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Research Article

Formulation of Eco-friendly Medicated Chewing Gum to Prevent Motion Sickness

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ABSTRACT. An attempt was made to formulate medicated chewing gum to prevent motion sickness using natural gum base for faster onset of action and easy administration, anywhere and anytime, without access to water. To avoid the discard issue of gum cud, natural gum base of *Triticum aestivum* (wheat grain) was explored because of its biodegradable and biocompatible nature and easy availability. Prolamin, extracted from wheat, showed good chewing capacity, elasticity, high water retention capacity, antifungal activity, and compatibility with the drug. Formulations were prepared based on a two-factor and three-level factorial design. Amount of calcium carbonate (texturizer) and gum base were selected as independent variables. Elasticity and drug release were considered as the dependent variables. All batches were evaluated for the content uniformity, elasticity study, texture study, *in vitro* drug release study, and chewiness study. Results revealed that medicated chewing gum containing 80 mg of calcium carbonate and 500 mg of gum base showed good elasticity and more than 90% drug release within 16 min. Thus, this study suggested that both good elasticity and chew ability and abundant availability of wheat grain can act as a potential gum base for medicated chewing gum.

KEY WORDS: biodegradable gum; gum base; medicated chewing gum; plasticizer; wheat prolamin.

INTRODUCTION

Medicated chewing gum (MCG) has gained increasing acceptance as a drug delivery system. In this system, drug is buccally absorbed eventually reaching the systemic circulation [1]. When formulating drugs intended to act locally and systemically in the oral cavity, chewing gum should be considered as a potential drug delivery system. Medicated chewing gum is defined by the European Pharmacopoeia and the guidelines for pharmaceutical dosage forms issued in 1991 by the Committee for Medicinal Products for Human Use (CPMP) as "solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not to be swallowed, providing a slow steady release of the medicine contained" [2]. During the chewing process, the drug in the gum product is released from the mass into saliva and absorbed through the oral mucosa or swallowed reaching stomach for gastrointestinal absorption. Mostly the residue (gum cud) remained after chewing is spit out once the drug is released out. As conventional chewing gum bases are not biodegradable or digestible, the disposal of gum cud is a social problem and causes unsightly litter. Natural gum bases are more beneficial than synthetic gum bases because of biodegradable and biocompatible nature and easily availability [3]. Gliadin, a storage protein of *Triticum aestivum* (wheat grain) (family Gramineae) called as prolamin, is one example of the natural gum base having good chewiness [4]. Gliadin is extracted from wheat flour grain using 70% aqueous ethanol.

Medicated chewing gum is beneficial than other conventional dosage forms because it offers faster onset of action and an excellent possibility for the delivery of metabolically unstable drugs. Problems such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route [5]. Moreover, rapid onset of action can be achieved relative to the oral route and, if required, therapy can be discontinued. This drug delivery is suitable for administering to those patients who are less co-operative to oral therapy.

A new chewing gum device in the form of a three-layer tablet (3TabGum) has been developed for freely and poorly water-soluble drugs. Water solubility of drug and chewing time was found to affect the release of drug [6]. Recently, spray-dried microparticles comprising nicotine bitartrate and hypromellose were formulated for incorporation into medicated chewing gum [7].

Motion sickness is a common issue making travel uncomforted. Motion sickness induces nausea and gastric statis, with a very short warning; hence, administrating a drug by oral route is not effective. Patient requires faster onset of action of drug as well as formulation should be convenient to take anytime and anywhere without the use of water. Medicated chewing gum is found to satisfy these needs [8]. Diphenhydramine hydrochloride, with higher salivary solubility and fewer side effects (no extra pyramidal effect), is the suitable

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candidate for formulation of medicated chewing gum to prevent motion sickness.

The purpose of this study was to formulate a medicated chewing gum of natural gum base prolamin isolated from *T. aestivum* to avoid discard of gum cud as well as to get faster drug delivery of diphenhydramine hydrochloride for person having a problem of motion sickness.

MATERIALS AND METHODS

Diphenhydramine hydrochloride was gifted by Indoco Remedies Ltd., Aurangabad, India. Calcium carbonate, glycerin, polyvinyl acetate, and sodium saccharin were purchased from Aryan Scientific, Pune, India. *T. aestivum* grain was procured from local market.

Isolation of Prolamin (Gliadin) from Wheat

To accurately weigh quantity of *T. aestivum* flour (100 g), 70% ethanol (300 mL) was added, stirred for 2 h, and extracted using a multilayer muslin cloth to remove the marc from the solution. The solution was made concentrated to one fifth of its volume by heating at 50°C to get pure prolamin (gliadin). To this, equal amount of water was added and heated at 70°C until solid gum base was formed [9].

Characterization of Isolated Gum Base

Gum base was characterized for swelling index and water retention capacity to determine the amount of water retained required to release the drug. To determine the swelling index, previously weighed isolated gum base powder (1 g) was transferred to a 100-mL measuring cylinder, initial volume was noted, and distilled water was added. After gentle shaking, the measuring cylinder was kept aside for 24 h at ambient temperature and humidity. The volume occupied by the powder sediment was noted [10]. To determine the water retention capacity, the content remained in the measuring cylinder during the study of the swelling index was filtered through muslin cloth. The water was allowed to drain and volume was measured. The difference between the initial and final volume of the drained water was referred as water retention capacity. To know the loss on drying, accurately weighed gum base (1.0 g) was heated in a hot air oven (Remi, India) at 105°C. Gum mass was reweighted and loss on drying was calculated. Loss on drying (LOD) was the difference between the initial weight and the final weight of the sample expressed as a percentage.

The antimicrobial activity of the gum base prolamin was determined using the cup plate method using selected bacteria *Bacillus subtilis* and *Escherichia coli* and fungus *Aspergillus niger*. The prolamin powder was dissolved in the dimethyl sulfoxide to get 100 and 1000 µg/mL solution. Nutrient agar media was prepared, sterilized, and aseptically poured into sterilized petri plate. Bacterial culture was inoculated into the media under aseptic condition and allowed to solidify. Three cups of 6-mm diameter were made with borer at equal distance using sterilized steel borer in each plate. Each cup was filled with 0.1 mL test solution (A=1000 µg, B=100 µg). Standard and control petri plates were prepared by similar method. Petri dishes were kept in the refrigerator for 30 min to allow the diffusion of sample to the surrounding agar medium. All the plates were incubated at 37°C for 24 h in an incubator (Labline, India). After 24 h, zone of inhibition was measured [11].

