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Formulation and texture characterization of medicated chewing gum delivery of Dimenhydrinate Hydrochloride

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ABSTRACT

Nausea can occur immediately or with a very short warning. Thus, the patient requires not only fast onset of action, but also a product that can be taken anywhere without too much difficulty. A Medicated Chewing gum formulation addresses these concerns perfectly.Water soluble drugs are released rapidly from gum base,various methodologies are available to slow the release and to provide extended release profile.Use of medicated chewing gum for smoking cessation and oral candidiasis have been studied and reported.Satisfactory texture profile analysis are obtained which indicate uniformity, flexibility for medicated chewing gum.Patients values those benefits that are easily understood. Patients will favor products that are convenient and will help them carry on with their daily lives without betraying outward signs of illness or disease. Consequently, a Medicated Chewing gum formulation is ideal.

Key words: Oral candidiasis; Smoking cessation; Texture profile analysis, Extended release profile;Water soluble drug.

INTRODUCTION

Medicated chewing gum is solid, single-dose preparations that have to be chewed & not swallowed; chewing gums contain one or more active ingredient that is released by chewing. A 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 into saliva & could be absorbed through the oral mucosa or swallowed reaching stomach for gastro-intestinal absorption.

Empiric findings had shown that people chewing gum was better at keeping awake and alert, and that gum chewing eased tension. The acceptance of this somewhat anecdotally understood effect achieved a better scientific basis in the summer 2002 when L Wilkinson and co-workers (1) published a study of 75 healthy volunteers who were led through a number of cognitive, recognition, and memory tests. The results provided the first evidence that the chewing of gum can improve episodic memory and working memory.

The anecdotal effect of chewing gum on weight loss has also been studied recently. In December 1999, The New England Journal of Medicine (2) revealed that while chewing gum, energy expenditure increases from 58 kcal per hour to 70 kcal per hour – an increase of 19%. The conclusion was that if a person chewed gum during walking hours, this alone would mean a yearly weight loss of more than 5 kg. Though there are many other interesting anecdotal effects that result from gum chewing, such as the easing of blocked ears.

The advantages of utilizing a chewing gum drug delivery system are highlighted by T Imfeld (3) in his 1999 review of gum chewing and oral health.

There are two absorption pathways which are possible to introduce the active ingredient into the systemic circulation giving rise to a systemic effect. Drug absorbed directly via the buccal membrane avoids metabolism in the G.I tract & the first-pass effect of the liver; it might therefore be to administer a reduce dose in chewing gum compared to other oral delivery system.

Local effect

To obtain the optimal local effect to treat a health condition requires that the relevant active substance be available at a therapeutic level near or within the tissue being treated, regardless of the delivery system. For the treatment of oral cavity conditions, it is beneficial to achieve a therapeutic level of active substance in the saliva, and different formulations (e.g. oral gel, mouth rinse) have been created to meet this goal. Chewing gum is an ideal drug delivery system for this treatment area; the active substances are released as the gum is chewed, thus providing the potential for a high level of active substance to obtain local effect in the oral cavity. It is possible to design a chewing gum that releases active substances over a prolonged period. The “Oral health and caries prevention” and “Oral fungal infection” provide a more comprehensive review of the advantages of chewing gum drug delivery systems for the local treatment of oral health conditions.

Systemic effect

Systemic effects of active substances released from chewing gum can be achieved in two ways (4): in the “traditional” way, by swallowing the active substance, or buccally via absorption through the oral mucosa. The latter is of special interest. As buccal absorption avoids first-pass hepatic metabolism of the active substance, it could provide better bioavailability. Buccal absorption may also lead to fast onset of the active substance as the vascular supply of the buccal mucosa is rich and lead directly into the systemic circulation. Chewing gum promotes buccal absorption by releasing active substances at carefully controlled rates, thus allowing for extended exposure in the oral cavity.

The objective of the present work is to develop and characterize medicated chewing gum delivery of Dimenhydrinate hydrochloride for motion sickness,it is also planned to identify the important formulation parameters affecting the behaviour of medicated chewing gum.The drug which is used in this work is an antihistamine H1 receptor antagonist.

