Original Research Article

Directly compressible medicated chewing gum formulation for quick relief from common cold

Shivang A Chaudhary, Aliasgar F Shahiwala

National Institute of Pharmaceutical Education and Research (NIPER), Department of Pharmaceutics & Pharmaceutical Technology, Ahmedabad, Gujarat, India

Abstract

Introduction: Common cold is the most frequently recurring disease in the world and is a leading cause of doctor visits and missed days from school and work. Cold reliever medicated chewing gum (MCG) will be a definitive patient acceptable solution for this condition. Anti-allergic, cetirizine (CTZ) is a BCS class-I (highly soluble and highly permeable) non-sedating antihistaminic drug and this study was based on the hypothesis that CTZ as a BCS class I drug will be easily released from chewing gum into the salivary fluid within few minutes of chewing and can be easily permeated from oral mucosa by the pressure created by the chewing action and absorbed to a larger extent into the systemic circulation. Therefore, ultimately patients will get quick relief from symptoms of common cold with greater compliance compared to other conventional dosage forms. **Materials and Methods:** This study mainly focuses on taste masking of CTZ by inclusion complexation method, its formulation development in the MCG form and its quality and performance evaluation with the study of potential factors affecting drug release by 3^2 full factorial experimental design. A "chew out" study is carried out to assess *in vivo* drug release from MCG, in which residual amount is extracted from the chewed sample. **Results:** Formulation ingredients, such as elastomers, softeners, bulking agents, play an important role in the feel of the final product and its consistency; while sweeteners and flavors play a very essential character in its sensory properties. **Conclusion:** Interindividual variation in chewing frequency and chewing intensity is the main factor which affects release of active ingredient from MCG; while salivary dilution and involuntary swallowing are main reasons for variability in the absorption site, i.e., either from buccal mucosa or from gastrointestinal tract.

Key words: Cetirizine, common cold, full factorial experimental design, medicated chewing gum, performance, quality

INTRODUCTION

People of every society chew varieties of gums and gum-like substances (resins and waxes) for thousands of years.[1] Medicated chewing gum (MCG) is not different from those, but it is the gum base incorporating drug(s).[2] MCGs are 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 swallowed, providing a slow steady release of the medicine contained".[3] It can be either used for local treatment of mouth disease or systemic delivery by direct intraoral absorption through the buccal mucosa.[4] MCG offers numerous advantages over other drug delivery systems,[5] among which some important advantages are highlighted in Figure 1.

Common cold is the most frequently recurring disease in the world, and it is a leading cause of doctor visits and missed days from school and work.[6] Cold reliever MCG will be a definitive patient acceptable solution for this condition, because it allows trouble-free self-medication with complete control and it allows patients to live an active life during treatment.[7] In addition, it makes per-oral administration of drugs possible anywhere anytime without simultaneous intake of water, which promotes very high patient compliance.[2] Moreover, cetirizine is a BCS class-I (highly soluble and highly permeable) non-sedating antihistaminic drug.[8] This study was based on the hypothesis that CTZ as a BCS class I drug will be easily released from chewing gum into the salivary fluid within few minutes of chewing and can be easily permeated from oral mucosa and

Address for correspondence:
Mr. Shivang A. Chaudhary,
National Institute of Pharmaceutical Education and Research (NIPER) at B.V. Patel Pharmaceutical Education, Research and Development (PERD) Center, Ahmedabad-380054, Gujarat, India.
E-mail: shivaniper@gmail.com

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DOI: 10.4103/2230-973X.104395

absorbed into systemic circulation[9] by means of pressure generated during chewing action, which will ultimately produce quick-onset of pharmacological action without producing sedation a common sode effect.

There is a necessity of reformulation of an existing drug into novel drug delivery systems (NDDS) to extend or protect product patents thereby delaying, reducing, or avoiding generic erosion at patent expiry. By formulating the drugs in MCG composition, re-vitalization of old products and re-formulation of new patented products are possible to distinguish from future generics competition in the market. In the current market, cetirizine 2HCl is available in the forms of film coated tablets, chewable tablets and syrup. In this fastest world, a cold reliever tablet takes at least an hour for onset of action, but the cold reliever MCG will give therapeutic effects within few minutes. This is because in the case of MCG active ingredients may be systemically delivered through direct intraoral absorption, which will permit very quick onset of action.[10] Therefore, ultimately patients will get quick relief from symptoms of common cold with greater compliance compared to other conventional dosage forms.

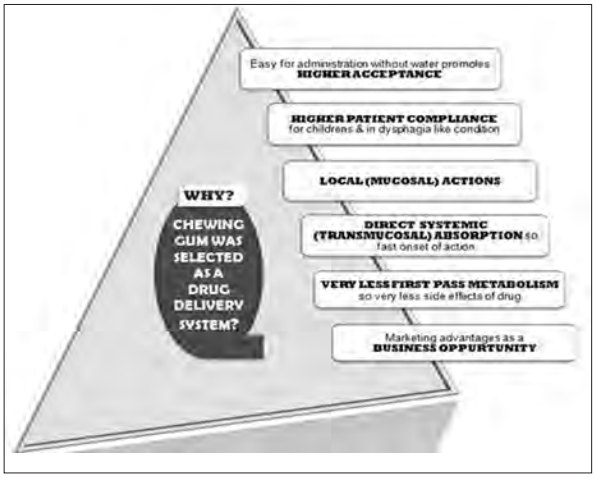


Figure 1: Pros of medicated chewing gum as a potential drug delivery option

MATERIALS AND METHODS

Materials used in formulation development

Cetirizine × 2HCl complies with BP procured from Ranbaxy Research Laboratories, India. Gum material (Health In Gum®) was received as a gift sample from Cafosa gum, S.A.U., Spain. β-Cyclodextrin (Kleptose® DC) was procured from Roquette® Signet Chemicals, India. Soya lecithin (E 322) of Food and Drug (FD) grade was procured from Modi Flour Merchant, India. Aspartame (E 951) of FD grade was purchased from Akhil Healthcare Pvt. Ltd, India. Menthol, peppermint flavor, and vanilla flavor (Trusil® Special) of FD grade were received as gift samples from International Flavors and Fragrances (IFF). Colloidal silicon dioxide (Aerosil® 200) was purchased from Degusa, Frankfurt, Germany. Magnesium stearate of the vegetable origin was purchased from Ferro Synpro, USA. Purified Talc (Luzenac® UM) was purchased from Rio Tinto Minerals, UK. Titanium dioxide (Kronos® 1171) was received as a gift sample from Signet Chemicals, India.

