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Research Article

Formulation and Evaluation of Novel Gum Based Drug Delivery System of An Antiemetic Drug

Rajnikant Vegada*[1], A.K. Seth[1], Chauhan Sachin[1], Parth Parikh[1], Pratik Kheini[1], Shah Chainesh[1], Ramani Vinod[2].
[1] Sumandeep Vidyapeeth, Piparia, Waghodiya. Vadodara. Gujarat
[2] C.K. Pithawalla Institute of Pharmaceutical Science & Research, Surat. Gujarat.
***Corresponding Author** email: rajnikantpharma@gmail.com*
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ABSTRACT
The study was to formulate and evaluate medicated chewing gum of meclizine hydrochloride, an antiemetic drug used in nausea, vomiting and motion sickness. The chewing gums were prepared by direct compression method using different ratio of directly compressible gum base (Pharmagum S) in order to obtain optimized formulation. Eight different formulations of chewing gums of meclizine hydrochloride were prepared, which contained various concentration of pharmagum S and Soya powder. The chewing gums which prepared by direct compression method were characterized by pre- compression characters, post compression character, buccal absorption study, drug content and *in vitro* drug release studies. All the formulations gave satisfactory results in terms of pre compression characters, post compression character, drug content, and *in vitro* drug release. The best compression characters and 97.88±0.69 % in vitro drug release profile were achieved in formulation MCG5 with a gum and soya powder concentration of 775 mg and 140 mg and FTIR study of optimized MCG5 has shown satisfactory result in terms of drug: polymer compatibility. So MCG5 was taken as optimized batch.

Key words: Meclizine hydrocloride, Pharmagum S, Soya powder, Motion sickness.

INTRODUCTION

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 swallowed, providing a slow steady release of the medicine contained. According to European pharmacopeia, 4th edition, 2002 medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose, after which the remaining mass is discarded. During the chewing process, the drug contained in the gum product is released from the mass in to saliva and it could be absorbed through the oral mucosa or swallowed reaching the stomach for gastro-intestinal absorption, thus, two absorption pathways are possible to introduce the active ingredient, giving rise to a systemic effect. [1] Drug absorbed directly, via the buccal membrane, avoids metabolism in the gastro-intestinal tract and the first pass effect of the liver, therefore it might be possible to administer a reduced dose in chewing gum compared to other oral delivery systems. Alternatively, drug released from medicated chewing gum which is not absorbed through the oral cavity membranes, will be swallowed and reach the stomach in a diluted or very dispersed form, thus being very easily available with a consequent faster on set of action.[2, 3] The present work will do with an objective to formulate novel gum based drug delivery system of an antiemetic drug (Meclizine hydrocloride) with a view to achieve. [1]

To obtain fast/rapid onset of action, to get high bioavailability, to provide pleasant taste, to obtain of ease of administration without water and promotes higher patient compliance, To reduce side effects, to get the effect on dry mouth (xerostomia) to formulate a product distinctiveness from a marketing perspective,[2] Excellent for acute medication, Counteracts dry mouth, prevents candidacies and caries.

Meclizine is an antihistamine with antiemetic (anti-nausea) and antispasmodic (anti-muscle spasm) activity. It also suppresses the nervous system by blocking the action of the neurotransmitter acetylcholine. (Neurotransmitters are chemicals that nerves use for communicating with each other.)[4] Meclizine prevents nausea and vomiting by reducing the activity of the center in the brain that controls nausea. It also prevents motion sickness by reducing excitability of neurons in the motion and balance center (vestibular region) of the brain. Along with its actions as an antagonist at H_1 receptors, meclizine also possesses anti cholinergic, central nervous system depressant, and local anesthetic effects. Meclizine depresses labyrinth excitability and vestibular stimulation and may affect the modularly chemoreceptor trigger zone.[5] These compounds cannot form supersaturated solutions. When the pH is right, they fall out of solution immediately the solubility limit is exceeded. We call these compounds Non-Chasers. The kinetic solubility and intrinsic solubility of non-chasers is equal.

MATERIALS & METHODOLOGY

Compatibility Studies: [7,8,9]

A proper design and formulation of a dosage form requires considerations of the physical, chemical and biological characteristics of both drug and excipients used in fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. As a part of compatibility studies, the binary mixtures (1:1) of the drug and one of the excipients, one at a time was taken and incubated in stability chambers at 25^0C and 60% RH and 40^0C and 75% RH for a period of 2 months. In the present study, potassium bromide (KBr)

pellet method was recorded in range of4000 – 400cm^{-1}. The samples were thoroughly mixed with dry powdered potassium bromide. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded.

