King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

CrossMark

ORIGINAL ARTICLE

Formulation development and evaluation of medicated chewing gum of anti-emetic drug

Mansi Paradkar [a,*], **Balaram Gajra** [a], **Bhautik Patel** [b]

[a] Department of Pharmaceutics & Pharmaceutical Technology, Ramanbhai Patel College of Pharmacy, CHARUSAT, Changa, Gujarat 388421, India
[b] Intas Pharmaceuticals Ltd., Sarkhej-Bavla Highway, Moraiya, Sanand Taluka, Ahmedabad, Gujarat 382 210, India

Abstract *Context:* Medicated chewing gum (MCG) of Domperidone Maleate (DM) was developed by direct compression method with the goal to achieve quick onset of action and to improve patient compliance. *Objective:* Formulation development of MCG of DM and optimization of the formulation by screening of different excipients. *Material and methods:* MCG containing DM was prepared by screening different concentrations of sweeteners, flavouring agents, softening agents, lubricants and anti-adherents by changing one variable at a time. Performance evaluation was carried out by evaluating size, shape, thickness, taste, scanning electron microscopy, texture analysis, in vivo drug release study, ex vivo buccal permeation study and by studying statistical analysis for quality. *Results and discussion:* The statistical analysis showed significant improvement in organoleptic properties such as chewable mass, product taste, product consistency, product softness, total flavour lasting time and pharmaceutical properties like micromeritic properties after incorporation of appropriate excipients in an optimum amount in final optimized MCG formulation. In vivo drug release study showed 97% DM release whereas ex vivo buccal permeation study through goat buccal mucosa exhibited 11.27% DM permeation within 15 min indicating its potential for increasing bioavailability by decreasing time of onset. The optimized formulation showed good surface properties and the peak load required for drug release was found to be acceptable for crumbling action. *Conclusion:* The developed formulation of medicated chewing gum can be a better alternative to mouth dissolving and conventional tablet formulation. It may be proved as a promising approach to improve the bioavailability as well as to improve patient compliance.

* Corresponding author at: Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology, CHARUSAT Campus, Changa, Anand 388 421, Gujarat, India. Tel.: +91 9016970248.
E-mail address: mansiparadkar.ph@charusat.ac.in (M. Paradkar).

ELSEVIER **Production and hosting by Elsevier**

1. Introduction

Nausea and vomiting are the most commonly occurring symptoms in majority of pathophysiological conditions such as motion, cancer, pregnancy, and postoperative conditions. Nausea refers to feeling of impending vomiting. Vomiting

refers to forceful expulsion of contents of the stomach and the proximal small intestine (Pleuvry, 2006).

Antiemetic drugs are used to prevent or suppress vomiting. They act by blocking several receptors located in vomiting centres such as H_1 histaminic, dopamine D_2, 5-HT_3 receptor, muscarinic, and neurokinin1(NK_1) receptor. Drugs such as Anticholinergics, H_1-antihistamines, Neuroleptics, 5-HT_3 antagonists act by penetrating blood brain barrier which leads to sedation. Prokinetic drugs such as metoclopramide and domperidone maleate act as dopamine D_2 blockers. Their antiemetic activity is due to antagonism of D_2 receptors in Chemoreceptor Trigger Zone (CTZ) which is located outside of the blood brain barrier so they do not cause side effects related to brain and hence do not cause disturbance in regular activities such as driving, and office work. It is reported that metoclopramide has more side effects as compared to Domperidone maleate (Tripathi, 2003).

Domperidone Maleate (DM) has very low oral bioavailability (15%) owing to its extensive metabolism in liver and gut wall (Tripathi, 2003). It is available in the form of tablets, capsules, suspensions, injections, sustained release capsules, etc. But these formulations have several disadvantages such as difficulty in swallowing tablets or capsules which also requires water. Besides these, suspension does not possess pleasant taste and dose accuracy. Patients suffering from trypanophobia experience difficulty in medication by needle. In addition, drug if given by oral route, undergoes first pass metabolism that decreases bioavailability of DM. Formulations of DM investigated by various researchers are coevaporates (Nagarsenker et al., 2000), fast dissolving tablet (Bhatt and Trivedi, 2012), orodispersible tablet (Islam et al., 2011), etc.

Chewing gum is a pleasure that almost everyone enjoys. Chewing gum usually consists of a gum core, which may or may not be coated. Medicated chewing gums 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 to be swallowed, providing a slow steady release of the medicine contained' (European Pharmacopoeia, 2010). Chewing gum has also being exploited for the drug delivery and many times referred as mobile drug delivery system (Ingole et al., 2012). Medicated chewing gum (MCG) gives local (treatment of oral disease) as well as systemic action (buccal absorption or by swallowing saliva). MCG helps to increase patient compliance by fast onset of action and by improved bioavailability of drug as some amount of drug is absorbed through the buccal mucosa. It can also be administered without water (Jacobsen et al., 2004; Chaudhary and Shahiwala, 2010; Chaudhary and Shahiwala, 2012). MCG has been exploited for various drugs such as cetirizine (Stojanov and Larsen, 2012; Swamy et al., 2012), dextromethorphan hydrobromide (Swamy et al., 2012), dimenhydrinate hydrochloride (Mehta and Trivedi, 2011), nicotine (Morjaria et al., 2004; Cherukuri et al., 2000), antacids (Zyck et al., 2003), miconazole (Pedersen and Rassing, 1990), aspirin (Woodford and Lesko, 1981), caffeine (Tyrpin et al., 2002), antimicrobial decapeptide (Dong et al., 2005), ondansetron hydrochloride (Nagaich et al., 2010), and nystatin (Andersen et al., 1990).

The aim of present research work was to formulate medicated chewing gum of DM to fasten the onset of action and to improve the bioavailability so as to get the quick relief from nausea and vomiting with greater patient compliance.

2. Methods

2.1. Materials

DM was received as gift sample from Vasudha Pharma Chemical Limited (Hyderabad, India). Health In Gum® (HIG PWD 02) was received as gift sample from Cafosa (Barcelona, Spain). All other ingredients and solvents used were of analytical or pharmaceutical grade.

2.2. Drug excipients compatibility study

2.2.1. Fourier Transform Infrared Study (FTIR)

The drug-excipient compatibility study was carried out by FTIR. FTIR spectra of the (a) pure drug, (b) gum base and (c) mixture of drug:excipients (1:99) were recorded. The samples were prepared by weighing and homogenously dispersing with dried KBr in a mortar and pestle, and compressing the powder under vacuum with a compression force using round flat face punch for three minutes to produce a pellet compacts. The sample was placed in the IR light path using a FTIR Instrument (NICHOLET 6700, Thermo Scientific, USA). Spectra were recorded in the wavelength region of 4000–400 cm^{-1}. The peaks were observed for any types of interaction between the drug and excipients (Dixit, 2013).

2.3. Formulation development of MCG

The technique of screening of one excipient at a time was adopted. The whole process of the formulation development is given in Fig. 1.