Experimental methods

Formulation development

Hurdles in prototype formulation development

Prototype formulation is defined as "a first or preliminary basic formulation from which other formulations are developed." In the case of MCG, prototype formulation consisted mainly of gum base, fillers, active ingredients (drug), and flavoring agents as shown in Table 1. The major hurdles which had come during CTZ-MCG prototype formulation development are depicted in Figure 2.

Taste masking of drug

Taste is one of the most important parameters in governing patient compliance. CTZ is an extremely bitter drug, which is non-pala for oral administration. Therefore, inclusion complexes of CTZ with β-cyclodextrin (β-CD) were prepared at four different molar ratios, i.e. 1: 1, 1: 2, 1: 3 and 1: 4 by wetting the physical mixture of CTZ and β-cyclodextrin in a mortar with a

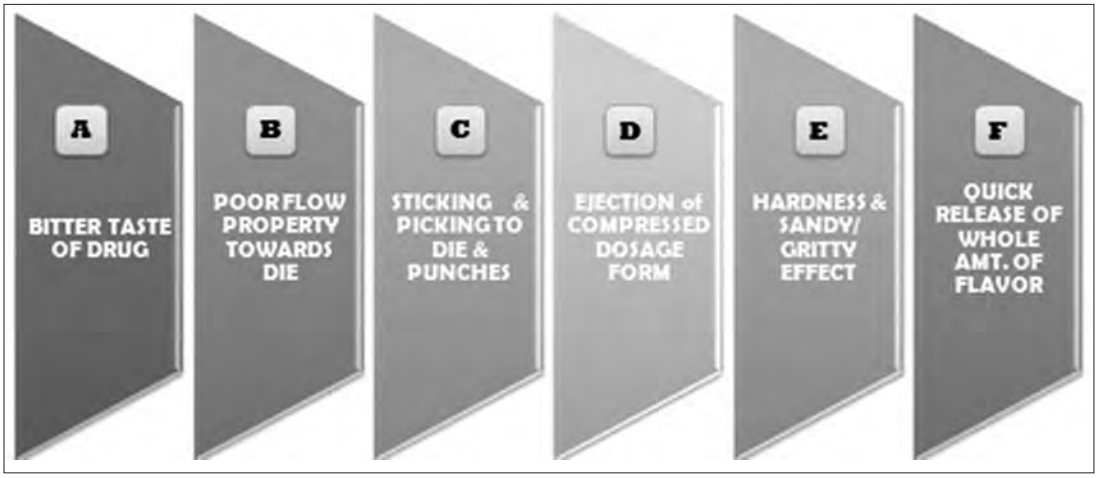


Figure 2: Hurdles faced during prototype formulation development of CTZ-MCG

Table 1: Selection and optimization of excipient in CTZ-MCG formulation

Screening		Optimization																												
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Total chewable base mass	Health in Gum	1287	1273	1259	1245	1231	1217	1244	1242	1241	1239	1238	1225	1211	1197	1183	1169	1204	1201	1197	1194	1190	1190	1187	1183	1180	1176	1173	1169	1166	1162
	CTZ-βCD	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	98.5
	Menthol	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14
	Peppermint	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sweetener	Aspartame	–	14	28	42	56	70	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42 (3.0%)
Glidant	Colloidal Silicon dioxide	–	–	–	–	–	–	1.4	2.8	4.2	5.6	7	56	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6 (0.4%)
Anti-adherant	Purified Talc	–	–	–	–	–	–	–	–	–	–	–	14	28	42	56	70	28	28	28	28	28	28	28	28	28	28	28	28	28	28 (2.0%)
Lubricant	Mg Stearate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7	11	14	18	21	14	14	14	14	14	14	14	14	14 (1.0%)
Softener	Soy lecithin	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7	11	14	18	21	21	21	21	21 (1.5%)
Opacifier	Titanium dioxide	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3.5	7	11	14 (1%)
Total weight of MCG (in miligram)																	1400														

minimum volume of purified water and kneading thoroughly for at least 20 min with a pestle to obtain a homogenous smooth paste, which was then dried in hot air oven at 50°C, sieved through 30# sieve. The cavity size of β-D fits in the aromatic ring present in the drug molecule and physical forces such as van der Waal's forces and hydrophobic interactions stabilize the complex that is formed.[11] Taste acceptability was measured by a taste panel of six volunteers with 10 mg drugs and subsequently complex equivalent to 10 mg CTZ held in the mouth for 5-10 s, then spat out, and the bitterness level was recorded. Volunteers were asked to gargle with distilled water between the drug and complex administration.

Formulation development and optimization

Blending with direct compression was the developed generalized platform technology used for preparation of CTZ-MCG.[12] In this method, the volatile liquid flavor was slowly added in free flowing compactable gum material with continuous mixing in a sigma blade mixer for 5 min. Then, flavored gum was screened through 30# sieve followed by addition of accurately weighed and 30# pre-sifted active, anti-adherent and organoleptic additives and blending for another 10 min. Afterwards 30# pre-sifted lubricant and glidant were precisely added and blended for another 10 min. Finally, the prepared blend of formulation was compressed on a Cadmach® tablet compression machine. Selection and optimization of an individual excipient were done by an individual problem to solution approach.[13-15] Among all preliminary feasibility batches for weight adjustment to achieve proper chewable mass, 1400 mg unit weight of CTZ-MCG was finalized having a good proper chewable mass.