Preparation of medicated chewing gum of meclizine hydrochloride

All the ingredients were weighed accurately as per the formula; weighed ingredients were passed through sieve no. 16 for reduce the particle size and kept a side. First the flavor and aeroperl were mixed and thoroughly and kept a side. The drug, pharmagum S, soya powder, and aspartem were mixed with Perlitol SD 200. Finally to this the weighed quantities of magnesium stearate were added. The mixture was then regranulated by passing through sieve no 30. The granules were weighed and then compressed using a 14mm punch in rotary tablet punching machine. In the present study eight sets of formulations were prepared and studied.

Determination of pre-compression characteristics [10, 11]

Bulk density (ρ_b): It is the ratio of total mass of the powder to the bulk volume of powder. It was measured by pouring the weighed powder in to measuring cylinder and the volume was noted. It is expressed in gm/ml and given by,

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume}} \quad \ldots\ldots\ldots\ldots\ldots (1)$$

Tapped density: It is the ratio of total mass of the powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by,

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume}} \quad \ldots\ldots\ldots\ldots\ldots (2)$$

Compressibility index: The compressibility index of the powder blend was determined by carr's compressibility index. It is simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's index is as below,

$$\%\text{Compressibility index} = 100 \times \left(1 - \frac{\text{bulk density}}{\text{tap density}}\right)$$

Hausner's ratio: It is calculated from bulk density and tap density,

$$\textbf{Hausner's ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}} \quad \ldots\ldots\ldots\ldots\ldots (3)$$

Angle of repose: The frictional forces in loose powder can be measured by the angle of repose θ. This is the maximum angle possible between the surface of the pile of powder and the horizontal plane. The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the formed powder heap.

Loss on drying: Loss on drying was measured in halogen moisture balance instrument for 4 minute at 105^{0}C.

Determination of post-compression characteristics [12, 13, 14]

Hardness: The Monsanto hardness tester measures the force required to break the chewing gum.

Friability: It is usually measured by the use of them 'Veego friabilator'. 10 tablets were randomly selected, weighed and were tested using the Veego friabilator.

$$\textbf{Friability} = \frac{(W_{\text{initial}} - W_{\text{final}})}{W_{\text{initial}}} \times 100 \quad \ldots\ldots\ldots\ldots (4)$$

Weight variation: The weight variation test of the chewing gum was done as per the guidelines of USP 20. Chewing gum was randomly selected, weighed and weight was noted and the mean weight was calculated. Percentage deviation of each chewing gum from the mean was calculated.

Estimation of Drug Content: [15,16]

Chewing gums unlike tablets cannot be assayed by the conventional method that is by crushing the tablet and weighing an accurate amount of medicament and estimating its content. For estimation of the drug content in chewing gums and for the study of drug release process from chewing gums a new apparatus (Erweka's DRT 6 Chewing apparatus) has been designed which mimics the natural chewing actions.

Figure 1 Photograph of Erweka's DRT 6 apparatus

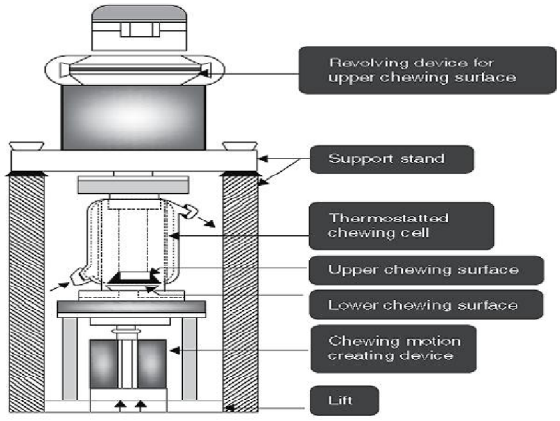

Figure 2 Schematic representation of different part of Erweka's DRT 6 apparatus

The material and the form of the parts that are in contact with the chewing gum are decisive for the function of the apparatus. The material of chewing surface (jaw) is acid proof stainless steel with a blasted surface. The blasted surface makes the jaws get a good grip of the chewing gum during the mastication process. The upper jaw is stationary in relation to the lower jaw and also completely fixed against up and down going movements although it is turning around its axis by a revolving device. The lower

jaw is moving up and down by a device for linear/axial chewing movements but is fixed against revolving movements.