Formulation of Medicated Chewing Gum

Medicated chewing gum was prepared by using natural gum base wheat prolamin, calcium carbonate (texture imparting agent), glycerin (plasticizer), sodium saccharin (sweetener), polyvinyl acetate (to increase the elasticity of the gum), and peppermint oil (flavor). Based on the trial and error of batches, the concentration range of gum base, calcium carbonate, and polyvinyl acetate was selected. The best possible levels obtained for gum base and calcium carbonate were 450 to 550 mg and 70 to 90 mg, respectively. Hard solid or sticky gum mass was formed, if deviated these ranges. Accurately weighed quantities of gum base, calcium carbonate, and saccharin were mixed properly in mortar. The polyvinyl acetate was dissolved in small quantity of ethanol and mixed in above excipients. Then glycerin and peppermint oil were added. 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 [12].

Experimental Design

Optimization technique was used to get the best possible combination of two parameters, gum base and calcium carbonate. Various batches of medicated chewing gum of diphenhydramine hydrochloride were prepared based on the 3^2 factorial design using Design-Expert® (version 9.0.3.1) software. Two factors were evaluated each at three levels. Amount of calcium carbonate (X_1) and gum base (X_2) were selected as independent variables (Table I). Elasticity (Y_1) and drug release (Y_2) were selected as the dependent variables of the response parameters.

Evaluation Parameters of Medicated Chewing Gum

Medicated chewing gum was evaluated by performing following tests.

Physical Appearance

All the batches were visually evaluated for physical appearance, color, odor, and taste. The texture study was performed manually by pressing the gum between the thumb and the finger. The texture feel was characterized into sticky, good, or solid mass.

Table I. Coded Levels of Factorial Design

	Levels used		
Factor	Low (−1)	Medium (0)	High (+1)
Amount of calcium carbonate (mg) (X_1)	70	80	90
Amount of gum base (mg) (X_2)	450	500	550

Determination of Content Uniformity

Three chewing gums were selected randomly. Each gum was dissolved in 100 mL phosphate buffer pH 6.8. The amount of diphenhydramine hydrochloride was analyzed by measuring the drug absorbance at 258 nm using double beam UV spectrophotometer (UV-1800, Shimadzu, Japan).

Elasticity Study

Elasticity of chewing gum is one of the important parameters. Appropriate elasticity of chewing gum contributes to increase the patient compliance as well as the proper release of the drug. The elasticity of F1 to F9 was determined using CT3 texture analyzer (Brookfield Engineering Inc., USA). To determine the elasticity, TA3/100 probe and fixture of TA-RT-KI was used for the study. The tension was selected as a test mode at target of 80 mm. Trigger load and load cell were kept at 10 kg and 10,000 g, respectively. Chewing gum of size 1×1 mm^2 was randomly selected and was fixed between the two clamps of probe TA3/100. The lower clamp was held stationary and chewing gum was pulled apart by the upper clamp. It was pulled and stretched till the chewing gum broke, losing its elasticity. The force required at this point was recorded. Data collection and calculations were performed using texture-pro CT V1.3 build 14 software [13].

Drug Release Study

In Vitro Dissolution Study in Phosphate Buffer. The dissolution study of the chewing gum is relatively different than the conventional dosage forms. The mechanical force is required to release the drug from the chewing gum. The chewing activity of the patient and oral health of mouth cavity also influences the drug release. Because of these reasons, apparatus consisted of following parameter was considered for the release of gum formulations which simulated human chewing behavior [14]. *In vitro* drug release of diphenhydramine hydrochloride chewing gum was performed by using dissolution test apparatus of medicated chewing gum based on European Pharmacopoeia at 40 mL dissolution medium of pH 6.0 phosphate buffer maintained at temperature 37±0.5ºC [15]. Five milliliters of aliquots was withdrawn at periodic time interval and replaced with preheated fresh dissolution media.

In vitro Dissolution Study in Simulated Saliva. In vitro drug release study in simulated saliva was performed to depict the influence of various substances present in the saliva comparable to phosphate buffer. Drug release of F5 in simulated saliva was carried out using dissolution test apparatus as mentioned above. Simulated saliva was consisted of the following components: potassium chloride (0.720 g), calcium carbonate dehydrate (0.220 g), sodium chloride (600 g), potassium phosphate monobasic (0.680 g), sodium phosphate (0.866 g), potassium bicarbonate (1.500), and citric acid (0.030 g). These components were dissolved in 1000 mL water maintained at 37 ±0.5°C [16]. The study was performed in triplicate.

Buccal Absorption Test (Beckett and Triggs test)

Beckett and Triggs developed a method to measure the drug permeability of drug through the buccal cavity at various pH values [17]. The test was carried out in human volunteers by swirling 25 mL drug solution for 15 min at pH values 6.0, 6.5, and 7.0 followed by the expulsion of the solution. The volunteers were asked to rinse the oral cavity with distilled water. The expelled solution and rinse was combined together. The amount of drug remaining in the expelled volume was then analyzed to assess the amount of drug absorbed into the oral mucosa.

Chewing Study of Gum Formulation

The chewing gum should provide the good mouth feel and comfort during chewing without sticking to the teeth. However, the amount of saliva secreted contributes mainly in chewing the formulation. Three male and three female volunteers were asked to chew the placebo chewing gums (without drug) F1 to F9 for 1 min without swallowing saliva. The outcome of chewing process provided by volunteers was categorized accordingly as good, bad, and sticky.