- **Problem:** F_1 batch had somewhat off or slightly bitter taste. Thus, aspartame was selected as an artificial sweetener and incorporated in the formulation in different weight proportions i.e. from 1% to 5% in batch # F_2 to F_7. Among all five batches, F_4 batch of 3.0%w/w aspartame was perfectly suitable.
- **Problem:** In batch F_4, total flavor lasting time was only 2–4 min. Solution: Gum base was pre-saturated with peppermint oil by slowly dropwise addition of volatile oil in the gum base material with continuous blending up to 30 min to achieve sufficient adsorption of flavor onto the surface of gum material. Then, it was screened through 30# sieve and utilized in formulation, which increased total flavor lasting time of up to 5–8 min.
- **Problem**: Powder blend of batch F_4 had passable flow property with an angle of repose of 43.60. Thus, colloidal silicon dioxide as a flow promoter (glidant) was incorporated in a different weight proportion, i.e. from 0.1% to 0.5% in batch# F_7 to F_{12}. Among all batches, F_{10} batch containing 0.4%w/w colloidal silicon dioxide showed very good flow property (angle of repose: 34.59); but in more than 0.4%w/w, colloidal SiO_2 acts as a super disintegrant, which did not allow gum to remain as a cohesive mass.
- **Problem: Sticking to the die and Picking by punches**[16]

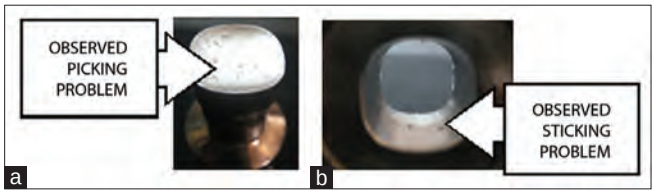


Figure 3: Observed sticking and picking problems. **(a)** Sticking: material got off from the MCG surface and adhered to the punch face. **(b)** Picking: material adhered to the die wall.

(as represented in Figure 3). Purified talc was incorporated in the formulation, and its concentration was optimized. Among all weight proportions of the talc, i.e. from 1% to 5% in batch # F_{12} to F_{16}, batch # F_{13} containing 2% w/w talc was selected, because more than 2% talc act as an adherent.

- **Problem: Hard to the eject compressed dosage form.** To promote smooth ejection during compression, Mg stearate was selected as a lubricant and its weight proportion was optimized from 0.5% to 1.5%. Batch# F_{19} having 1.0% w/w Mg stearate was sufficient to solve ejection problem.
- **Problem: Still chewing gum of batch # F_{19} had somewhat hard chewability.** To solve this problem, soya lecithin was incorporated and its weight proportion was optimized from 0.5% to 1.5%. Among all five batches, batch# F_{26} having 1.5% w/w soya lecithin has appropriate soft chewability.
- **Problem:** Off-white appearance; not looking esthetic for patient acceptance. Among all four batches, F_{27} to F_{30} batch having 1.0%w/w TiO_2 had immense white patient acceptable appearance as shown in Figure 4.

Optimized formulation was directly compressed on a Cadmach® tablet compression machine and packed in a suitable plastic container made up of high density polyethylene (HDPE) with the label of Reliiif® (brade name) until further evaluation was carried out.

MCG quality evaluation

Unofficial product quality tests (texture analysis)

Texture analysis is primarily concerned with how a product material feels, behaves, and performs. There are two principle approaches that can be taken to measure texture. One is sensory based, in which texture treated as a perception or human experience, which is correlated to what we feel. Another is instrumental engineering based, in which texture treated as a condition, which can be monitored during manufacture.

Texture analysis by instruments

Instrumental texture analysis is mainly concerned with the evaluation of mechanical characteristics where a material is subjected to a controlled force from which a deformation curve of its response is generated.[17] For evaluating texture properties of directly compressed MCG a "compression" probe was used in this deformation method using the Brookfield® QTS-25 texture analyzer. Squashing solid and self-supporting samples enabled a number of textural properties to be evaluated, including hardness (peak force that results from a sample being compressed to a given distance, time, or % of deformation) and adhesiveness (stickiness-related to how a MCG adheres to the inside of the mouth surfaces during chewing). It was recommended to use a compression probe with a greater surface area than that of the sample being tested, so a compression platen probe of 50 mm ∅ was used. During evaluation, a constant force was applied on the surface of self-supporting MCG as shown in Figure 5 and upon fracture it was withdrawn. Through which, a deformation curve was recorded and interpreted.

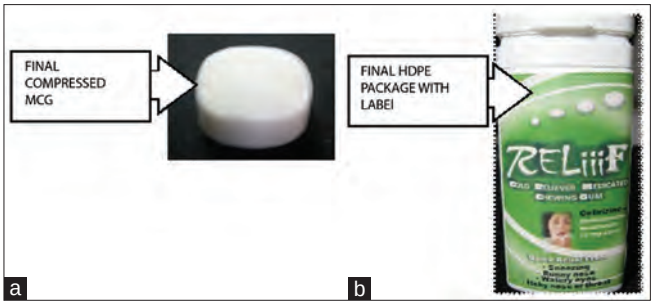


Figure 4: (a) Final compressed CTZ-MCG. (b) Final high density poly ethylene (HDPE) plastic package with a label for storage of compressed CTZ-MCG

Figure 5: Texture analysis of final compressed CTZ-MCG

Sensory evaluation of MCG texture properties

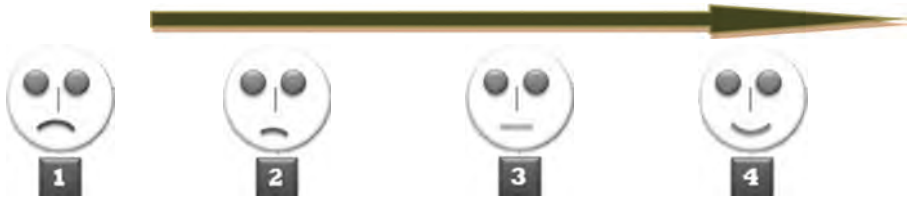
For assessment of the product quality, volunteers had to just chew the product without swallowing for a particular time period. Then, they were allowed to give the score by ticking in the box in a scorecard that they felt appropriate for respective qualities of the cold reliever MCG product, i.e. product feel, product consistency, its taste, and total flavor lasting time during chewing the product according to Table 2.