The test cell follows the lower jaw in its movements. The chewing procedure consists of up and down going strokes of the lower jaw in combination with a shearing (twisting) movement of the upper surface which provides mastication of the chewing gum and at the same time an adequate agitation of the test medium.

It is possible to raise and lower the "lower jaw / test cell" by a lift device. If you lower it to down position it becomes completely free standing from the upper jaw which facilitates the preparations for analysis, sampling, emptying and cleaning after analysis. During sampling the mechanical processing and the stirring stops which means that the release of drug stops. The upper jaw has a flat underside which is parallel to the central part of the lower jaw. The small brim of the lower jaw is angled upwards (45 degrees) so that the lower jaw fashions a small bowl with flat bottom. This bowl prevents the chewing gum from sliding during mastication. It can be of advantage to use circular nets of inert polymer to keep the chewing gum in place between the jaws during the analysis.

The thermostatic test cell is made of glass and is transparent which allows visual inspection during test. It is complemented with a thermostat chamber of metal which is in thermal contact with the lower jaw. The upper jaw is not heated and is attached to a heat insulating axis. The water bath is to be filled with deionized water and is heated by a heater.

Procedure for estimation of drug content: The test cell was filled with 50ml of simulated salivary fluid (SSF). The chewing gum was placed in the equipment and the instrument was operated for a period of 30 minute at a chewing frequency of 56 strokes/ min, to ensure total release of the drug from the formulation in the simulated salivary fluid. From the dissolution medium 5 ml was withdrawn and volume was made up to 100ml with SSF and the absorbance of the resulting solution was read at 232nm. The amount of drug present in the formulation is calculated.

Table 2 Dissolution process parameter

Dissolution medium	SSF fluid pH 6.6
Temperature	37± 0.5 0 C
Chewing frequency	56 stroke/min
Vol. withdrawn and replaced	5 ml every 5 min
λ max	232nm
Blank Solution	Simulated salivary fluid pH-6.6
Duration of study	30 min
Volume of dissolution medium	50ml

***In vitro* drug release study:** [17, 18, 19]

The test cell of the apparatus was filled with 50ml of SSF and the chewing gum was placed in the apparatus. The apparatus was operated at a chewing frequency of 56 strokes / min. 5ml of the SSF from the test cell was withdrawn at regular intervals of 5, 10, 15, 20, 25 and 30 min 5ml of fresh SSF was replaced back in the test at every withdrawal of the sample. The volume withdrawn was made up to 100ml using SSF and absorbance of the resulting solution was read at 232nm, process parameter show in table 2.

Estimation of chewing gum consistency [20]

Here the studies are carried out by chew out method. For estimation of chewing gum consistency the dummy chewing gums (without drug) were prepared according to the formula, and they are given to the human volunteers to chew for certain time.

RESULTS AND DISCUSSION

In the present study an attempt was made to formulate medicated chewing gum containing Meclizine hydrocloride using Pharmagum S as the gum base. Meclizine prevents nausea and vomiting by reducing the activity of the center in the brain that controls nausea. It also prevents motion sickness by reducing excitability of neurons in the motion and balance center (vestibular region) of the brain. Meclizine hydrochloride has not any disagreeable taste and it is not irritant to mucosa. The drug has below 100µm particle size and suitable pKa for mucosal absorption. Chewing gum formulation obtains fast/rapid onset of action, high bioavailability, pleasant taste, ease of administration without water, promotes higher patient compliance, reduce side effects, product distinctiveness from a marketing perspective, Excellent for acute medication, Counteracts dry mouth. Pharmagum S and soya powder provides better chewing gum consistency to the medicated chewing gum.

Table 3: Preformulation Parameters

Parameter	Observation
Color	Slightly yellowish
Odor	Slight odor
Taste	Tasteless
Appearance	Crystalline powder
Melting Point	222^0C to 224^0C
λ max(nm)	232nm

The UV absorption studies of meclizine hydrocloride were carried out in simulated salivary fluid of 6.6 pH. 10µg/ml concentration solution of meclizine hydrocloride was scanned in the UV range from 200-400nm range. It showed absorption maxima of 232nm.

In order to determine possible interaction between the drug, gum base and other ingredients used in the formulation, compatibility studies were conducted using FTIR spectroscopy. There was no significant shift in the positions of the wave numbers when compared to that of the pure drug values. Thus there was no interaction between the drug and other excipients of the formulation.