Antihistamines are suitable candidate for motion sickness; their antiemetic effect appears to be based on anticholinergic, antihistaminic & sedative properties.Chemoreceptortrigger zone (CTZ) located in area postrena & the nucleus tractus solitarius (NTS) has variety of receptor H_1, D_2 serotonim 5-HT_3, cholinergic M & Opoid µ through which emetic signal are relayed which are possible target for antiemetic drug.Antiemetic drug metoclopramide, domperidone, cisapride (prokinetic drug), neuroleptic drug, chlorpromazine, prochlorperaazine, haloperidol, 5-HT_3 antagonists ondansetron are less suitable for treatment of motion sickness, they are more suitable for emesis induced by cytotoxic drug or emesis caused due to post operative vomiting.

Dimenhydrinate Hydrochloride based on its higher salivary solubility & fewer side effects (no extra pyramidal effect) is the suitable candidate for formulation of MCG for prevention of motion sickness.

MATERIALS AND METHODS

Dimenhydrinate Hydrochloride was purchased from Medopharm ltd, Malur Karnataka.Gum base purchased from Candico Pvt Ltd, Nagpur. Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Sodium chloride, Phosphoric acid, Polyvinyl acetate, Ether, Acetone, Ethanol, Sodium hydroxide, Sodium carbonate, Dichloromethane, Calcium carbonate, Polyisobutylene, Glycerol, Paraffin wax, Sorbitol and Glycerin purchased from Central drug house Ltd ,Delhi. Analytical grade methanol was purchased from Loba chem. Pvt Ltd, Mumbai. n-Octanol was purchased from S.D. Fine chem. Ltd, Mumbai.

Preparation of medicated chewing gum (5-8)
In a beaker wax (paraffin wax) was melted at 40 degree celsius to form into liquid state, then elastomer (polyisobutylene) was added with continues stirring, after 10 minutes of stirring plasticizer (glycerol), filler (calcium carbonate), lipid (Soya oil) & emulsifier (lecithin) was added to the molten mass at scheduled time interval and stirred on the mechanical stirrer with constant maintenance of temperature at 40 degree celsius. After 30 minutes of stirring, this mass was allowed to cool and poured in a round mould having dia 10mm & depth 0.7mm. Various optimized formulations of gum base are shown in table 6 below.

Coating of MCG was done by liquid coating solution of sorbitol & glycerin. This mixture was heated at 60 degree celsius for 15 min and allowed to mix uniformly. Gum piece was dipped in the solution, and after a specified time interval of 1 min, (to allow the liquid to spread evenly over the piece), a dry powder material (Sorbitol) was applied. This helps to dry the liquid coating; this is referred to as Dry Charging & is commonly used in soft panning operation. The drug (Dimenhydrinate Hydrochloride) was pre-blended with dry charge material & flavor. This was applied in about 3 to 12 dry charge application. After a dry charge 2 to 4 liquid application are made to cover dry charge material, than coating is dried in hot warm air in temperature range 27 ^{0}C to 38 ^{0}C.

Characterization of medicated chewing gum:

1. Physical evaluation of Medicated Chewing Gum: All Medicated Chewing Gum formulations were visually inspected; various physical properties of gum base were studied on basis of their solubility studies, relative humidity, color and moisture absorption. Following parameters were studied:

a) Weight variation: Weight variation of all formulation was done by method described in experimental work.
b) Physical evaluation of MCG (9): All formulation prepared by above procedure were physically evaluated for following parameters, Appearance, Color, Stickness,Hardness,Weight variation and texture analysis.
c) Hardness/Plasticity: Due to absence of any reported method, it was decided to use the Monsanto type hardness tester for determination of hardness of all MCG formulations. Texture analyser was used for determining strength and degree of deformation. Values obtained indicate flexibility of sample.
d) Weight variation: Weight of ten chewing gum was taken in one batch, then average weight is calculated ,from that standard deviation is calculated.
e) Stickiness: Texture analyzer from stable micro system model TA.XT-EXPRESS was used for determining stickness and degree of deformation. Values obtained indicate uniformity of sample.