Official (EP) product quality assessment tests

Uniformity of mass (weight variation test)

This test is specifically for uncoated compressed dosage forms. Twenty MCGs were taken randomly and weighed individually. The arithmetic mean weight was calculated. The formulation complies with the test; if not more than two of the individual masses deviate from the average mass by more than 5%.[19]

Table 2: Product quality assessment scorecard



Product feel	Very hard	Hard	Passable	Soft	Very soft
Product consistency	Very less	Less	Medium	High	Very high
Product taste	Extreme bitter	Moderate bitter	Slightly bitter or passable	Taste masked or sweet	Very sweet
Flavor lasting time	Up to 1 min	Up to 2 min	Up to 3 min	Up to 4 min	>5 min

Note: This study method did not involve any blood or urine sample collection. Paired *t*-test was exercised to test that "is there any significant improvement in product quality after excipient treatment?"[18]

Uniformity of content

Using a suitable analytical method, the individual contents of active substance(s) of 10 dosage units which were taken randomly was determined. The formulation complies with the test if the individual content is between 85% and 115% of the average content.[20]

Friability test

Ten units of MCG were randomly taken and carefully de-dusted prior to testing. Then, they were accurately weighed and placed in the drum of an Electrolab® EF-2 Friabilator. The drum was rotated 100 times at 25 rpm, and then they were removed. Loose dust was removed from the MCGs as abovementioned and reweighed accurately. The difference in the two weights represents friability. A maximum loss of mass (obtained from a single test or from the mean of three tests) not greater than 1.0% is considered acceptable.[21]

MCG performance evaluation

In vivo drug release from MCG by chew out study

The *in vivo* release of active ingredients from MCG during mastication was studied by recruiting a panel of sufficient numbers of volunteers and scheduled chew-out studies. For determination of % drug release from MCG, a panel of six human volunteers was formed. Then, each person was allowed to chew one sample of the CTZ chewing gum for a particular time period, i.e. 2, 5, 10, and 15 min. After chewing, chewed out gum samples were collected from volunteers, it had been stretched out up to maximum and cut into small pieces and dispersed in a 250 ml volumetric flask containing purified water–methanol mixture in a 70:30 v/v ratio, which was then sonicated for 1 h with heating. The sonicated sample was filtered and analyzed by a UV spectrophotometer at 230.4 nm to determine the residual drug content present in MCG. The "amount of drug released during mastication" is calculated by subtracting the "amount of the residual active ingredient" present in the gum after chewing from "the total content".[22]

In vitro buccal permeation study for drug released from MCG

In a Mucosal Membrane Permeation study, pig buccal mucosa was placed between a donor compartment and a receiver compartment of the Hanson Research® Variomag Telemodule 40s Franz diffusion cell compartmental system. To simulate oral conditions, phosphate buffer of salivary pH was placed in the donor compartment and phosphate buffer of blood pH was placed in the receiver compartment. Then, average proportion of CTZ in its complex form (88.7 mg of the complex equivalent to 9.0 mg of CTZ), which was released from optimized formulation after 15 min of chewing, was placed in the donor compartment of diffusion cell containing phosphate buffer of salivary pH. It was allowed to permeate through buccal mucosa for 5 min. After 5 min (which is normal average chewing time), the sample was collected from the receiver compartment and analyzed by the UV-spectrophotometer at 230.4 nm, to determine the total content of CTZ permeated through buccal mucosa. χ^2-test was exercised to investigate "is there significant agreement between observed value of % drug permeated and expected value of drug permeation or not?" [23]

Evaluation of factors affecting drug release from MCG

Selection and optimization of factors affecting % drug release from MCG by 3^2 Full Factorial Experimental Design

Independent significant factors [chewing time (A) and amount of gum base (B)] affecting the dependent factor (% CTZ release from MCG) were first extracted out by means of ANOVA and then extracted factors were optimized by 3^2 Full factorial experimental design. Here full factorial 3^2 designs were used for the optimization procedure, because it is suitable for investigating the quadratic response surfaces and for constructing a second-order polynomial model, thus enabling optimization of the chewing time and the amount of gum base to achieve sufficient drug release from MCG.[24] Mathematical modeling, evaluation of the ability to fit to the model, and response surface methodology (RSM) were performed by employing Design-Expert® software (Version 7.1.2, Stat-Ease Inc., Minneapolis, MN). RSM is a collection of mathematical and statistical techniques useful for the modeling and analysis of problems in which a response of interest is influenced by several variables and the objective is to optimize this response.[25] The most extensive applications of RSM are in the industrial world, particularly *in situ*ations where several input variables potentially influence some performance

Table 3: Independent and dependent variables along with their levels

Factors (independent variables)		Levels used			Response (dependent variable)
		−1	0	+1	
A	Chewing time (min)	578	1080	1582	% Drug release
B	Amount of gum base (%)				

Table 4: Experimental testing runs with values of variable factors

Experimental test run	Variable factors in coded terms (actual terms)	
	Chewing time (min)	Amount of gum base (%)
1	−1 (05)	−1 (78)
2	0 (10)	−1 (78)
3	+1 (15)	−1 (78)
4	−1 (05)	0 (80)
5	0 (10)	0 (80)
6	+1 (15)	0 (80)
7	−1 (05)	+1 (82)
8	0 (10)	+1 (82)
9	+1 (15)	+1 (82)

measure or quality characteristic of the product or the process. This performance measure or quality characteristic is called the response.