2.4. Pre-compression study

Flow properties of gum base and drug: excipient mixtures were determined by measurement of angle of repose, bulk density, tapped density, compressibility index (CI) and hausner's ratio.

2.5. Preparation of medicated chewing gum

Medicated chewing gums were prepared by direct compression method. In this method, the flavour was added in accurately weighed DM with continuous mixing in a mortar for 15 min. Flavoured drug was screened through 30# sieve (0.600 mm) followed by addition of accurately weighed and 30# pre-sifted gum base, anti-adherent and sweeteners and blended for 10 min. 30# pre-sifted lubricant was precisely added and blended for 10 min. Finally, the prepared blend of formulation was compressed on a tablet compression machine (Rimek Mini Press-II, Karnavati Engineering) (Rao et al., 2011).

2.6. Screening of excipients by human volunteers

MCGs were evaluated for several organoleptic properties such as chewability, flavour lasting time, sweetness, and softness in a panel of healthy human volunteers ($n = 6$). The permission for conducting these studies was obtained from Institutional
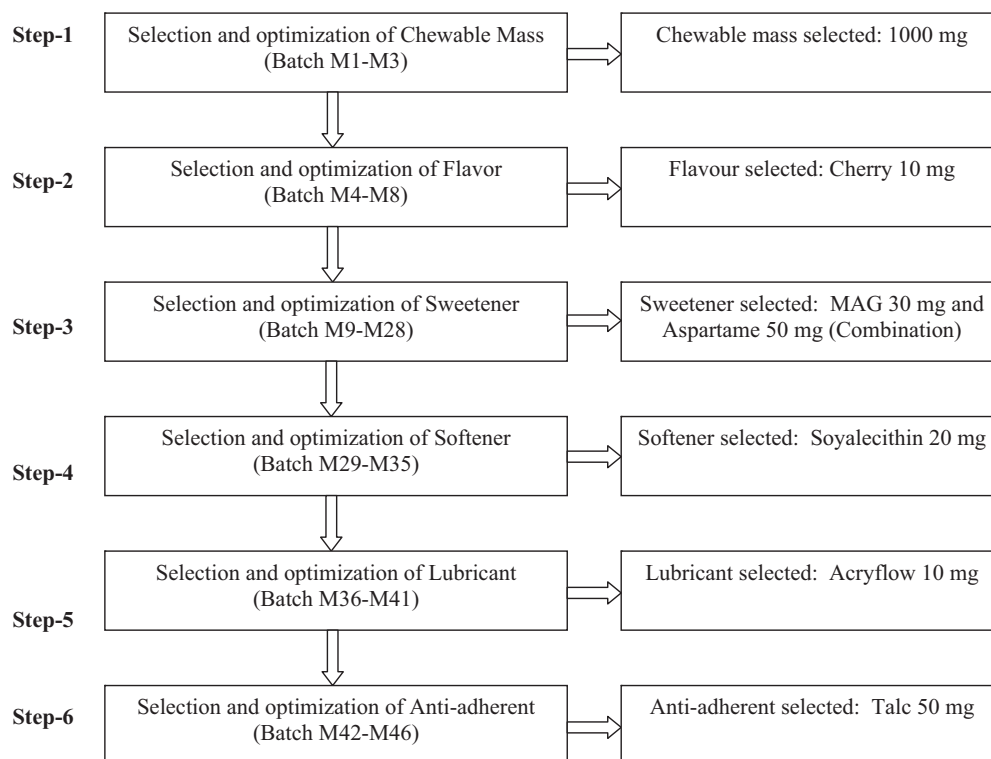
Figure 1 Steps of selection and optimization of the excipients.

Ethics Committee-Human Research. [Protocol No. RPCP/IECHR/PG/2012-2013/R11.02].

Volunteers those who signed the informed consent form (Annexure I) were selected. Before starting the experiment, all volunteers were instructed to rinse their mouth thoroughly and were asked about any adverse effect towards DM. They reported the responses of the tests in questionnaire form (Annexure II). Selection and optimization of an individual excipient was performed by screening each excipient with respect to desired criteria. The prepared formulation composition is shown in Table 1.

2.7. Optimization of chewable mass

To obtain good chewability of dosage form, the MCGs were formulated in different sizes (Batch M1–M3) and evaluated by healthy human volunteers. They were allowed to chew MCG of different sizes and MCG with good chewability was selected based on scale of chewability as mentioned in Table 2. The optimized mass was kept constant for further studies.

2.8. Screening of flavours

To formulate MCGs with good flavour lasting time, different flavours such as chocolate, cherry, peppermint oil, watermelon, orange were screened. MCGs containing different flavours were prepared (Batch M4–M8). MCGs were allowed to chew by healthy human volunteers up to 5 min and they were asked to report the flavour lasting time. MCG which had longer flavour lasting time was selected for further studies.

2.9. Screening of sweeteners

Sweeteners are the important part of the MCGs. Drug has moderate bitter taste and so it needs to be masked to enhance patient compliance. To mask the bitter taste of DM, different sweeteners such as mannitol, acesulfame, aspartame, glycyrrhiza, mono-ammonium glycyrrhizinate (MAG) (Batch M9–M28) were screened. Accurately weighed sweeteners were taken and MCGs were prepared by direct compression method. Taste acceptability was measured by a panel of volunteers ($n = 6$). Each volunteer was asked to hold MCG for 5–10 s, then spat out and to report taste rank as shown in Table 2. Formulation with excellent taste masking (taste rank: 4) was selected for further studies (Dixit, 2013).

2.10. Screening of softening agents

To obtain good softness in MCG, screening of different softening agents such as glycerol, stearic acid, soya lecithin was performed. Accurately weighed softener was taken (Batch M29–M35) and MCGs were evaluated by six healthy human volunteers based on the scale of softness as shown in Table 2.

2.11. Screening of lubricants

Different lubricants such as Magnesium Stearate and Acryflow™ were selected by taking different concentrations and by measuring flow characteristics of the drug: excipient mixture. MCGs containing different concentrations of lubricant (Batch M36–M41) were observed for smooth ejection during compression in tablet punching machine. MCG with

Table 1 Selection and optimization of DM Medicated chewing gum formulation (M1–M46).