2. **Chew out study:** Chew out study protocol was formulated based on input from Fertin Pharma pvt ltd. Denmark, one of the world largest manufactures of medicated chewing gum. Following scoring pattern was developed from specific input from Fertin Pharma Pvt. Ltd. Denmark. Initial phase of chew out study included various parameters like texture, elasticity, smoothness, crankiness, softness, cheesiness, sweetness, cooling effect, hardness, juiciness & lubricating feel.

3. ***In vitro* drug release based on:** (10)
i) Change in twisting angle of upper mastication jaw from ($5^0 – 30^0$).
ii) Change in distance b/w upper & lower masticating Jaw from (1-2mm).
iii) Change in chewing frequency of lower masticating Jaw from (20 strokes / minute to 120 strokes / minute).
iv) Change in temperature from (30^0C – 40^0C).

The chewing gum was inserted between the pistons on to the lower chewing surface. The chewing procedure consisted of up and down stroke of lower masticating surface combined with twisting movement of upper masticating surface, thereby masticating the chewing gum and consequently agitating the test medium. The optimized chewing frequency employed in the study was 60±2 strokes per minute. At predominant time interval aliquot of the artificial saliva, were removed and assayed for drug content by UV spectrophotometric analysis. The release medium was replaced with fresh artificial saliva after each sample was taken.

4. **Stability study of synthetic gum base:** 5 gm of synthetic gum base was stored in container at 40°C ± 2°C at 75% RH ± 5% RH(According to ICH Q1A(R_2) (4) guidelines for stability for a period of six months. After six months the gum was examined for signs of ageing and physical deformalities.

5.**Texture Analysis of formed medicated chewing gum :** Measurement of the hardness and resistance of chewing gum sticks to bend/flex

TA Settings
Sequence Title: Return to Start (Set Dist)
Test Mode: Compression
Pre-Test Speed: 1.0 mm/sec
Test Speed: 2.0 mm/sec
Post-Test Speed: 10.0 mm/sec
Distance: 15.0 mm
Trigger Type: Auto (Force)
Trigger Force: 5.0 g
Stop Plot At: Start Position

Accessory: HDP/3PB Three Point Bending Rig

Test Set-Up:
The two adjustable supports of the rig base plate were placed a suitable distance apart so as to support the sample i.e. 25mm. For comparison purposes this gap distance was be noted and kept constant. The base plate was then secured onto the Heavy Duty Platform. The Heavy Duty Platform was manoeuvred and locked in a position that enabled the upper blade to be equidistant from the two lower supports. The sample was removed from its packaging and placed centrally over the supports just prior to testing

RESULT AND DISCUSSION

Melting Point: The Melting point of the Dimenhydrinate hydrochloride was found to be in the range of 103°C to 107°C.Melting point was found to be 105°C.It means that the drug used is in pure form.

Identification Test: The λ max for Dimenhydrinate hydrochloride was found to be 280nm in phosphate buffer having pH 6.8.