Table 3 summarizes the independent and dependent variables along with their coded and actual levels. Totally, nine experimental testing runs which were carried out are enlisted in Table 4.

Statistical analysis of the data and validation of the model

Various RSM computations for the current optimization study were performed employing Design Expert software (Version 8.0.0.2, Stat-Ease Inc, Minneapolis, MN). Polynomial models including interaction (A*B) and quadratic terms (A^2 or B^2) were generated for the response variable using the Multiple Linear Regression Analysis (MLRA) approach. Statistical validity of the polynomials (A and B) was established on the basis of ANOVA provision in the Design Expert software. A model is considered significant if the *P*-value (significance probability value) < 0.05. 2D contour plots and 3D response surface graphs were constructed using the same software. One final formulation corresponding to the predicted amount of gum base was chewed according to the predicted chewing time and three additional random check points covering the entire range of experimental domain were carried out to determine the validity of the model generated. Subsequently, the resultant actual experimental data of the response properties were quantitatively compared with those of the predicted values by regression as well as χ^2 values. Then linear regression plot between observed and predicted values of the response properties was drawn using MS-Excel.

RESULTS AND DISCUSSIONS

Characterization of inclusion complex

A taste assessment study by Sensory panel of human volunteers ($n = 6$) was mentioned in Table 5, which clearly indicated that when CTZ to β-CD complex formed in a 1: 4 molar ratio then the complex will give tasteless organoleptic character.

Table 5: Taste assessment of CTZ–b-CD complex

CTZ:b-CD molar ratio	Taste of complex
1: 1	Moderate bitter (+)
1: 2	Bitter (++)
1: 3	Slightly bitter (+++)
1: 4	Tasteless (++++)

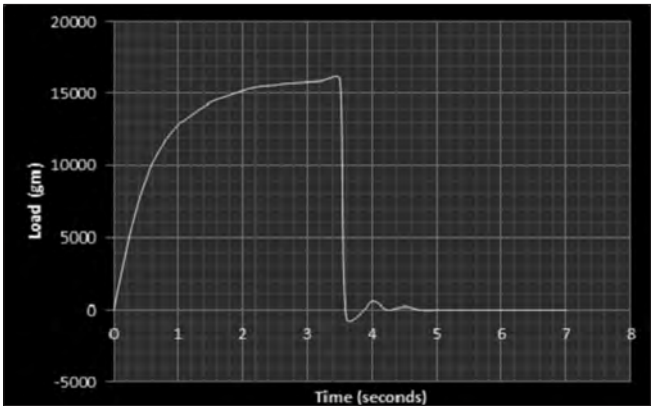


Figure 6: Deformation curve of CTZ-MCG

Formulation development

CTZ is a bitter drug; so for taste masking CTZ was incorporated as a CTZ-βCD inclusion complex in 1:4 molar ratios in formulation development. Final formulation of batch # F_{30}, which was prepared by adopting a problem to solution approach, was mentioned in Table 1, with a characteristic angle of repose of 34.6, Carr's compressibility index of 16.9, and Hausner's ratio of 1.20.

MCG quality evaluation

Unofficial MCG product quality assessment tests

Texture analysis by instruments

As the texture analyzer probe compressed CTZ-MCG, a small constant force was needed to reach the breaking point imitated the initial biting resistance or gum firmness, i.e. a bearing load of 16,138 g/cm as presented in Figure 6. Once the fracture point was reached, on withdrawal a compression probe a negative peak was observed as shown in the deformation curve, showing the adhesiveness of the gum. The gum initially crumbles and then comes together to form a gum. The crumbling of the gum allows the CTZ to be released and provides a faster release compared to conventional gums, which remain intact during the process.

Sensory evaluation of MCG rexture

For product quality assessment, a sensory panel of 24 human volunteers had been formed. They had given two formulations for chewing: (A) final optimized MCG formulation. (B) MCG containing only gum base with CTZ and menthol. Volunteers

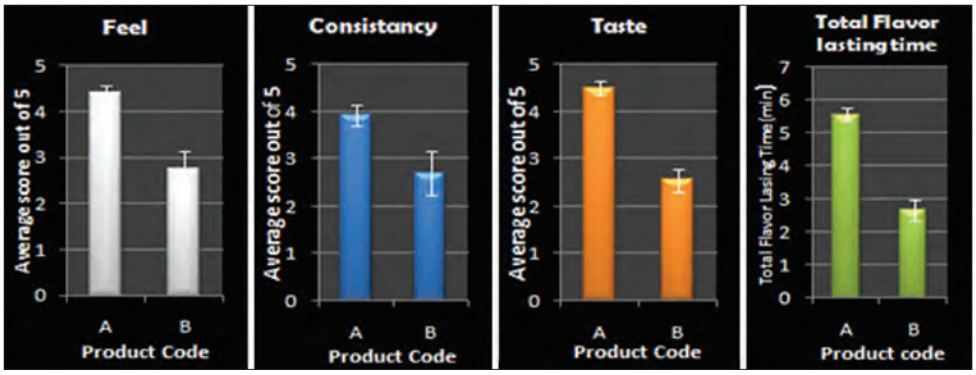


Figure 7: Column graphs for comparison of scores obtained by two different MCG products: (a) For product feel, (b) product consistency, (c) product taste, and (d) total flavor lasting time

Table 6: Average score for four different qualities of MCG (*n* = 24)

Feel		Consistency		Taste		Flavor lasting time	
A	B	A	B	A	B	A	B
4.42 ± 0.17	2.75 ± 0.38	3.92 ± 0.22	2.73 ± 0.47	4.51 ± 0.15	2.54 ± 0.24	5.54 ± 0.21	2.67 ± 0.32

Table 7: Results of applied paired *t*-test for MCG quality evaluation

MCG quality	t_{cal}	t_{tab}	Result with discussion
Product feel	10.36	2.07	Here, $t_{cal} > t_{tab}$. So for all the quality parameters; there is a significant improvement in product quality after treatment with excipients.
Product consistency	7.125	2.07	
Product taste	12.78	2.07	
Total flavor lasting time	8.894	2.07	

had given score individually by chewing for both products. After assessment, filled scorecards with score (x out of 5) were received from 24 volunteers. The average score was calculated for each of the four different qualities. Average scores for each quality were mentioned in Table 6 with clear comparison as shown by bar graphs in Figure 7.