Category	Ingredients	Batch code												
		M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13
Drug	DM	10	10	10	10	10	10	10	10	10	10	10	10	10
Gum base	Health in gum	480	580	980	980	980	980	980	980	880	973	880	920	880
Flavour	Cherry	–	–	–	10	–	–	–	–	10	10	10	10	10
	Orange	–	–	–	–	10	–	–	–	–	–	–	–	–
	Peppermint oil	–	–	–	–	–	10	–	–	–	–	–	–	–
	Water melon	–	–	–	–	–	–	10	–	–	–	–	–	–
	Chocolate	–	–	–	–	–	–	–	10	–	–	–	–	–
Sweetener	Mannitol	–	–	–	–	–	–	–	–	100	–	–	–	–
	Acesulfame	–	–	–	–	–	–	–	–	–	7	–	–	–
	MAG	–	–	–	–	–	–	–	–	–	–	100	–	–
	Aspartame	–	–	–	–	–	–	–	–	–	–	–	60	–
	Glycyrrhiza glabra	–	–	–	–	–	–	–	–	–	–	–	–	100
Total weight		500 mg		600 mg		1000 mg								

Category	Ingredients	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24	M25	M26	M27	M28
Drug	DM	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Gum base	Health in gum	963	953	943	933	923	913	820	820	830	840	850	870	890	900	910
Flavour	Cherry	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Sweetener	Mannitol	–	–	–	–	–	–	–	–							
	Acesulfame	7	7	7	7	7	7	7	–							
	MAG	–	–	–	–	–	–	100	100	100	100	80	60	40	30	20
	Aspartame	10	20	30	40	50	60	–	60	50	40	50	50	50	50	50
	Glycyrrhiza glabra	–	–	–	–	–	–	–	–		–	–	–	–	–	–
Total weight		1000 mg														

Category	Ingredients	M29	M30	M31	M32	M33	M34	M35	M36	M37	M38	M39	M40	M41	M42	M43	M44	M45	M46
Drug	DM	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Gum base	Health in gum	800	850	850	860	870	880	890	875	870	865	860	855	850	860	850	840	830	820
Flavour	Cherry	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Sweetener	MAG	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
	Aspartame	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Softener	Glycerol	100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Stearic acid	–	50	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Soyalecithin	–	–	50	40	30	20	10	20	20	20	20	20	20	20	20	20	20	20
Lubricant	Acryflow	–	–	–	–	–	–	–	5	10	15	20	25	30	10	10	10	10	10
Anti-adherent	Talc	–	–	–	–	–	–	–	–	–	–	–	–	–	10	20	30	40	50
Total weight		1000 mg																	

Table 2 Score of different test parameters.

Scale	0	1	2	3	4
Chewability	Very poor	Poor	Passable	Good	Very good
Bitterness	Bitter	Moderate to bitter	Slightly bitter	Tasteless/taste masked	Excellent taste masking
Softness	Very hard	Hard	Passable	Soft	Very soft

less concentration of lubricant and smooth ejection was selected for further studies.

2.12. Screening of anti-adherents

Different concentrations of anti-adherent (talc) were screened. MCGs containing different concentrations of anti-adherent (Batch M42–M46) were observed for smooth ejection and stickiness to die or punch of tablet punching machine. MCGs with less concentration of anti-adherent and less/no stickiness were selected for formulation of MCG.

2.13. Post-compression studies

Appearance, size, shape, thickness and diameter of MCG were observed by taking ten medicated chewing gum randomly.

Thickness and diameter were measured by digital vernier caliper and appearance, size, shapes of the medicated chewing gums were evaluated visually. The hardness of six medicated chewing gums was determined by diametrical compression using a Monsanto hardness tester and the average value was calculated and expressed as kg/cm^2. Weight variation test was performed by selection of twenty medicated chewing gum randomly. They were weighed individually and the average weight was calculated from total weight. Then percentage deviation from the average was calculated (European Pharmacopoeia, 2010).

$$\text{Percentage weight variation} = (\text{Weight of individual MCG}/$$
$$\text{Average weight of 20 MCGs}) * 100$$

2.14. Friability

Ten MCGs were randomly taken and carefully de-dusted prior to weighing. They were weighed and placed in the Roche Friabilator (EF-2, Electrolab®) which was rotated for 100 revolutions at 25 rpm. The medicated chewing gums were then de-dusted and reweighed. A maximum loss of mass (obtained from a single test or from the mean of three tests) was calculated in percentage (Chaudhary and Shahiwala, 2010).

2.15. Content uniformity test

The individual contents of active substance of 10 dosage units which were taken randomly were determined. The 10 dosage forms were crushed in mortar and powder equivalent to 10 mg of DM was taken. The powder was dissolved in 100 ml of conical flask containing phosphate buffer pH 6.8. The absorbance measurements of these solutions were taken by UV–Visible spectrophotometer at 284 nm. The formulation complies with the test if the individual content is between 85% and 115% of the average content (European Pharmacopoeia, 2010).

Table 3 Flow properties of gum base and Drug:Excipients (D:E) mixture.

Flow properties	Serial no	Average values[a]
Bulk density (gm/mL)	Gum base	0.66 ± 0.06
	D:E mixture	0.67 ± 0.025
Tapped density (gm/mL)	Gum base	0.73 ± 0.07
	D:E mixture	0.65 ± 0.051
Hausner's ratio	Gum base	1.09 ± 0.011
	D:E mixture	1.10 ± 0.02
Compressibility index (%)	Gum base	9.2 ± 0.72
	D:E mixture	9.46 ± 0.17
Angle of repose (θ)	Gum base	30.70 ± 1.02
	D:E mixture	29.49 ± 2.41

[a] Data are shown as average of $n = 3 \pm$ SD.

Table 4 Results of post-compression study of optimized MCG (M46).

Parameters	Average values
Weight variation[a]	1.004 ± 0.004
Diameter[b] (cm^2)	12.48 ± 0.030
Thickness[b] (mm)	6.671 ± 0.009
Hardness[c] (kg/cm^2)	2.666 ± 0.577
Friability[b] (%)	0.196 ± 0.099
Content uniformity[b] (%)	98.25 ± 8.404
Loss on drying[c] (%)	0.40 ± 0.005

[a] Data are shown as average of $n = 20 \pm$ SD.
[b] Data are shown as average of $n = 10 \pm$ SD.
[c] Data are shown as average of $n = 6 \pm$ SD.