Stability Study

Stability study of chewing gum was studied to obtain a stable product which assures safety and efficacy, till shelf life, at defined storage and package conditions. Stability study was done according to ICH guidelines to assess the combined effect of drug, gum base, and excipients on the stability of the formulation. Optimized formulation was placed in vials and stored in stability chamber (Thermolab, India) at 30°C ±2°C/65% RH±5% RH. The samples were evaluated for the color, taste, drug content, *in vitro* drug release study and growth of microorganisms after 7, 15, and 30 days and 3 months.

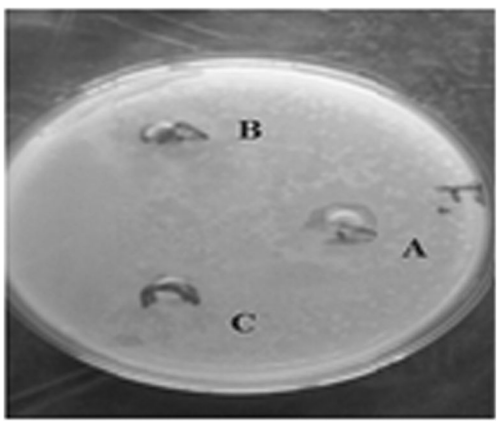

Fig. 1. Zone of inhibition showing antifungal activity of chewing gum base. *A* is gum base concentration (1000 μg/mL), *B* is gum base concentration (100 μg/mL), and *C* is control

Table II. Composition of Medicated Chewing Gum

Formulation code	Calcium carbonate (mg) (X_1)	Gum base (mg) (X_2)	Drug (mg)	PVA (mg)	Sodium saccharin (mg)	Glycerin (mL)	Peppermint oil (mL)
F1	−1	−1	5	50	10	0.05	0.01
F2	0	−1	5	50	10	0.05	0.01
F3	1	−1	5	50	10	0.05	0.01
F4	−1	0	5	50	10	0.05	0.01
F5	0	0	5	50	10	0.05	0.01
F6	1	0	5	50	10	0.05	0.01
F7	−1	1	5	50	10	0.05	0.01
F8	0	1	5	50	10	0.05	0.01
F9	1	1	5	50	10	0.05	0.01

*X*1 amount of calcium carbonate [70 mg (−1), 80 mg (0), 90 mg (1)], *X*2 Amount of gum base [450 mg (−1), 500 mg (0), 550 mg (1)], *PVA* polyvinyl acetate

RESULTS

Characterization of Gum Base

Extracted gum base showed no swelling index but was found to have high water retention capacity. The water retention capacity was found to be 2.366±0.023 mL. Chewing gum base showed very less loss on drying (0.50%), which indicated less moisture content, supportive to inhibit growth of microorganisms. No antibacterial activity was found on the gum base. However, the gum base showed the antifungal activity by forming zone of inhibition (11.66±0.23 mm), at concentration of 1000 μg/mL, but no activity at 100 μg/mL (Fig. 1). Therefore, the amount of gum base selected was above this concentration.

Experimental Design

Experimental trials were performed for nine possible runs suggested by factorial design. Mathematical treatment of the possible combinations of batches F1–F9 is shown in Table II.

Evaluation Parameters of Medicated Chewing Gum

Formulations F1 to F9 were found to be pale yellow in color with no bitter taste. All the formulation batches were found to have drug content within the prescribed range (94 to 97%).

Texture Feel Study

Varied results were obtained for texture feel test ranging from solid mass, sticky, good to very good. Outcomes of texture study performed for F1 to F9 are shown in the Table III. Formulations F1, F2, and F8 showed good texture feel. Formulations F4 and F7 were found to be sticky, while F3, F6, and F9 were hard to touch. Formulation F5 was found to have very good texture feel with appropriate softness and hardness.

Elasticity Study

The elasticity of F1 to F9 determined by using CT3 texture analyzer is depicted graphically in Fig. 2. F1–F3, F4–F6, and F7–F9 containing increase in level of calcium carbonate at same level of gum base showed decrease in elasticity. Formulations F4, F5, and F7 were found to possess highest elasticity. Formulations F1, F4, and F7 containing increase in level of gum base at same level of calcium carbonate (low level) showed increase in elasticity. F3, F6, and F9 containing increase in level of gum base at same level of calcium carbonate (high level) showed decrease in elasticity.

Drug Release Study

In vitro Dissolution Study in Phosphate Buffer. In vitro drug release study of formulations F1 to F9 performed in phosphate buffer is shown in Fig. 3. Formulations F2 to F6 showed faster drug release (more than 90%) within 16 min. F1, F6, F7, and F8 showed more than 80 to 87% drug release within

Table III. Evaluation Parameters of Medicated Chewing Gum

Formulation code	Color	Texture feel	Total weight	Drug content (%)	Elasticity study (mm)
F1	Pale yellow	Good	604.75±0.17	96.6	11.9
F2	Pale yellow	Good	614.7±0.212	96.0	10.5
F3	Pale yellow	Solid mass	624.8±0.14	94.0	10.22
F4	Pale yellow	Sticky	655±0.66	93.2	12.65
F5	Pale yellow	Very good	664.8±0.141	97.2	12.51
F6	Pale yellow	Solid mass	674.9±0.070	96.0	7.9
F7	Pale yellow	Sticky	705.05±0.035	94.6	12.77
F8	Pale yellow	Good	714.95±0.035	94.6	10.29
F9	Pale yellow	Solid mass	724.9±0.63	95.2	4.8

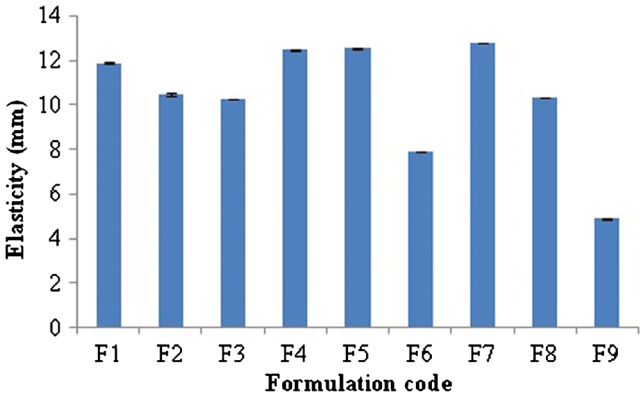

Fig. 2. Elasticity study of the medicated chewing gum

16 min. F9 showed incomplete drug release (76%) within 16 min. F5 showed highest drug release (94%) within 16 min.