Paired *t*-test was applied to test that "*is there any significant improvement in product quality after excipient treatment*?" Results of the paired *t*-test, which were mentioned in Table 7, confirmed that there is a significant improvement ($P = 0.05$) in the product feel, product consistency, product taste and total flavor lasting time after involvement of appropriate excipients in an optimum amount in final MCG formulation.

Official (BP/EP) product quality assessment tests

Final MCG formulation passed tests for uniformity of mass with an average mass of 1402.3 mg and no one was deviated from ±5% of average mass of MCG. All 10 MCGs, which were sampled randomly, have passed the test for the uniformity of content because contents of CTZ in all 10 MCGs have fallen within a compliance limit of 85–115% and the average content of CTZ was found to be 9.78 mg ± 0.53%. In friability testing, after 100 rotations the total weight loss of 10 MCG was found to be 0.24% which was less than the compliance limit of 1.0%; so final MCG formulation have passed in the friability test.

MCG performance evaluation

In vivo drug release from MCG by a 'chew out' study

For determination of % CTZ release from MCG, a panel of six human volunteers was formed. Then each person was allowed to chew one sample of the CTZ chewing gum for a particular time period, i.e. 1, 2, 5, 10 and 15 min. After chewing, chewed out gum samples were analyzed by a UV spectrophotometer at 230.4 nm to determine residual the drug content present in MCG. Individual % CTZ release as well as average % CTZ release were mentioned in Table 8 and average % CTZ release was graphically demonstrated in Figure 8 with standard deviation. After 15 min of chewing, average 90.28% of drug was released from optimized CTZ-MCG formulation, which is sufficient to produce the therapeutic effect.

Interindividual variability in % CTZ release

From the Radar graph as depicted in Figure 9, it was illustrated that there was a high inter-individual variability in % drug release in first 2 min of chewing with the asymmetrical hexagonal pattern, which was decreased as a function of time; there was a very less inter-individual variability in % drug release after 10 min of chewing with the symmetrical hexagonal pattern. The possible reason for high interindividual variability in the first 2 min of chewing may be due to great variation in the chewing rate and chewing intensity in first 2–4 min of chewing. After 2–4 min, the chewing rate and intensity was observed almost the same in individuals.

In vitro Buccal permeation study for released drug

In an *in vitro* Franz diffusion Buccal permeation study, average proportion of CTZ which was released from optimized formulation after 15 min of chewing (90.28% = 9.00 mg of CTZ) was placed in the donor compartment of diffusion cell containing phosphate buffer of salivary pH. It was allowed to permeate through buccal mucosa for 30 min. After 30 min (which is normal

Table 8: Individual % CTZ release from MCG by six individuals

Chewing time (in minutes)	Individual % drug release by individual volunteer						Average % drug release by six volunteers
	Volunteer no.						
	1	2	3	4	5	6	
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	28.4	26.1	32.6	19.8	27.7	22.6	26.2
2	58.8	56.5	63.2	48.1	52.1	47.2	54.32
5	80.6	75.6	77.3	79.1	77.8	74.4	77.47
10	87.9	84.4	87.7	86.4	83.3	82.3	85.33
15	90.8	87.3	91.5	88.3	91.7	92.1	90.28

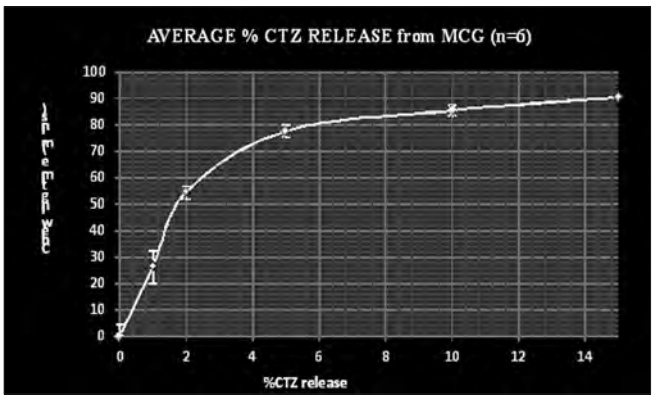


Figure 8: Average % CTZ release profile as a function of time in minutes (n = 6)

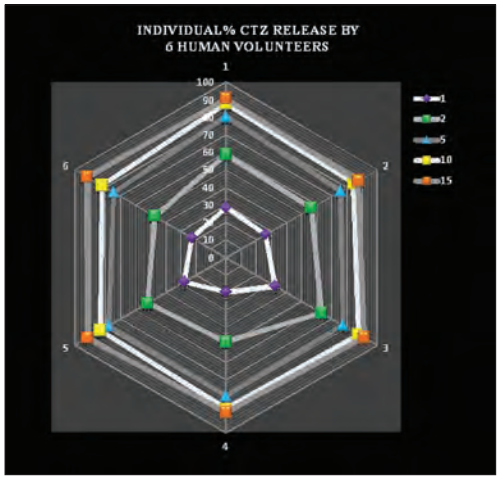


Figure 9: Individual % CTZ release profile as a function of time in minutes by six individual volunteers

average chewing time), the sample was collected from the receiver compartment and analyzed by the UV-spectrophotometer at 230.4 nm, to determine the total content of CTZ permeated through buccal mucosa. Average in vitro% permeation of CTZ through pig buccal mucosa was found to be 36.67 ± 5.202%. χ^2-test was exercised to investigate "is there significant agreement between observed value of % drug permeated and expected value of drug permeation or not?" Results of the χ^2-test suggested that there was a significant agreement between observed values and expected values (40.00%) with a high level of significance (P = 0.05). Results of the applied χ^2-test was mentioned in Table 9.