2.16. % Loss on drying

% Loss on drying was measured in IR moisture balance instrument (MA 45 model, Sartorius, India) for 4 min. The
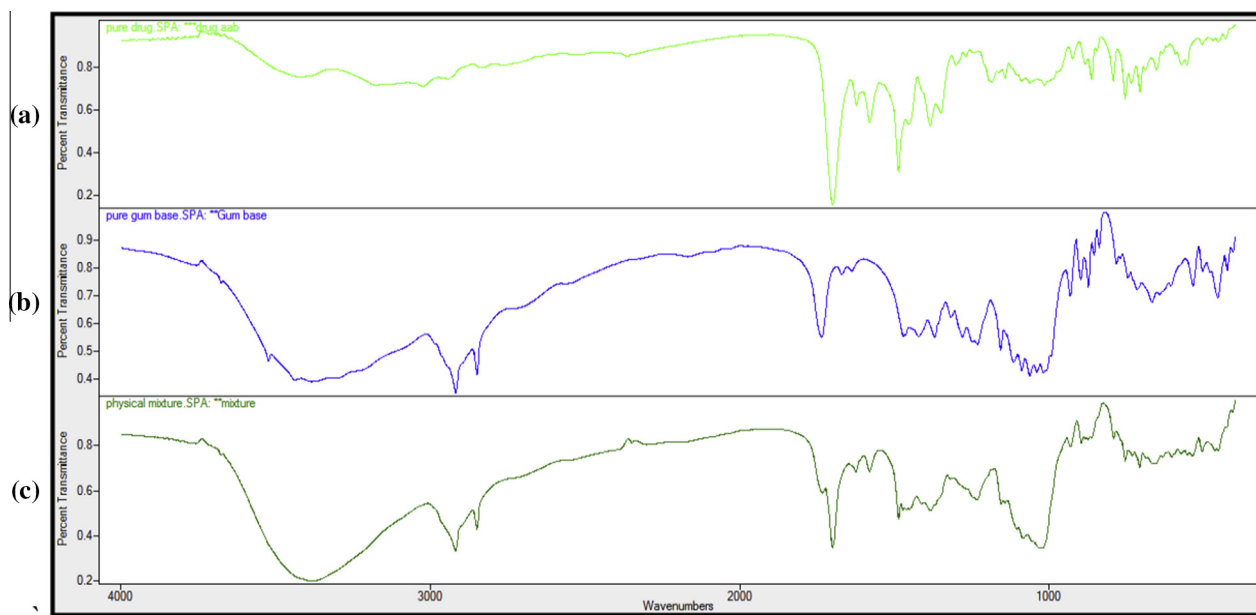

Figure 2 FTIR spectra of (a) pure drug, (b) pure gum base and (c) drug:excipients (1:99).

optimized MCG (M46 batch) was placed in aluminium disc in moisture balance. The temperature was set at 105 °C and the % loss on drying (% LOD) was determined (Vegada et al., 2012).

2.17. Evaluation of optimized batch

2.17.1. Statistical analysis of MCG quality

For product quality assessment, a sensory panel of 6 human volunteers had been formed. They had given two formulations for chewing (a) M46 (final optimized MCG) (b) M4 (MCG containing only gum base with DM and flavour) to evaluate organoleptic properties such as Taste, Consistency, Softness, Flavour lasting time. Volunteers had given score individually by chewing both the products. After assessment, filled forms with score (x out of 4) were received from volunteers. The average score was calculated for each of the four different qualities. Paired t-test was applied to test whether there is any significant improvement in product quality after excipient treatment or not (Chaudhary and Shahiwala, 2010).

2.17.2. Scanning electron microscopy (SEM)

Morphological surface characteristic of prepared MCG was analysed using scanning electron microscope. The medicated chewing gums of M46 (optimized batch) and M34 (MCG without lubricant) were fixed on aluminium stubs with double sided tape and examined in Jeol scanning electron microscope 5610 LV using an accelerating voltage of 2.0–30 kV, at magnification of 250×, 500× and 1000× (Bratbak, 1993).

2.17.3. Texture analysis by instrument

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. Texture property of directly compressed MCG was evaluated using Brookfield® QTS-25 texture analyser. It was recommended to use a compression probe with surface area of 4 mm^2. During evaluation, a constant force was applied on the surface of self-supporting MCG and upon fracture it was withdrawn. Deformation curve was recorded and interpreted. Peak load required for deformation of MCG was determined (Chaudhary and Shahiwala, 2010).

2.17.4. In-vivo drug release study

The in vivo drug release of DM from MCG during mastication was studied by recruiting a panel of six numbers of volunteers and scheduled chew-out studies for determination of % drug release from MCG. Each person was allowed to chew one sample of the DM MCG for a particular time period, i.e. 0.5, 1, 2, 5, 10, and 15 min. After chewing, chewed out gum samples were collected from volunteers, stretched out up to maximum and cut into small pieces and dispersed in a 100 ml volumetric flask containing phosphate buffer pH 6.8, which was then sonicated for 10 min with heating. The sonicated sample was filtered and analysed by a UV spectrophotometer at 284 nm to determine the residual drug content present in MCG. The "amount of drug released during mastication" was calculated by subtracting the "amount of the residual active ingredient"

presents in the gum after chewing from "the total content" (Chaudhary and Shahiwala, 2010; Noehr-Jensen et al., 2006).

Amount of drug released during mastication = Total content − Amount of the drug in residual active ingredient.

2.17.5. Ex-vivo buccal permeation study

Buccal mucosa was obtained from the approved slaughter house. The permission for conducting this study was obtained from Institutional Animal Ethics Committee (IAEC). [Protocol No: RPCP/IAEC/2012-2013/MPH-PT-26]. Goat buccal mucosa was cleaned and placed between a donor compartment and a receiver compartment of the Franz diffusion cell. To simulate oral conditions, phosphate buffer of salivary pH (pH 6.8) was filled in the donor compartment and phosphate buffer of blood pH (pH 7.4) was filled in the receiver compartment. The average amount of DM, which was released from optimized formulation after 15 min of chewing, was placed in the donor compartment. It was allowed to permeate through buccal mucosa for 30 min. At 5 min interval the sample was collected from the receiver compartment and analysed by the UV-spectrophotometer at 284 nm, to determine the total content of DM permeated through buccal mucosa. The study was performed in triplicate (Chaudhary and Shahiwala, 2010).

3. Result and discussion

3.1. Drug excipients compatibility study

The FTIR spectra as shown in Fig. 2 indicated that there were no changes in standard wave number of the drug and excipients. So, there is no interaction between pure drug, pure gum base and excipients. It indicates that drug and excipients are compatible.

3.2. Pre-compression studies

The results of pre-compression studies are shown in Table 3. Angle of repose of gum base and drug: excipients mixture was found to be 30.70 ± 1.02 and 29.49 ± 2.41, respectively. Angle of repose less than or equal to 30 indicates excellent flow property so it was concluded that the gum base and drug:excipients mixture had excellent flow property. Compressibility index for gum base and drug: excipients mixture was found to be 9.20 ± 0.72% and 9.46 ± 0.17%, respectively, which indicates excellent compressibility of gum base and mixture. Compressibility is the parameter used to determine compression efficiency of powder during compression. Compressibility index less than 10% indicates excellent compressibility. Hausner's ratio for gum base and mixture was found to be 1.09 ± 0.011 and 1.10 ± 0.02, respectively, which represents good flowability because Hausner's ratio between 1.00 and 1.11 represents excellent flowability. Thus, from the results it was indicated that the gum base and mixture of drug and excipients showed excellent flow property and compressibility which is favourable for direct compression.
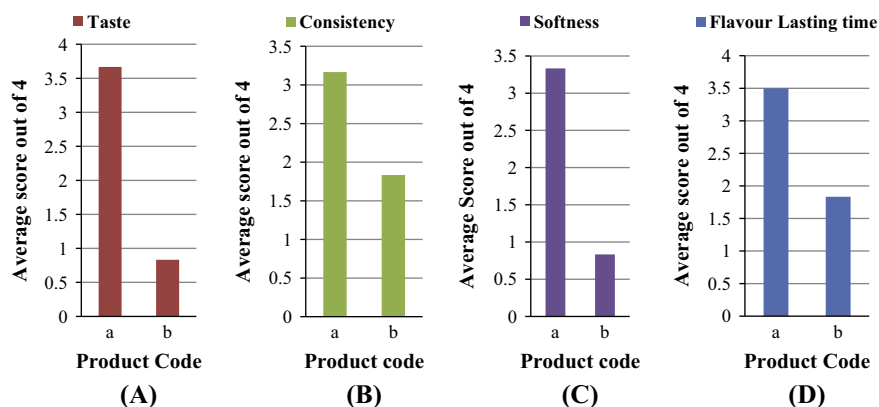
Figure 3 Comparison of scores obtained by two different MCG products: (A) Taste, (B) Consistency, (C) Softness and (D) Flavour Lasting Time.