In vitro Dissolution Study in Simulated Saliva. *In vitro* dissolution study performed for F5 in simulated saliva released more than 94.63% of drug within 16 min (Fig. 3).

Buccal Absorption Test (Beckett and Triggs test)

Buccal absorption test of diphenhydramine revealed that more than 95% of drug was buccally absorbed within 5 min when available to the buccal mucosa at pH 6.0 (Fig. 4).

Chewing Study

The outcomes of chewing of placebo formulations (F1 to F9) expressed by three male and three female volunteers are as shown in Table IV. All six volunteers highlighted F5 formulation possessing very good texture feel, good mouth feel, and chewing easiness.

Stability Study

The formulation was found to be stable for 3 months at accelerated conditions. There was no change in color and taste after periodic removal of samples (7, 15, and 30 days and 3 months). Drug content of F5 was found to be reduced from 97.2% to 96.6%, which was within acceptable range. Drug release did not get much affected and reduced from 94% to 93.4% within 16 min and found to be within acceptable range. No growth of microorganisms was observed after completion of accelerated stability study of 3 months.

DISCUSSION

Characterization of Gum Base

Due to high water retention capacity, more amount of saliva was available for the dissolution of the drug, facilitating the release of drug in the saliva. High water retention capacity of gum base facilitated more retention of saliva which helped to solubilize the drug. The water holding capacity of the gum helped to increase the dissolution rate of the drug. The prolamin gum base was found to have good water retention capacity suitable for the drug release in the buccal cavity. Low value of loss on drying of prolamin gum base indicated less moisture content and other volatile components, which helped to prevent the growth of microorganism, even though the gum base is of natural origin.

No antibacterial activity was determined in the gum base against bacteria *B. subtilis* and *E. coli* and fungus *A. niger*. The antifungal activity of gum base at higher concentration reduced the risk of contamination by fungi, which is a major issue while using a natural gum base.

Evaluation Parameter of Medicated Chewing Gum

The evaluation parameters of chewing gum are shown in Table III. Uniformity in drug content and color of all batches

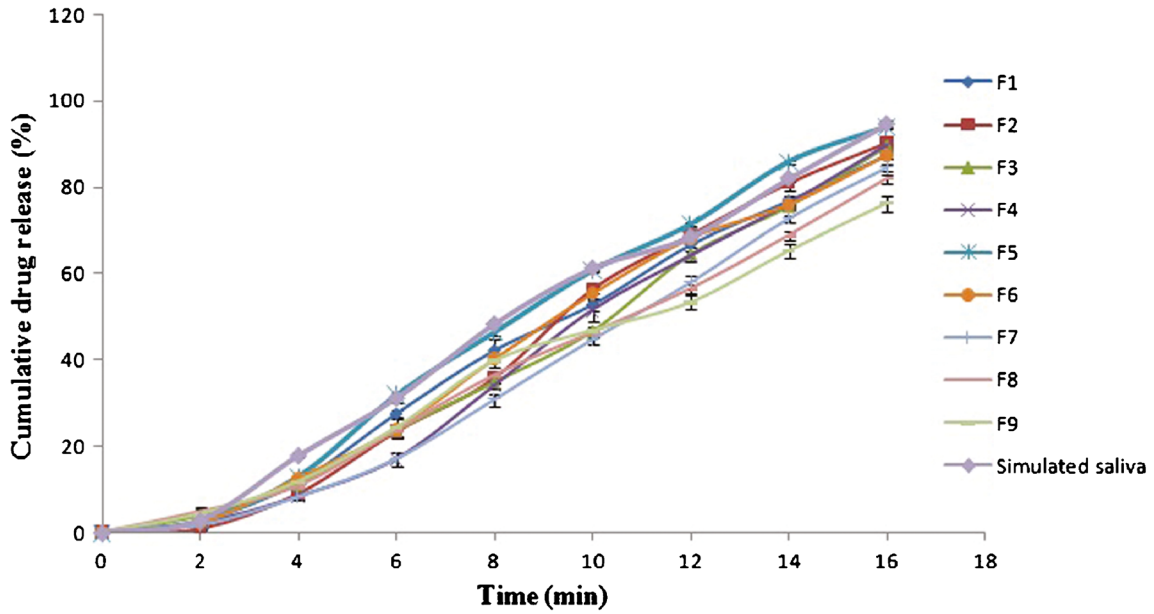

Fig. 3. *In vitro* dissolution profile of medicated chewing gum

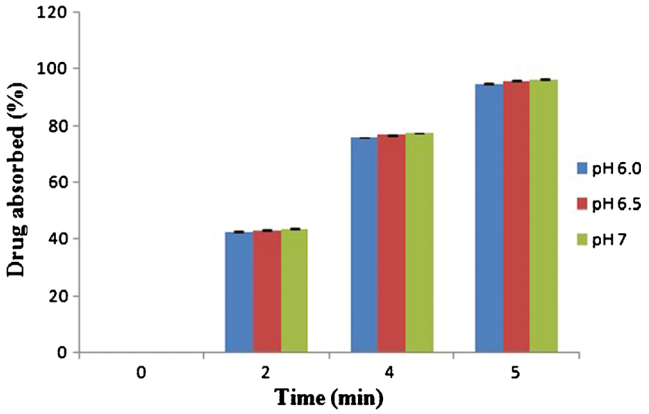

Fig. 4. Buccal absorption test

revealed that the method of preparation did not differ batch to batch. Weight of each formulation varied due to varying concentrations of gum base and calcium carbonate.

Texture Study

Formulation F5 was found to have very good texture feel. The texture of the chewing gum was found to be dependent on the concentration of the calcium carbonate. Good texture of chewing gum contributes to the patient compliance as well as affects the esthetic appeal. Calcium carbonate, added as texturizer, provided hardness to the chewing gum base. Appropriate amount of calcium carbonate (80 mg) offered very good texture (F5); the less amount of calcium carbonate made formulations sticky, while the amount more than 80 mg retarded the drug release.