Table 9: Results of applied χ^2-test for *in vitro* Buccal permeation study

Sample no.	Observed % permeation (O)	Expected %permeation (E)	$Chi_{cal} = \sum(O - E)^2/E$
01	36.6	40.0	0.289
02	40.9	40.0	0.020
03	29.7	40.0	2.652
04	37.9	40.0	0.110
05	31.7	40.0	1.722
06	43.2	40.0	0.256

Results: $Chi_{cal} = \sum(O - E)^2/E = 5.05$; $Chi_{tab} = 11.07$. So, $Chi_{cal} < Ch_{tab}$. Therefore, experimental values are in significant agreement with expected values.

Table 10: Experimental 3^2 = 9 test experimental run with corresponding response

Run	Factor A: chewing time (in min)	Factor B: gum base (in %)	Response (drug release) in %
1	5.00	82.00	72.6
2	15.00	78.00	91.2
3	5.00	78.00	76.1
4	15.00	80.00	91.1
5	15.00	82.00	91.7
6	10.00	82.00	84.7
7	10.00	78.00	86.4
8	10.00	80.00	86.1
9	5.00	80.00	75.3

Evaluation of factors affecting drug release from MCG Optimization of drug release from MCG by 3^2 FFED

To develop a MCG drug delivery system, the amount of gum base (%) and chewing time (min) are the most important factors affecting the drug release profile, regardless of the core composition. A multivariate optimization strategy was carried out with the aim of finding the optimum amount of gum base and chewing time to achieve a sufficient amount of drug release within few minutes of chewing. CTZ release profiles of the nine experimental runs performed in 3^2 Full Factorial Experimental Design (FFED) in accordance with Table 10.

Multiple regression and mathematical model building

The targeted response parameters were statistically analyzed by applying one-way ANOVA (analysis of variance), at the 5% significance level and the significance of the model was estimated using the statistical package Design-Expert®. The individual parameters were evaluated using the F-test, and the mathematical relationship was generated between the factors (dependent variables) and response (independent variable) using multiple linear regression analysis, for determining the

levels of factors which yield optimum dissolution responses. A second-order polynomial regression equation that fitted to the data is as follows:

$$DR = C + b_1A + b_1B + b_{12}AB + b_{11}A^2 + b_{22}B^2$$

where *c* is the intercept representing the arithmetic averages of all the quantitative outcomes of nine runs; b_1, b_2, b_{12}, b_{11} and b_{22} are the coefficients computed from the observed experimental values of DR; and *A* and *B* stand for the main effects. The terms *AB*, A^2, and B^2 $i = 1$ and 2 represent the interaction and quadratic terms, respectively, used to simulate the curvature of the designed sample space.

Factor effects of the 3^2 FFED model and associated *P*-values for the response (drug release) are represented in Table 11, a factor is considered to influence the response if the effects significantly differ from zero and the *P*-value is not more than 0.100. The predicted equation of % drug release in terms of coded factors is mentioned below:

$$DR = +85.99 + 8.33A - 0.78B + 1.00AB - 2.73A^2 - 0.38B^2$$

where A is the chewing time in minutes and *B* is the amount of Gum base in %.

Here the *P* value for the term B^2 (0.3137) was greater than 0.100. Therefore, a backward elimination procedure was adopted to fit the data into predictor equations. The final equation for the % predicted drug release (DR) is given below:

$$DR = +85.99 + 8.33A - 0.78B + 1.00AB - 2.73A^2$$

where *A* is the chewing time in minutes, *B* is the mount of gum base in %.

The equations represent the quantitative effect of factors (*A* and *B*) upon the response (DR). Coefficients with one factor represent the effect of that particular factor while the coefficients with more than one factor and those with second-order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. A positive sign in front of the terms indicates synergistic effects while the negative sign indicates the antagonistic effect of the factors.

Response surface analysis

The quadratic models generated by regression analysis were used to construct the 2-dimensional contour plot and 3-dimensional response surface plot in which response parameter DR was represented by a curvature surface as a function of *A* and *B*. Figure 10 shows the effect of the chewing time and amount of gum base in the contour plot as well as response surface plot.

A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. In this study optimization was performed with constraints for DR (90 % < DR < 95 %) set as goals to locate the optimum settings of the independent variables in the new formulation. The optimal parameters to achieve predicted CTZ release of 91.81% (90.0% to 95.0%) as calculated from predicted

Table 11: Factor Effects of 3^2 FFED model and associated p-values for the response DR

Response for drug release (in %)
Where, Factor A=Chewing Time (in minutes) & B= Amount of gum base (in %)

Analysis of Variance (ANOVA) for Response Surface Quadratic Model [Partial sum of squares- Type III]

Source	Sum of squares	Degree of freedom	Mean square	F value	*P* value Prob>F	Model
Model	439.58	5	87.92	436.35	0.0002	Significant
A	416.67	1	416.67	2068.01	<0.0001	
B	3.68	1	3.68	18.27	0.0235	
AB	4.00	1	4.00	19.85	0.0210	
A2	14.94	1	14.94	74.16	0.0033	
B2	0.29	1	0.29	1.46	0.3137	
Residual	0.60	3	0.20			
Core Total	440.19	8				

The Model F-value of 436.35 implies the model is significant. There is only a 0.02% chance that a "Model F-value" this large could occur due to noise. Values of "Prob>F" less than 0.0500 indicate model terms are significant. In this case A, B, AB, A^2 are significant model terms. Probability of failure values greater than 0.1000 (in this case B^2) indicate the model terms are not significant.