Table 5 Average score for four different qualities of optimized MCG (M46).

Parameter	Taste		Consistency		Softness		Flavour lasting time	
Batches[a]	a	b	a	b	a	b	a	b
Average score[b]	3.66 ± 0.516	0.833 ± 0.752	3.16 ± 0.751	1.83 ± 0.75	3.33 ± 0.816	0.83 ± 0.752	3.5 ± 0.547	1.83 ± 1.47

[a] Where "a" is batch M45 and "b" is batch M4.
[b] Data are shown as average of $n = 6 \pm$ SD.

3.3. Formulation and development of medicated chewing gum

The details of all the batches are given in Table 1.

3.4. Optimization of chewable mass

The batches from M1 to M3 were formulated to optimize chewable mass from the response of healthy human volunteers ($n = 6$) and it was found that MCG of Batches M1 (500 mg) and M2 (600 mg) showed poor chewability due to less chewable mass which was not favourable for MCG. The batch M3 (1000 mg) showed very good chewability due to proper chewable mass. So, the size of medicated chewing gum was fixed as 1000 mg for further formulation.

3.5. Screening of flavours

The batches of MCGs containing different flavours were formulated (M4–M8). The responses were observed in healthy human volunteers ($n = 6$) and it was observed that the flavour lasting time for M5 (orange) and M7 (water melon) was about 1 min so imparted bitter taste during mastication. M6 (peppermint oil) had flavour lasting time up to 2 min. The M8 (chocolate) has good flavour lasting time up to 4 min but that was lower as compared to cherry flavour. The highest flavour lasting time observed with M4 (cherry) was up to 5 min. So, M4 batch containing cherry as flavour was selected.

3.6. Screening of sweeteners

Sweeteners are the important part of the MCGs. Drug has moderate bitter taste and so, it needs to be reduced or to be masked to enhance patient compliance. The batches

Table 6 Applied paired t-test for optimized MCG (M46) quality evaluation.

MCG quality	t_{cal}	t_{tab}
Taste	9.219	2.015
Consistency	3.162	2.015
Softness	7.319	2.015
Flavour lasting time	2.5	2.015

M9–M28 were formulated using different concentration of sweeteners. The responses were observed in healthy human volunteers ($n = 6$). Based on the response it was concluded that batch M4 (without sweetener) has bitter taste which is rated 0 as per the taste rank shown in Table 2. In the batches M9–M13 containing different sweeteners, it was observed that these batches had moderate bitterness. So, it was decided to formulate MCG with the blend of sweeteners so as to get the complete taste masking.

In the MCGs containing different Blend of Sweeteners, it was found that the batch M21 containing highest amount of MAG: Aspartame (100 mg: 60 mg), masked the bitter taste but it had some bitter after taste that may be due to aspartame or MAG. To optimize the concentration of MAG and aspartame, further batches (M22–M28) were formulated. Batch M22 containing 50 mg of aspartame showed complete taste masking so it was optimized for further formulation. To test the effectiveness of MAG on taste masking the amount of MAG was decreased further. Monoammonium glycyrrhizinate (MAG) can be used as sweetness potentiator. The MCGs of M27 (30 mg of MAG) showed proper taste masking. It was concluded that batch M27 at amount (30 mg MAG: 50 mg Aspartame) had excellent taste masking, so, this ratio was selected for further formulation.
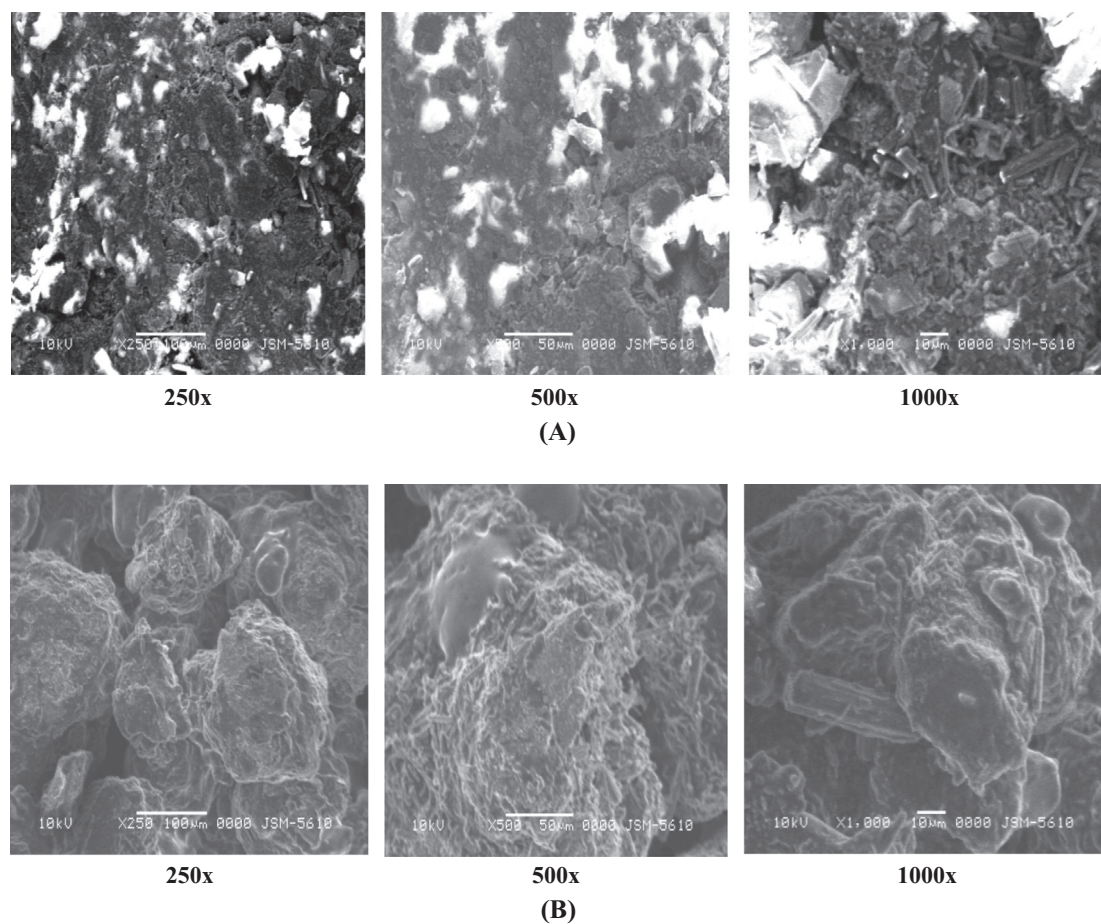
250x   500x   1000x

(A)

250x   500x   1000x

(B)

Figure 4   Scanning electron microscope images of medicated chewing gum: (A) M45. (B) M36 at 250× 500×, 1000× magnification.