Elasticity Study

The elasticity of formulation was found to be dependent on the amount of calcium carbonate. The elasticity of the chewing gum was increased with decrease in the amount of calcium carbonate at the same level of the gum base. Elasticity of formulation considered as one of the dependent variables was further discussed in detail in the next section.

Table IV. Chewing Study Performed by Human Volunteers

Formulation code	Number of human volunteers					
	1	2	3	4	5	6
F1	+	−	+	+	−	+
F2	+	+	+	+	+	+
F3	+	+	+	+	+	+
F4	−	−	−	−	−	−
F5	++	++	++	++	++	++
F6	+	+	+	+	+	+
F7	−	−	−	−	−	−
F8	+	+	+	+	+	+
F9	+	+	+	+	+	+

++ represents very good, + represents good, and − represents sticky

Effect of Formulation Variables on Elasticity

A mathematical relationship between factors and variables was generated by response surface regression analysis using Design-Expert® (version 9.0.3.1) software. Equation 1 shows the relationship between variable and response of elasticity (Y_1).

The regression coefficient for Y_1 (elasticity) is as follows:

$$Y_1 = 11.75 - 2.46X_1 - 0.88X_2 - 1.70X_1X_2 - 1.17X_1^2 - 0.98X_2^2 \quad (1)$$

where Y_1 is elasticity, X_1 is the amount of calcium carbonate, and X_2 is amount of gum base.

The quadratic model was found to be significant with F value 10.82 ($p<0.05$), indicated that the model was significant (Table V). A negative sign before a factor in polynomial equation indicated that the response has reciprocal effect on the factor.

Contour Plot and Three-Dimensional Response Surface Plot of Elasticity. Two-dimensional contour plot and three-dimensional response surface plot are shown in Figs. 5 and 6. These plots are very useful tools to understand interaction effects of the two factors on the responses at a time. The contour plot did not show straight line, which indicated that there was no linear relationship between the factor X_1 and X_2. Elasticity of the gum increased with decrease in the concentration of calcium carbonate at the same concentration of the gum base prolamin.

The combined effect of factors X_1 (calcium carbonate) and X_2 (gum base) can be further elucidated with the help of three-dimensional response surface plot (Fig. 6). High level of factor X_2 attained less elasticity at the high level of the factor X_1 but showed high value of elasticity at low level of the factor X_1. It indicated significant effect of factor X_2 on the elasticity. The increase in elasticity was observed at increasing concentration of gum base and low level of calcium carbonate of all three formulations (F1, F4, F7). However, at same high level of calcium carbonate, elasticity was found to be decreased (F3, F6, F9). These results attributed that the amount of gum base contributed more on the effect of elasticity when used in combination with calcium carbonate.

Confirming Optimization Capability. The experimental factorial design suggested F5 as the optimized batch (80 mg of calcium carbonate and 500 mg of gum base). According to factorial design, the predicted value of response (Y_1) elasticity was 11.75 and actual value was 12.51. The percent error was found to be 6.46%, which was found to be very less.

Table V. Summary of ANOVA for Response Parameter of Elasticity

Source	Sum of squares	Degree of freedom	Mean squares	F value	p value prob > F
Model	57.25	5	11.45	10.82	0.0390 (S)
Residual	3.18	3	1.06		
Total	60.43	8	12.51		