Table 12: Comparison of experimental and predicted % drug release

Test conditions (*A*:*B*) in coded terms	Observed experimental values (*O*)	Expected or predicted values (E)	Chi_{cal} value	% Relative error
+1.0: +0.5 (optimum)	90.3	91.58	0.01789	−1.41
+0.4: +1.0 (random)	86.8	88.16	0.02098	−1.56
−0.2: +1.0 (random)	83.9	82.84	0.013563	+1.26
−0.8: +1.0 (random)	79.2	77.57	0.034252	+2.05

Results: $Chi_{cal} = \sum (O - E)^2/E = 0.0866$; $Chi_{tab} = 7.81$. So, $Chi_{cal} < Chi_{tab}$.
Therefore, experimental values are in significant agreement with predicted values.

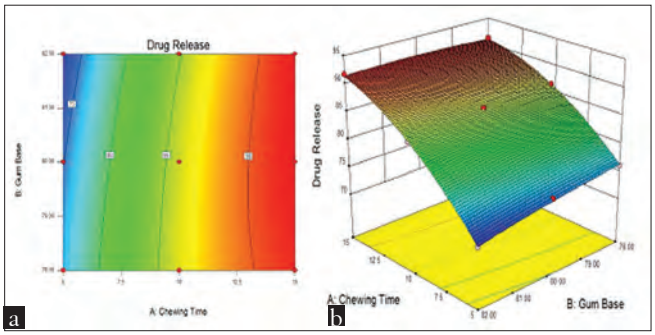


Figure 10: (a) 2D-contour plots. (b) 3D-response surface plot

equation of drug release

A. Chewing time = 15 min

B. Amount of gum base = 82.00%

Validation of response surface methodology

In order to assess the reliability of the developed mathematical model, a chew out study corresponding to the predicted optimum chewing time and gum base along with three additional random check points covering the entire range of experimental domain was performed. Additional check points are those points which were not selected before in the construction of the response surface model, within the range of coded factors (−1, 0, +1). Table 12 lists the test conditions of the optimum and the random check points, their experimental and predicted values with calculated χ^2 values for % CTZ release, along with the calculated percentage bias in terms of % relative error.

Figure 11 shows linear correlation plots between the observed and predicted response variables. The graph demonstrates high significant values of correlation coefficient, $r^2 = 0.988$ (>0.9) and the lower magnitude of percentage relative error (−1.66 to + 2.05) indicates the robustness of the mathematical model and high prognostic ability of RSM. As desired, the MCGs formulated according to optimum formulation achieved 90.3% CTZ release within 15 min of chewing time.

CONCLUSION

Following conclusions are drawn based on overall results of investigations

Optimized formulation of directly compressed CTZ-MCG

- have soft chewability, high consistency, sweet taste, and total average flavor lasting time of 6–8 min; which were assessed by a sensory panel of human volunteers and confirmed by paired *t*-tests ($P = 0.05$), which indicates very good texture property.
- soft chewability was also confirmed by measurements of hardness and adhesiveness like texture properties by a texture analyzer instrument and it showed that health in gum have less hardness and less adhesiveness.
- have passed all official MCG quality tests including uniformity of mass, assay for uniformity of content, and friability testing as per compliance criteria mentioned in the official monograph of MCG in BP.

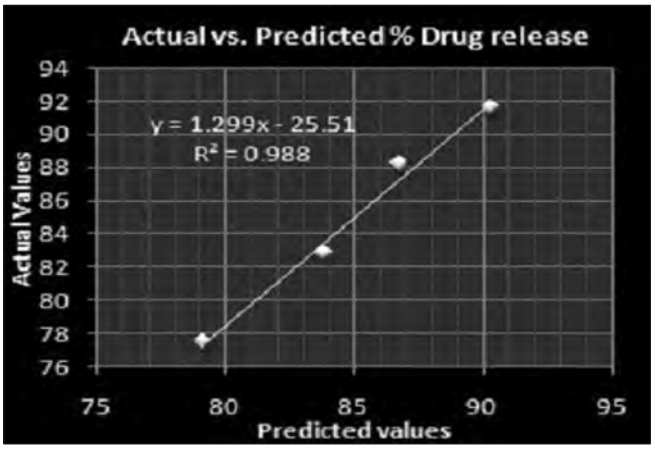


Figure 11: Correlation plot between actual experimental and predicted values

- released average 90.28% of CTZ ($n = 6$) within 15 min of chewing (which is half of the normal average chewing time) in an *in vivo* chew out study and out of which average 36.67% of CTZ ($n = 6$) was permeated through buccal mucosa within 30 min (which is the total normal average chewing time) in *in vitro* permeation study, which was in significant agreement ($P = 0.05$) with predicted permeation, i.e. 40.00% confirmed by the χ^2-square test.
- Interindividual variability in % CTZ-release was remained only up to 1–3 min, afterwards very less interindividual variability was observed in %CTZ release.

Therefore, this study demonstrated that cetirizine×HCl could be successfully delivered by MCG into systemic circulation *via* direct intraoral buccal absorption. Concerning statistical analysis, it was shown that the 3^2 full factorial experimental design (FFED) and optimization technique can be successfully used in the development of optimized formulation of MCG and for deciding appropriate chewing time for sufficient drug release. The optimized formulation exhibited drug release profiles which were close to the predicted responses which was confirmed by high significant $r^2 = 0.988$ (>0.9) value.

From overall results, it was concluded that developed formulation of directly compressible taste masked MCG of cetirizine present a better alternative to any other dosage form because it will give quick symptomatic relief from common cold due to direct intraoral absorption without producing sedation. Moreover, CTZ-MCG can be taken anywhere anytime without preventing patient from living an active life which promotes very high patient acceptance and higher patient compliance.

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How to cite this article: Chaudhary SA, Shahiwala AF. Directly compressible medicated chewing gum formulation for quick relief from common cold. Int J Pharma Investig 2012;2:123-33.
Source of Support: Nil. **Conflict of Interest:** None declared.