3.7. Screening of softening agents

It was observed that batch M29 containing glycerol had good softening property but it affects the flow properties because of viscous nature. The batch M30 containing stearic acid was very hard to chew and had grittiness during mastication while the batch M31 containing soya lecithin provided very good softness and consistency to the MCG, so, it was selected as softening agent for further study.

Soya lecithin also helps to suppress bitter taste of DM (Sharma and Lewis, 2010). Further, it was found that the concentration of softener may affect the release of drug from MCG. So, concentration of softener was optimized based on drug release. The batches M31–M35 containing different concentration of soya lecithin (1–3% w/w) was formulated and drug release study was performed in healthy human volunteers. It was found that M34 (2% soya lecithin) showed highest drug release. The MCGs containing soya lecithin more than 2% were split into pieces during chewing which showed poor acceptability. So, 2% soya lecithin concentration was optimized and kept constant for further formulation.

3.8. Screening of lubricants

The batches (M36–M41) containing different concentrations (0.5–3% w/w) of lubricant (Acryflow™) were prepared.

Magnesium stearate is most widely used as lubricant but it was found that it retards dissolution of some APIs and the magnesium salt sometimes shows incompatibility with APIs (Allen and Luner, 2009). Acryflow™ is poly-hydroxy stearate derivatives and it has nonreactive functional group, so, it does not have incompatibility with APIs (Corel Pharma Chem, 2013). The selection of lubricant was performed based on its flow properties and the results showed that the angle of repose ranges from 31 to 36 which indicates good flowability. Hausner's ratio was found in the range 1.071–1.081 which indicates excellent flowability. The compressibility index was found to be 6.66 which indicates excellent compressibility. Acryflow™ in the concentration of 1% w/w i.e. 10 mg (Batch M37) was selected as lubricant as it showed good flow properties, excellent compressibility and smooth ejection from tablet punching machine.

3.9. Screening of anti-adherent

The batches M42–M46 containing different concentration of talc were prepared. The amount of talc selected based on stickiness of MCGs to punch. It was found that in batch M46, MCG did not stick to punch and was easy to eject out. So, batch M46 containing 50 mg talc was selected for final formulation.

Table 7 Peak load of optimized batch (M46) by texture analysis.

Serial no.	Probe (mm)	Compression cycle	Peak load (gm)	Average[a] (gm)
1	4	1	12,248	11,062 ± 1225.6
2	4	1	9847	
3	4	1	11,043	

[a] Data are shown as average of $n = 3 \pm$ SD.

3.10. Post-compression study

The results of the post-compression studies are shown in Table 4. From the visual inspection by healthy volunteers, it was found that the appearance, size, shape of optimized MCG were aesthetic. The mean thickness ($n = 10$) and mean diameter ($n = 10$) were uniform with value ranging between 6.662–6.681 mm and 12.46–12.52 mm^2, respectively. The average weight of compresses MCG formulations was within the range of 0.998–1.008 mg. So, all compressed MCGs passed weight variation test for compressed tablets as per European Pharmacopoeia. The weight of all the MCGs was found to be uniform with low standard deviation values. The measured hardness of tablets ranged between 2 and 3 kg/cm^2 which ensures good handling characteristics of MCG. The % friability was less than 1% in all the formulations ensuring that the MCGs were mechanically stable. The percentage drug content of the all the MCGs ranged within 98.25% to 105.67%, which was within acceptable limits indicating dose uniformity in each MCG. The mean % of loss on drying of optimized MCGs was found to be in range of 0.40–0.41%, which is within acceptable limits indicating higher stability of MCGs.

3.11. Evaluation of optimized batch

3.11.1. Statistical Analysis of MCG quality
The statistical analysis of MCG (a) M46 (b) M4 was performed for its quality evaluation. The Organoleptic properties such as taste, consistency, softness, flavour lasting time were 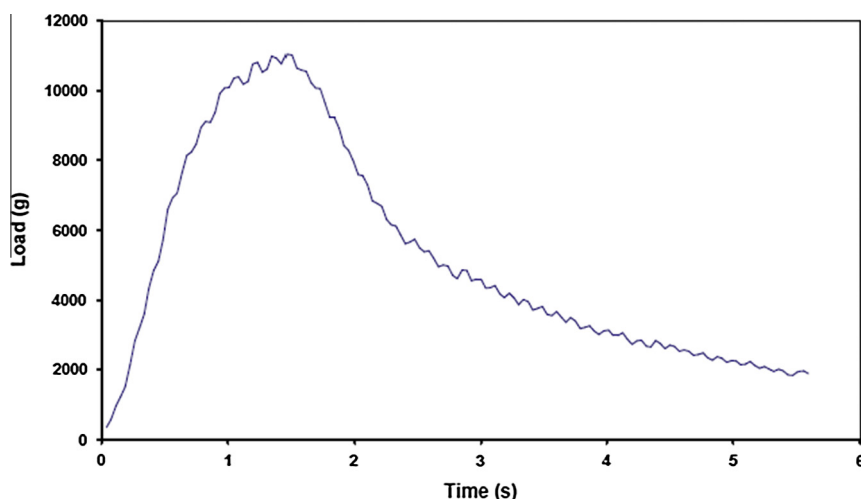evaluated from the response of healthy human volunteers ($n = 6$). The Comparison of score obtained from responses was represented in Fig. 3. The average score was calculated for each of four different qualities and the results of which are as shown in Table 5.

Paired t-test was applied to test any significant improvement in product quality after excipients treatment and the results for which are as shown in Table 6. It was concluded that for all quality parameters, $t_{cal} > t_{tab}$ so there is a significant improvement in product quality after treatment with excipients. It was confirmed that there is a significant improvement in the product taste, product consistency, product softness and total flavour lasting time after incorporation of appropriate excipients in an optimum amount in M45 (final optimized MCG formulation).

3.11.2. Scanning Electron Microscopy (SEM)
The SEM images (Fig. 4) clearly indicate that optimized formulation has smoother surface as compared to MCG without lubricants. So, it was concluded that M45 can increase patient acceptance due to aesthetic surface property.