S significant

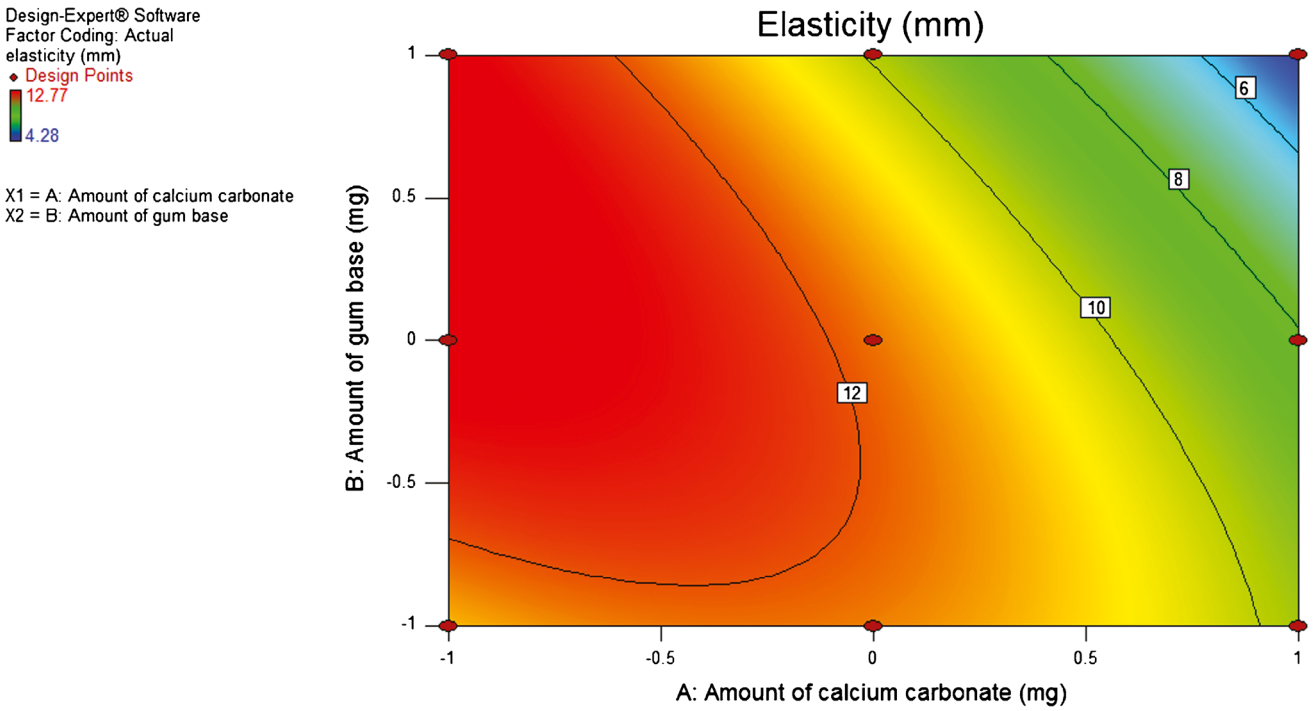

Fig. 5. Contour plot showing effect of factors on elasticity

Drug Release Study of Medicated Chewing Gum

In vitro Dissolution Study in Phosphate Buffer. In vitro drug release of chewing gum was found to be dependent on the concentration of the gum base and calcium carbonate (texturizer). To get the best possible combination having the highest drug release with good elasticity, the drug release study was performed in self-designed apparatus based on European Pharmacopoeia. The drug release of F1 to F9 is represented in Fig. 3. Formulations F7, F8, and F9 contained maximum amount of gum base (550 mg) and showed slow and incomplete release. These formulations were also found to be somewhat sticky after 5 min, when placed in dissolution medium. Formulations F1, F2, and F3 (gum base 450 mg) released the drug rapidly. Formulations F5 and F6 (gum base 500 mg) showed completed drug release. However, texture modifier calcium carbonate was found to play an important role in the drug release while providing good texture. Less amount of texturizer (70 mg) did not provide sufficient strength to the gum,

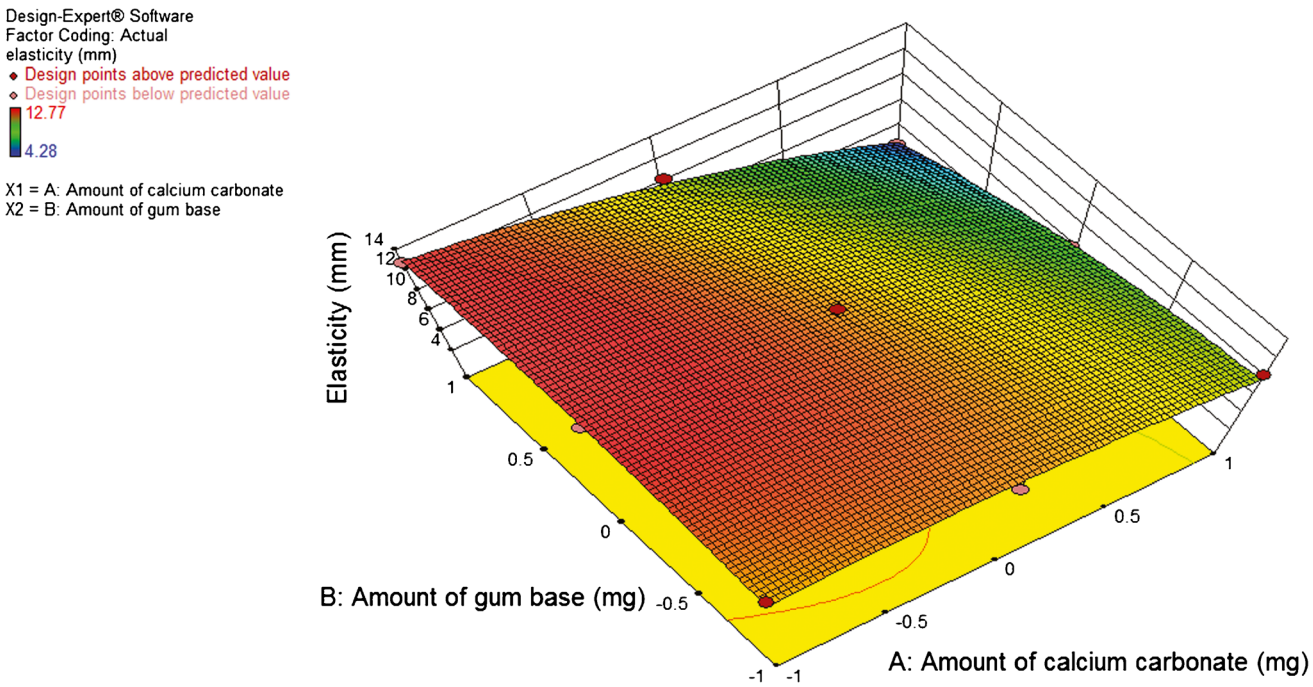

Fig. 6. Response surface plot showing combined effect of factors on elasticity

Table VI. Summary of ANOVA for Response Parameter of Drug Release

Source	Sum of squares	Degree of freedom	Mean squares	*F* value	*p* value prob > F
Model	214.80	5	42.96	18.61	0.0182 (S)
Residual	6.92	3	2.31		
Total	221.72	8	45.17		

S significant

while increased amount (80 mg and further 90 mg) provided good texture. However, presence of more amount of texturizer and gum base retarded the drug release (F9).

In Vitro Dissolution Study in Simulated Saliva. Formulation F5 showed no significant deviation in drug release in simulated saliva when compared against the release of drug in phosphate buffer pH 6.0 (Fig. 3). Thus, it confirmed the suitability of phosphate buffer of pH 6.0 as dissolution medium to study the drug release of medicated chewing gum.

Effect of Formulation Variables on Percent Cumulative Drug Release

The regression coefficient for Y_2 (drug release) is as follows:

$$Y_2 = 92.29 - 1.42X_1 - 4.12X_2 - 2.58X_1X_2 - 2.87X_1^2 - 5.36X_2^2 \quad (2)$$

where Y_2 is drug release, X_1 is the amount of calcium carbonate, and X_2 is amount of gum base.

The quadratic model was found to be significant with *F* value 18.61 ($p<0.05$), indicated that the model was significant (Table VI). Negative sign before both the factors X_1 and X_2 in polynomial Eq. 2 shows the reciprocal effect on drug release. Higher numerical value of X_2 shows more influence of factor X_2 than X_1.