Different formulations were prepared as per the procedure. Before punching of the powder mass into tablets different pre-compression characteristics of the powders was studied namely, Bulk density, tapped bulk density, Car's compressibility Index, Angle of repose and Loss on drying. The results of the mentioned tests are given in the Table 4. The angle of repose for all the formulations was in the range of 26.56 to 31.22, Car's compressibility index of all the formulations was in the range of 8.56 to 12.65 and Hausner's ratio was in the range of 1.095 to 1.144.

After compression, different post compression parameters like Hardness, Friability, Weight variation and thickness of the formulations were determined. The results

are mentioned in Table 5. The hardness was maintained between 5.0 to 6.5 kg/cm^2, resulting friability in the range of 0.36 to 0.59%. The weight variation was in the range of 997.85±2.63 to 1000.4±1.93. The thickness of all the formulation was in the range of 4.91 to 5.35mm.

Table 4 Pre-compression data of medicated chewing gum of Powder blends

Formulation	Bulk density (Mean±SD) g/cm^3	Tapped density (Mean ±SD) g/cm^3	Compressibility index (%) (Mean±SD)	Hausner's Ratio (Mean ±SD)	Angle of repose (θ) (Mean ±SD)	Loss on drying (%)
MCG1	0.68±0.08	0.77±0.08	11.20±0.68	1.126±0.008	26.56±0.56	2.30
MCG2	0.63±0.008	0.71±0.01	11.39±0.14	1.128±0.002	26.94±0.33	3.33
MCG3	0.63±0.008	0.72±0.01	12.65±0.16	1.144±0.002	28.39±0.65	2.43
MCG4	0.63±0.009	0.70±0.02	10.20±0.15	1.113±0.001	28.39±0.65	2.86
MCG5	0.64±0.009	0.71±0.01	10.29±0.15	1.114±0.001	29.75±0.70	3.10
MCG6	0.63±0.02	0.70±0.02	10.13±0.34	1.112±0.004	29.06±0.67	2.00
MCG7	0.62±.0.00	0.68±0.03	8.75±0.11	1.095±0.001	30.47±0.73	3.20
MCG8	0.63±0.008	0.69±0.04	8.86±0.11	1.096±0.001	31.22±0.76	2.80

The prepared formulation was analyzed for the drug content and it was found to be in the range of 42.27 to 49.41mg of meclizine hydrocloride /chewing gum. The formulation with highest drug content was MCG5 with 49.41mg of meclizine hydrocloride /chewing gum and the formulation with lowest drug content was MCG1 with 42.27mg of meclizine hydrocloride/chewing gum. The results are shown in table 6.

Table 5 Post-compression data medicated chewing gum

Formulation	Thickness (mm) (Mean±SD)	Hardness (Kg/cm^3) (Mean±SD)	Friability (%) (Mean±SD)	Weight variation (mg) (Mean±SD)	Drug content (mg)
MCG1	4.91±0.02	5.4±0.16	0.44±0.01	1000±3.24	42.27
MCG2	5.00±0.03	5.2±0.35	0.59±0.02	999±2.28	43.57
MCG3	5.14±0.03	5.0±0.15	0.41±0.01	999.2±2.58	44.87
MCG4	5.01±0.03	5.6±0.24	0.51±0.01	998.7±3.03	48.11
MCG5	5.35±0.02	6.1±0.18	0.36±0.01	1000.4±1.93	49.41
MCG6	5.11±0.02	6.2±0.29	0.48±0.02	998.75±2.69	42.47
MCG7	5.00±0.03	6.0±0.20	0.40±0.01	997.85±2.63	46.82
MCG8	5.11±0.02	6.5±0.27	0.46±0.02	998.1±2.09	44.87

All formulation of medicated Chewing gum consistency is studied on volunteers and data are tabulated in table 7.

Table 6 Drug content of medicated chewing gum

Formulation	Drug content (%)	Drug content (mg)
Mcg1	84.55	42.27
Mcg2	87.14	43.57
Mcg3	89.74	44.87
Mcg4	96.23	48.11
Mcg5	98.83	49.41
Mcg6	94.94	42.47
Mcg7	93.00	46.82
Mcg8	89.74	44.87

The prepared formulations were analyzed for the in-*vitro* drug release. The apparatus used was 'Erweka's DRT 6 Chewing apparatus'. The study was conducted for a period of 30 minutes using simulated salivary fluid as the dissolution medium. The chewing frequency of 56 strokes/ minute was applied. The results of Cumulative drug release are given in Figure 3. Formulation MCG5 showed highest drug release of 97.88% at the end of 30 minutes and formulation MCG1 showed lowest drug release of 84.03% at the end of 30 minutes.