3.11.3. Texture analysis study
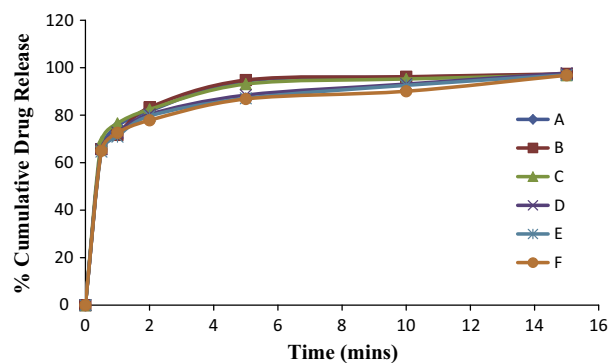It was found that peak load required for deformation of medicated chewing gum was 11062 ± 1225.6 g with 4 mm probe.

Figure 6 In-vivo drug release in healthy human volunteers (A–F).

Figure 5 Peak load curve of optimized batch (M46) obtained from texture analyzer.

Table 8 *In-vivo* drug release in six healthy volunteers.

Serial no.	Time (minutes)	% Drug release[a]					
		Volunteer A	Volunteer B	Volunteer C	Volunteer D	Volunteer E	Volunteer F
1	0	0	0	0	0	0	0
2	0.5	65.76 ± 0.885	65.72 ± 3.500	68.90 ± 3.059	65.73 ± 0.689	64.67 ± 1.271	65.01 ± 2.259
3	1	75.48 ± 0.413	71.71 ± 2.63	76.56 ± 2.121	72.71 ± 1.574	72.71 ± 1.574	72.59 ± 2.1452
4	2	81.81 ± 2.390	83.25 ± 2.95	82.45 ± 2.492	80.35 ± 0.560	79.63 ± 2.283	77.86 ± 2.888
5	5	94.37 ± 1.414	94.80 ± 1.013	93.10 ± 3.103	88.44 ± 2.318	87.11 ± 2.938	86.84 ± 1.550
6	10	96.03 ± 0.915	96.20 ± 0.679	95.23 ± 1.389	93.09 ± 0.536	92.55 ± 2.117	90.09 ± 1.254
7	15	97.14 ± 0.122	97.42 ± 0.805	96.84 ± 0.921	97.72 ± 1.011	96.95 ± 1.211	96.82 ± 1.345

[a] Data are shown as average of $n = 6 \pm$ SD.
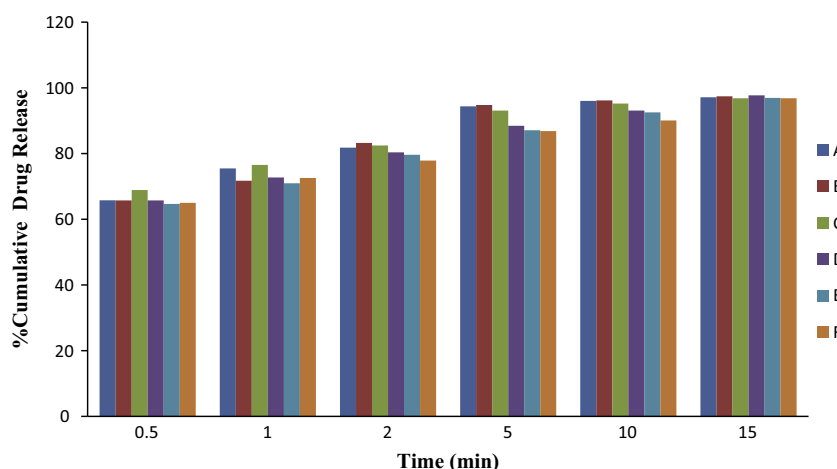
Figure 7 *In-vivo* drug releases of six healthy human volunteers and comparison at specific time.
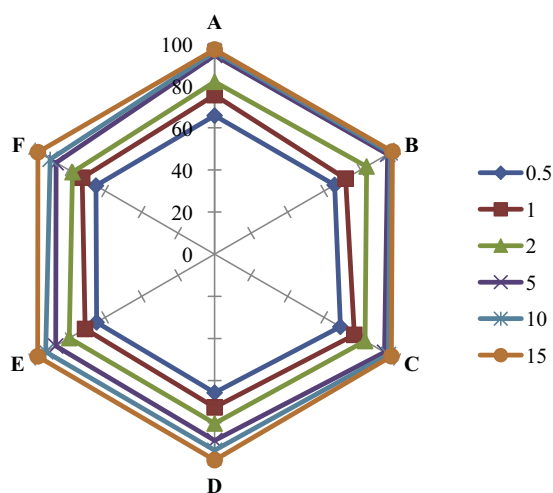
Figure 8 Radar plot of drug release in healthy human volunteers at specific time.

The MCG initially crumbles and then comes together to form a chewable gum mass. The crumbling of the MCG allows DM to be released and provides a faster release as compared to conventional gums, which remain intact during the process

(Jójárt et al., 2013). The results of texture analysis study are given in Table 7 and Fig. 5.

3.11.4. In-vivo drug release study

The results of in vivo drug release at different time intervals are as shown in Fig. 6. Individual % DM release is mentioned in Table 8 and Fig. 7. From the results, it was observed that drug release after 15 min of chewing was 97.15%. Initially, due to the breaking of the MCG, the release of the drug was very fast as it was observed that almost 80% of the drug was released within 2 min. This is a good indication as the fast release of drug resulted in the fast absorption and ultimately the fast onset of action. The radar plot (Fig. 8) showed the % drug release from MCG at specific time (0.5, 1, 2, 5, 10 and 15 min) in healthy human volunteers (A–F).

3.11.5. Ex-vivo buccal permeation study

The results of buccal permeation study of DM performed on goat buccal mucosa are given in Fig. 9. From the results, it was observed that the amount of drug permeated through buccal mucosa was 1.09 mg (11.27%) in 15 min. It is hypothesized from the results of the buccal permeation that the significant amount of the drug may permeated (absorbed) through the buccal route, which may increase bioavailability of DM and decrease onset time.
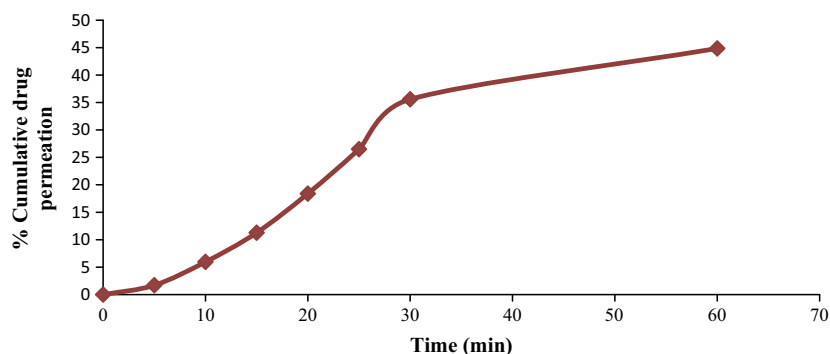
Figure 9 Ex-vivo buccal permeation data.