Contour Plot and Three Dimensional Response Surface Plot of Percent Drug Release. Two-dimensional contour plot and three-dimensional response surface plot are shown in Figs. 7 and 8. Absence of straight line in the contour plot indicated no linear relationship between the factors X_1 and X_2. The percentage release increased with increase in concentration of gum base (X_2) till medium level and then decreased. At the high and low level of factor X_2, the drug release was less and at medium level of factor X_2 showed high amount of drug release.

The combined effect of factor X_1 (calcium carbonate) and X_2 (gum base) can be further elucidated with the help of response surface plot (Fig. 8). The medium level of factor X_2 showed high percent of drug release. Increase in the concentration of factor X_1 decreased the drug release. The medium level of both the factors X_1 and X_2 showed high value of drug release which indicated that factor X_1 also showed significant effect on the drug release. The obtained data revealed that medium level of both, the calcium carbonate and gum base, showed highest drug release, hence considered as optimum range for formulation.

Confirming optimization capability. According to factorial design, the predicted value of response (Y_2) percent drug release was 92.28 and actual value was 94. The percent error was found to be 1.86%. The experimental factorial design suggested F5 as optimized batch.

Buccal Absorption Test (Beckett and Triggs test)

The test confirmed the rapid drug absorption through buccal mucosa at pH 6.0, when available in dissolved form,