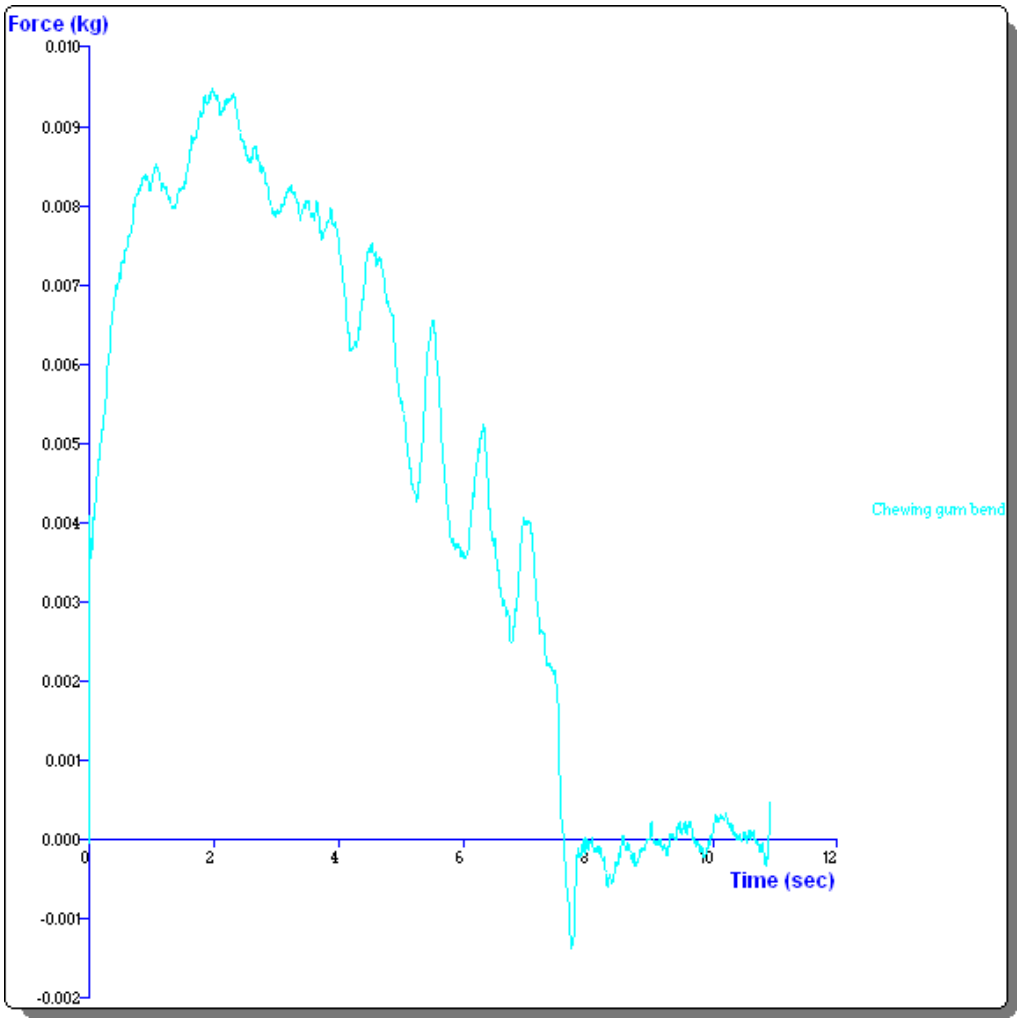

Fig 1: Measurement of the hardness and resistance of chewing gum sticks to bend/flex

Infrared Spectroscopy: The IR values of Dimenhydrinate hydrochloride shows the peak at following value which shows characteristic of drug.

IR spectra of Dimenhydrinate hydrochloride indicated characteristic peaks belonging to major functional groups which are similar to standard peaks, such as C-Cl streaching around 700-750 cm^{-1}.The peaks around 1675 cm^{-1} and 1650 cm^{-1} may be due to C=O and C=C peak.

Moisture absorption study of synthetic gum: Synthetic gum base made of polyisobutylene absorb very less percentage of moisture means gum base is stable during shelf life.

***In vitro* drug release: *In vitro* drug release based on:**

i) Change in twisting angle of upper mastication jaw from (5^0 – 30^0).
ii) Change in distance b/w upper & lower masticating Jaw from (1-2mm).

iii) Change in chewing frequency of lower masticating Jaw from (20 strokes / minute to 120 strokes / minute).
iv) Change in temperature from (30^0C – 40^0C).

The chewing gum was inserted between the pistons on to the lower chewing surface. The chewing procedure consisted of up and down stroke of lower masticating surface combined with twisting movement of upper masticating surface, thereby masticating the chewing gum and consequently agitating the test medium. The optimized chewing frequency employed in the study was 60±2 strokes per minute (Table-1 and fig-2). At predominant time interval aliquot of the artificial saliva, were removed and assayed for drug content by UV spectrophotometric analysis. The release medium was replaced with fresh artificial saliva after each sample was taken.

