole Chewing Gum. *Galen Med J*. 2021; 10: e1084-e1093p.

12. Marzouk MA, Darwish MK, Abd El-Fattah MA. Development of medicated chewing gum of taste masked levocetirizine dihydrochloride using different gum bases: In vitro and in vivo evaluation. *Drug Devel Indus Pharm*. 2020; 46(3): 395-402p.

13. Agrawal A, Sudhakar CK. Design, development, characterization and in-vitro evaluation of medicated chewing gum: granisetron hydrochloride. *J Drug Deliv Ther*. 2018; 8(6-A): 43-7p.

14. Soekanto SA, Levina A, Irianto EN, Adzima AH, Hermansyah H, Wijanarko A, Sahlan M. Chewing gum containing propolis wax from apis mellifera bees for prevention of dental caries disease. *Int J Appl Pharm*. 2019; 11: 141-5p.

15. Salih NM, Kadhim RJ. Manufacturing of Medicate Chewing Gum Against Oral Pathogens by the Extract of Seeds of Lepidium sativum L. *Adv Environ Biol*. 2019; 13(5): 1-6p.

16. Zieschang L, Klein M, Jung N, Krämer J, Windbergs M. Formulation development of medicated chewing gum tablets by direct compression using the SeDeM-Diagram-Expert-System. *Eur J Pharm Biopharm*. 2019; 144: 68-78p.

17. Faraj JA, Dorati R, Schoubben A, Worthen D, Selmin F, Capan Y, Leung K, DeLuca PP. Development of a peptide-containing chewing gum as a sustained release antiplaque antimicrobial delivery system. *AAPS PharmSciTech*. 2007; 8(1): E177-85p.

18. Viljoen JM, van der Walt S, Hamman JH. Formulation of medicated chewing gum containing Sceletium tortuosum and process optimization utilizing the SeDeM diagram expert system. *AAPS PharmSciTech*. 2021; 22(3): 1-5p.

19. Mostafavi SA, Varshosaz J, Arabian S. Formulation development and evaluation of metformin chewing gum with bitter taste masking. *Adv Biomed Res*. 2014; 3: 27-38p.

20. Na DH, Faraj J, Capan Y, Leung KP, DeLuca PP. Chewing gum of antimicrobial decapeptide (KSL) as a sustained antiplaque agent: preformulation study. *J Contr Rel*. 2005; 107(1): 122-30p.

21. Shete RB, Muniswamy VJ, Pandit AP, Khandelwal KR. Formulation of eco-friendly medicated chewing gum to prevent motion sickness. *AAPS PharmSciTech*. 2015; 16(5): 1041-50p.

22. Pundir S, Varma AM. Formulation development and evaluation of antiemetic lozenges of Promethazine hydrochloride. Int J Pharm Res BioSci. 2014; 16: 365-72p.