4. Conclusion

The study concludes the possibility of the formulation of the directly compressible MCG of DM using HealthinGum® (gum base) with the improved taste by using combination of the sweeteners. The first pass metabolism associated with DM can also be solved by the MCG, as the main site of absorption is buccal. The MCG formulation of DM is a novel approach for the treatment of nausea and vomiting associated with motion sickness and other pathophysiological conditions. MCG can increase patient compliance and patient acceptance as well as increase the bioavailability of DM as it showed significant permeation through buccal mucosa. However, clinical pharmacokinetic data are needed to prove it further.

5. Declaration of interest

The authors report no conflicts of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jsps.2015.02.017.

References

Allen Jr., L.V., Luner, P.E., 2009. Magnesium Stearate. In: Raymond, C., Rowe, P.J. (Eds.), Handbook of Pharmaceutical Excipients. The Royal Pharmaceutical Society of Great Britain, p. 405.

Andersen, T., Gram-Hansen, M., Pedersen, M., Rassing, M.R., 1990. Chewing gum as a drug delivery system for nystatin influence of solubilising agents upon the release of water insoluble drugs. Drug Dev. Ind. Pharm. 16 (13), 1985–1994.

Bhatt, S., Trivedi, P., 2012. Development and evaluation of fast dissolving tablets using domperidone: peg 6000 solid dispersions. Int. J. Pharm. Pharm. Sci. 4 (2), 246–249.

Bratbak, G., 1993. Microscope methods for measuring bacterial biovolume: epifluorescence microscopy, scanning electron microscopy, and transmission electron microscopy. Handbook Methods Aquatic Microbial Ecol., 309–317.

Chaudhary, S.A., Shahiwala, A.F., 2010. Medicated chewing gum-a potential drug delivery system. Expert Opin. Drug Delivery 7 (7), 871–885.

Chaudhary, S.A., Shahiwala, A.F., 2012. Directly compressible medicated chewing gum formulation for quick relief from common cold. Int. J. Pharm. Invest. 2 (3), 123.

Cherukuri, S.R., Pinney, J.M., Henningfield, J.E., Sasan, A., Cone, E.J., Shiffman, S., Gitchell, J., Malvestutto, C.D., 2000. Medicated Chewing Gum Delivery System for Nicotine. US Patent No. US6344222: 1–24.

Corel Pharma Chem. 2013. Available at: http://www.corel-pharmachem.com/acryflow.htm, accessed on 8th June, 2014.

Dixit, Y.D., 2013. Formulation and evaluation of mucoadhesive buccal tablet of domperidone maleate. Indonesian J. Pharm. 24 (1), 47–55.

Dong, H.N., Jabar, F., Yilmaz, C., Kai, P.L., DeLuca, P.P., 2005. Chewing gum of antimicrobial decapeptide (KSL) as a sustained antiplaque agent: preformulation study. J. Controlled Release 107, 122–130.

European Pharmacopoeia, 2010. Directorate for the Quality of Medicines, Council of Europe, 709.

Ingole, B.D., Daga, A.S., Joshi, U.M., Biyani, K.R., 2012. Chewing gum: a mobile drug delivery system. Int. J. Pharm. Sci. Rev. Res. 14 (2), 106–114.

Islam, A., Haider, S.S., Reza, M.S., 2011. Formulation and evaluation of orodispersible tablet of domperidone. Dhaka Univ. J. Pharm. Sci. 10 (2), 117–122.

Jacobsen, J., Christrup, L.L., Jensen, N.-H., 2004. Medicated chewing gum. Am. J. Drug Delivery 2 (2), 75–88.

Jójárt, I., Kelemen, A., Kása Jr., P., Pintye-Hódi, K., 2013. Tracking of the post-compressional behaviour of chewing gum tablets. Composites: Part B 49, 1–5.

Mehta, F., Trivedi, P., 2011. Formulation and texture characterization of medicated chewing gum delivery of dimenhydrinate hydrochloride. Pharm. Lett. 3 (6), 179–192.

Morjaria, M., Irwin, W.J., Barnett, P.X., Chan, R.S., Conway, B.R., 2004. In vitro release of nicotine from chewing gum formulations. Dissolution Technol., 12–15 (May).

Nagaich, U., Chaudhary, V., Karki, R., Yadav, A., Sharma, P., 2010. Formulation of medicated chewing gum of ondansetron hydrochloride and its pharmacokinetic evaluations. Int. J. Pharm. Sci. Res. 1 (2), 32–40.

Nagarsenker, M.S., Garad, S.D., Ramprakash, G., 2000. Design, optimization and evaluation of domperidone coevaporates. J. Control. Release 63, 31–39.

Noehr-Jensen, L., Damkier, P., Bidstrup, T.B., Pedersen, R.S., Nielsen, F., Brosen, K., 2006. The relative bioavailability of loratadine administered as a chewing gum formulation in healthy volunteers. Eur. J. Clin. Pharmacol. 62 (6), 437–445.

Pedersen, M., Rassing, M.R., 1990. Miconazole chewing gum as a drug delivery system application of solid dispersion technique and lecithin. Drug Dev. Ind. Pharm. 16 (13), 2015–2030.

Pleuvry, B.J., 2006. Physiology and pharmacology of nausea and vomiting. Anaesthesia Intensive Care Med. 7 (12), 473–477.

Rao, M., Prasanthi, G., Ramesh, Y., 2011. Formulation and evaluation of medicated chewing gum of Promethazine hydrochloride. J. Pharm. Res. 4 (9), 10.

Sharma, S., Lewis, S., 2010. Taste masking technologies: a review. Int. J. Pharm. Pharmaceut. Sci. 2 (2), 6–13.

Stojanov, M., Larsen, K.L., 2012. Cetirizine release from cyclodextrin formulated compressed chewing gum. Drug Dev. Ind. Pharm. 38 (9), 1061–1067.

Swamy, N.G.N., Shilpa, P., Abbas, Z., 2012. Formulation and characterization of medicated chewing gums of dextromethorphan hydrobromide. Indian Drugs 49 (12), 29–35.

Tripathi, K.D., 2003. Essentials of Medical Pharmacology, fifth ed. Jaypee Brothers Medical Publishers (P) LTD, p. 604.

Tyrpin, H.T., Russell, M.P., Witkewitz, D.L., Johnson, S.S., Ream, R.L., Corriveau, C.L., 2002. Caffeine coated chewing gum product and process of making. US Patent no. 6444241, pp. 1–15.

Vegada, R., Seth, A., Sachin, C., Parikh, P., Kheini, P., Chainesh, S., et al, 2012. Formulation and evaluation of novel gum based drug delivery system of an antiemetic drug. Int. J. Pharm. Res. Technol. 2 (2), 16–20.

Woodford, D., Lesko, L., 1981. Relative bioavailability of aspirin gum. J. Pharm. Sci. 70 (12), 1341–1343.

Zyck, D.J., Greenberg, M.J., Barkalow, D.G., Marske, S.W., Schnell, P.G., Mazzone, P., 2003. Method of making coated chewing gum products containing various antacids. US Patent no. US 6645535, pp. 1–14.