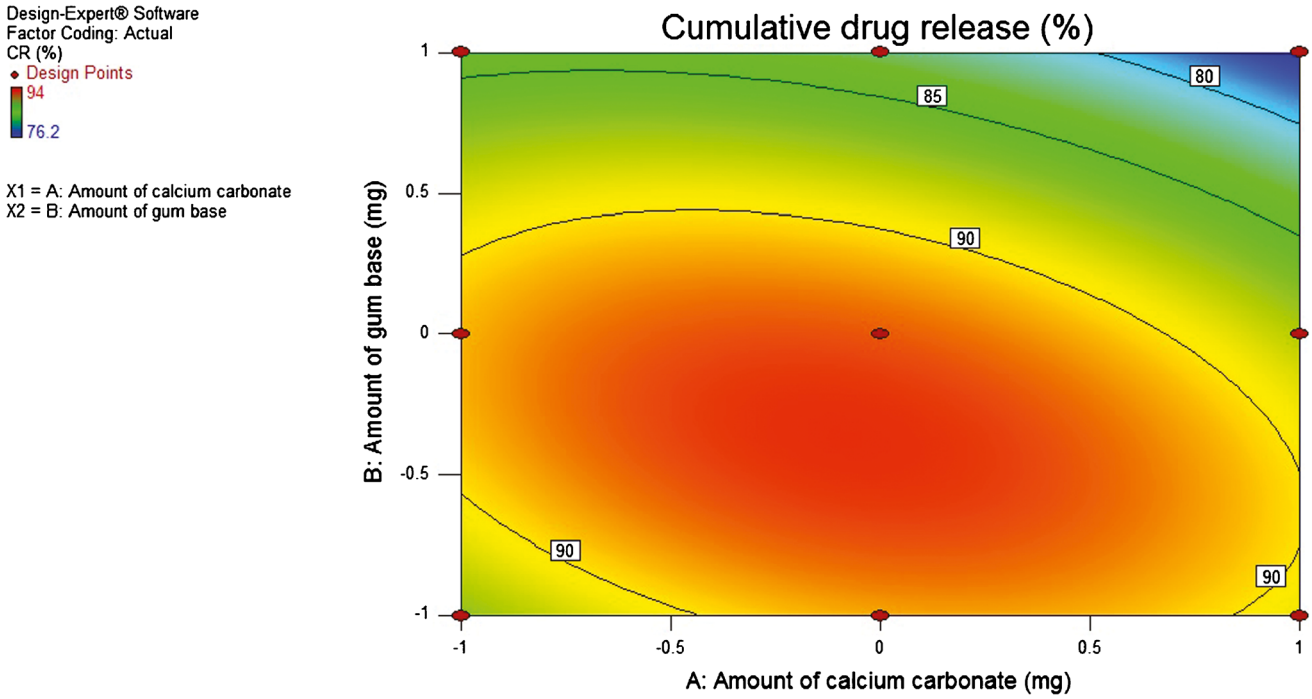

Fig. 7. Contour plot showing effect of factors on drug release

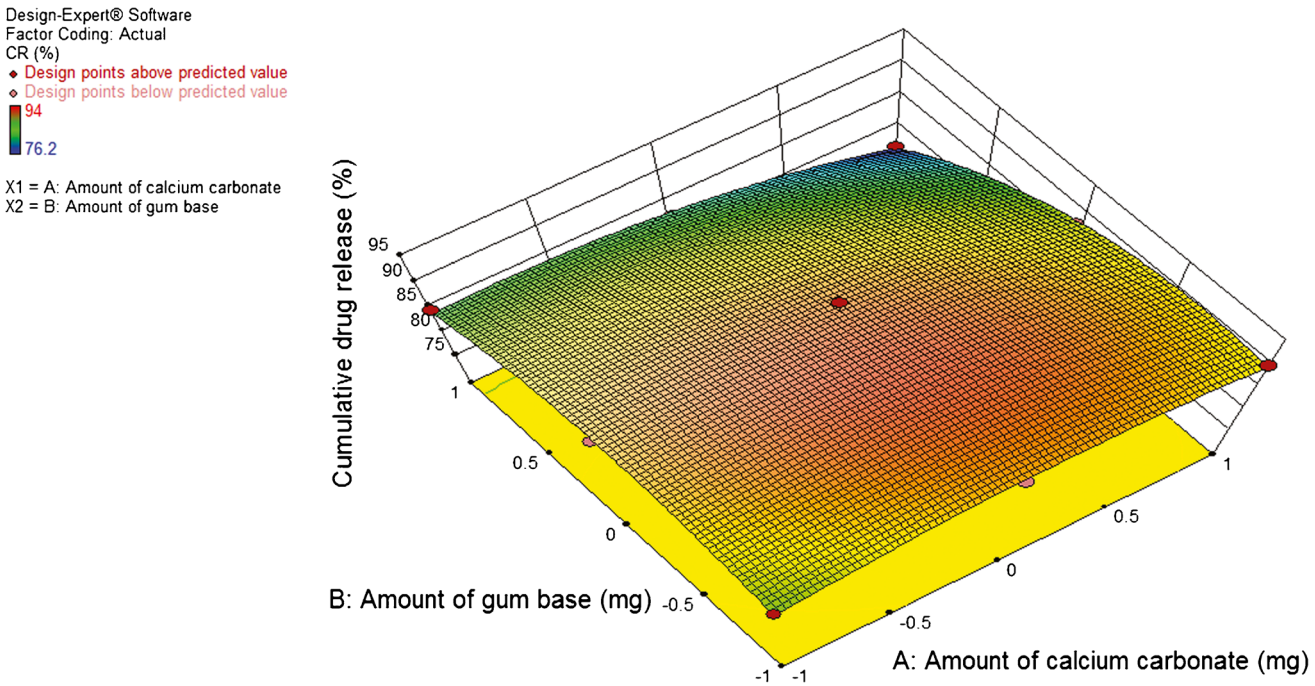

Fig. 8. Response surface plot showing combined effect of factors on drug release

thus avoiding first pass metabolism. Hence, once the drug was released from the chewing gum and available in the oral cavity, and it was immediately absorbed buccally. Therefore, medicated chewing gum is proved to be the best drug delivery system for faster onset of action needed in motion sickness.

Chewing Study

Saliva secretion and chewing activity varies person to person. These factors further affect the drug release from the formulation. Also, the chewing gum should have good mouth feel to attain patient compliance. Based on the outcome suggested by volunteers, no significant change in the chewing ability was observed categorized as male and female volunteers. Formulation F5 was suggested as the best formulation out of nine formulations.

Optimization

The software which generated mathematical relationship between factors and variables was used to get the optimum formulation. The factorial design was used to optimize the response variables elasticity (Y_1) and drug release (Y_2). The optimized formula was achieved by setting the maximum elasticity in the range of 12.0–12.6 mm and drug release of 90% within 16 min. Formulation F5 showed maximum elasticity and drug release as well as passed the texture test and the chewing test study. Formulation F5 was found to be an optimized formulation which contained 80 mg of calcium carbonate and 500 mg of gum base.

Stability Study

No change in color and taste of medicated chewing gum attributed to stable formulation. Drug content and release within the range confirmed the stability of formulation. Use of natural gum base as an excipient in the chewing gum highlighted the risk of growth of microorganisms. However, accelerated stability study performed for the period of 3 months revealed the absence of growth of microorganism in the formulation. Thus, natural gum base can be a good choice for formulation of medicated chewing gum.

CONCLUSION

The present study was focused on the eco-friendly formulation of medicated chewing gum by exploring the natural gum base for rapid drug release. Wheat prolamin was proved to be better gum base to avoid the disposal issue of gum cud. Wheat prolamin showed antifungal activity and high water retention capacity, suitable for more amount of saliva to get available to facilitate the drug release. Medicated chewing gum consisted mainly of calcium carbonate and gum base showed good elasticity, chew ability, and satisfactory drug release. Therefore, wheat prolamin can be considered as suitable candidate for chewing gum base. Thus, faster onset of action desired in motion sickness can be achieved by buccal drug delivery of medicated chewing gum.

REFERENCES

1. Rassing MR. Chewing gum as a drug delivery system. Adv Drug Delivery Rev. 1994;13:89–121.
2. General monograph on dosage forms. Chewing gums, medicated, drug release. In: European Pharmacopoeia, 4th ed.; European directorate for the quality of medicines, Council of Europe: Strasbourg. France; 2002.p. 227.
3. Barcelon SA. Chewing gum containing wheat gluten. Patent number WO1994017673 A1, Aug 18; 1994.
4. Sramkova Z, Gregova E, Sturdik E. Chemical composition and nutritional quality of wheat grain. Acta Chimica Slovaca. 2009;2:115–38.

5. Bandyopadhyay AK, Sudhakar Y, Kuotsu K. Buccal bioadhesive drug delivery—a promising option for orally less efficient drugs. J Controlled Release. 2006;114:15–40.
6. Maggi L, Segale L, Conti S, Machist EO, Salini A, Conte U. Preparation and evaluation of release characteristics of 3TabGum, a novel chewing device. Eur J Pharm Sci. 2005;24:487–93.
7. Sander C, Neilsen HS, Sogaard SR, Stoving C, Rantanen J. Process development for spray drying of sticky pharmaceuticals; case study of bioadhesive nicotine microparticles for compressed medicated chewing gum. Int J Pharm. 2013;452:434–7.
8. Graudins LV. Preventing motion sickness in children. Aust Prescr. 2009;32:61–3.
9. Yajima M, Katahira R. Chewing gum composition containing gliadin and transglutaminase. U. S. Patent 5,858,423. 1999
10. Mukharjee PK. Quality control herbal drugs. 5th ed. Business horizons pharmaceutical; 2012.
11. Kokare CR. Pharmaceutical microbiology experiments and techniques. 2nd ed. Career publication; 2008.
12. Pandit AP, Joshi SB. Formulation development of chewing gum as a novel drug delivery system for diltiazem hydrochloride. Indian Drugs. 2006;43(9):724–8.
13. Salako M, Podczeck F, Newton JM. Investigations into the deformability and tensile strength of pellets. Int J Pharm. 1998;168:49–57.
14. Gajendran J, Kraemer J, Knudsen SR. Product performance test for medicated chewing gums. Dissolution Tech. 2010;2:15–8.
15. Chewing gum, medicated release from, General Chapter 2.9.25. In: European Pharmacopoeia, 6th ed.; European directorate for the quality of medicines, Council of Europe: Strasbourg. France; 2008.p. 260.
16. Marques MRC, Loebenberg R, Almukainzi M. Simulated biological fluids with possible application in dissolution testing. Dissolution Tech. 2011;18:15–28.
17. Rathbone MJ, Hadgraft J. Absorption of drugs from the human oral cavity. Int J Pharm. 1991;74:9–24.