Effect of gum base and soya powder – The dissolution profile of the drug changes with respect to the amount of gum base and soya powder present in the formulation. The results showed that the release of drug from the formulation increases as the amount of gum base increases and amount of soya powder decreases but at one stage due to excess amount of gum and less amount of soya powder drug release is decreasing.

Table 7 Consistency study of medicated chewing gum

Formulation	Volunteers					
	1	**2**	**3**	**4**	**5**	**6**
MCG1	-	-	-	-	-	-
MCG2	-	-	-	+	-	-
MCG3	+ +	+ +	+ +	+ +	+ +	+ +
MCG4	+ +	+ + +	+ +	+ + +	+ +	+ +
MCG5	+ + +	+ + +	+ + +	+ ++	+ + +	+ + +
MCG6	+	+	+	+	-	-
MCG7	-	-	-	+	-	-
MCG8	-	+	-	-	+	-

(-) Not acceptable (+) Acceptable
(++) Good (+++) Very good

In order to determine the shelf life and storage condition of the formulations, Accelerated stability studies was conducted on mcg5 formulation using Remi Stability chambers. The formulation was evaluated for different parameters like physical appearance: No Change, Hardness: 6.10±0.18 to 6.40±0.28, Friability 0.36±0.01 to 0.36±0.06, Weight variation: 1000±1.00 to 1000.4±1.80, Thickness: 5.35±0.02 to 5.35±0.38, Drug content: 98.40 to 98.80 and Drug release profile: 97.04±0.31 to 97.38±0.52.

The results are compared in results the formulations MCG4 and MCG6 showed good drug release rate but these formulation did not show sufficient chewing gum like

consistency. But the formulation MCG5 is more promising in delivering the drug at required rate and at the same time they maintain the chewing gum like consistency. Remaining formulation MCG1, 2, 3, 7 and 8 have low drug release and not proper chewing gum like consistency. Mcg 7 and mcg 8 have sticking problem due to excess amount of gum.

It is seen that as the concentration of the gum base and soya powder maintained in proper amount than drug release is highest. Thus it can be said that with varying the concentration of gum base and soya powder in the formulation, the drug release can be controlled. Thus we have successfully formulated medicated chewing gums containing meclizine hydrocloride.

As the concentration of gum increases in excess amount the drug release from the formulation decreases i.e. we can sustain the release of drug. But as we increase the gum concentration it creates problem at the time of compression. Here the gum will stick to the punches and dies. So the formulations MCG 7 and MCG 8 cannot be prepared in large batch size.

The study showed that modifying parameter like gum base and soya powder concentration, the drug release from the chewing gum can be adjusted to the desired rate and at the same time mask the slight bitter taste of drugs.

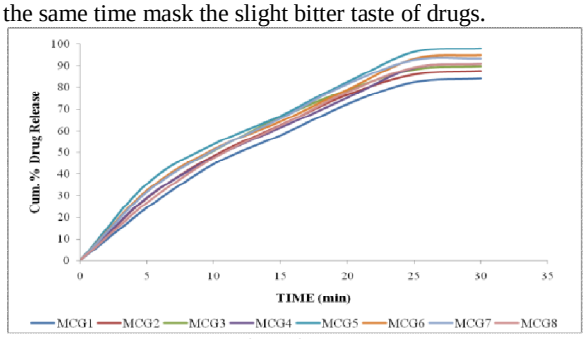

Figure 3 Dissolution profile of mcg1 to mcg8

CONCLUSION

Medicated chewing gums containing meclizine hydrochloride were successfully formulated using Cafosa Pharmagum S as the gum base and soya powder to obtain cost effective formulation and for better patient compliance. Meclizine hydrocloride shows a buccal absorption of about 9% to 10% which makes it a drug choice in preparing medicated chewing gum of antiemetic & antihistaminic drug.

Formulation MCG5 showed highest drug release of 97.88% at the end of 30 minutes. The drug release profiles were found to be satisfactory and hence the therapeutic dose of Meclizine hydrocloride (50 mg) can be effectively administered through chewing gums. Among all 8 formulations MCG5 showed better pre-compression characters, post-compression characters, drug content, in vitro drug release and good stability. So MCG5 was selected as a optimized batch.

From this study it can be concluded that it is possible to design medicated chewing gum containing meclizine hydrochloride, mainly for the treatment of nausea and vomiting related conditions, where efficacy and patient compliance are of prime importance.

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