On setting 20^0 ,which is optimized setting for twisting angle (Table-4 and fig-5) as twisting angle movement for upper masticating Jaw after, 50 min. 90% drug release was noted, which emphasize that increasing twisting angle increase rate of release of drug significantly. It was noted that for optimized formulation that as we decrease the distance between the upper & lower masticating surface from 2 mm to 1mm, this lead to increase in rate of release since the force acting on the gum is larger with 1mm setting. When distance between Jaws increase from 1mm to 2mm for MCG % drug release decrease and time interval needed for drug release increases.

Chewing frequency of lower masticating Jaw is important factor in the mastication process. As we increase the frequency of chewing or movement of lower masticating Jaw to 120 strokes/min (Table-2 and fig-3) the drug release profile shows significant increase.

As we increase the number of frequency of the lower masticating jaw the release profile of drug show increase in lower time interval. High kneading speeds between the Jaws of the chewing apparatus led to increase in release rate of drug and decrease in the time interval for release is obtained.

As the temp increase from 30^0C-40^0C there was no significant effect on drug release profile for optimized batch of MCG.

MCG-1 formulation was found to be best optimized formulation. Gum base consist of polyisobutylene (10%) as elastomer having high molecular weight which assist in gum forming elastic property of MCG. Glycerol (30%) was used as plasticizer in formation of gum base. Elastomer & plasticizer are responsible for cohesiveness of the gum base. Paraffin wax (15%) used as texture enabling agent for the gum base. Soya oil (7%) was used as lipid enabling agent for gum base. Wax and soya oil are responsible for cooling effect and lubricating feel of the MCG. Lecithin (3%) was used as an emulsifier which was responsible for juicy feel of the gum. Peppermint (3%) was used as a flavouring agent which provided sufficient taste masking and flavour for the medicated chewing gum.

It was noted that for optimized formulation, decreasing the distance b/w the upper & lower masticating surface from 2 mm to 1.5mm(Table-3 and fig-4) lead to increase in the rate of release since the force acting on the gum is larger with 1mm setting. When distance between

Jaws increase from 1mm to 2 mm for MCG, % drug release decrease while time interval needed for drug release increases.

Texture profile analysis: Test results obtained from sample show the following typical mean maximum force value, the mean distance/deformation (Fig.1) at this point and their respective coefficients of variation:

Test ID	Mean Max. Force *'Strength'* g	Mean Distance at Flex mm
Chewing gum bend	9.492	3.748

Once the trigger force is attained the force is seen to increase and the product begins to bend. The maximum force is presented as the resistance of the sample to bend and is related to the 'strength' of the sample. The distance at which this maximum force occurs highlights the degree of deformation that needs to be applied to the sample before bending is fully initiated and hence indicates flexibility.

Table-1 *In vitro* drug release with setting of Chewing Frequency 60 Strokes/min

S. No.	Chewing Frequency (Strokes/min)	Time Interval (min.)	% Drug Release (Formulation Code)			
			MCG 1	MCG 6	MCG 7	MCG 8
1.	60	0	0	0	0	0
2.	60	5	24	20	19	25
3.	60	10	35	31	29	35
4.	60	15	45	42	41	46
5.	60	20	56	53	51	57
6.	60	25	68	64	62	70
7.	60	30	77	74	72	77
8.	60	35	88	81	80	87
9.	60	40	94	89	87	93
10.	60	45	99	95	94	99
11.	60	50	-	-	-	-

Table 2: *In vitro* drug release with setting of Chewing Frequency 120 Strokes/min

S. No.	Chewing Frequency (Strokes/min)	Time Interval (min.)	% Drug Release (Formulation Code)			
			MCG 1	MCG 6	MCG 7	MCG 8
1.	120	0	0	0	0	0
2.	120	5	59	56	53	60
3.	120	10	67	64	62	70
4.	120	15	78	74	72	80
5.	120	20	89	85	82	90
6.	120	25	98	94	91	98
7.	120	30	-	-	-	-
8.	120	35	-	-	-	-
9.	120	40	-	-	-	-
10.	120	45	-	-	-	-
11.	120	50	-	-	-	-

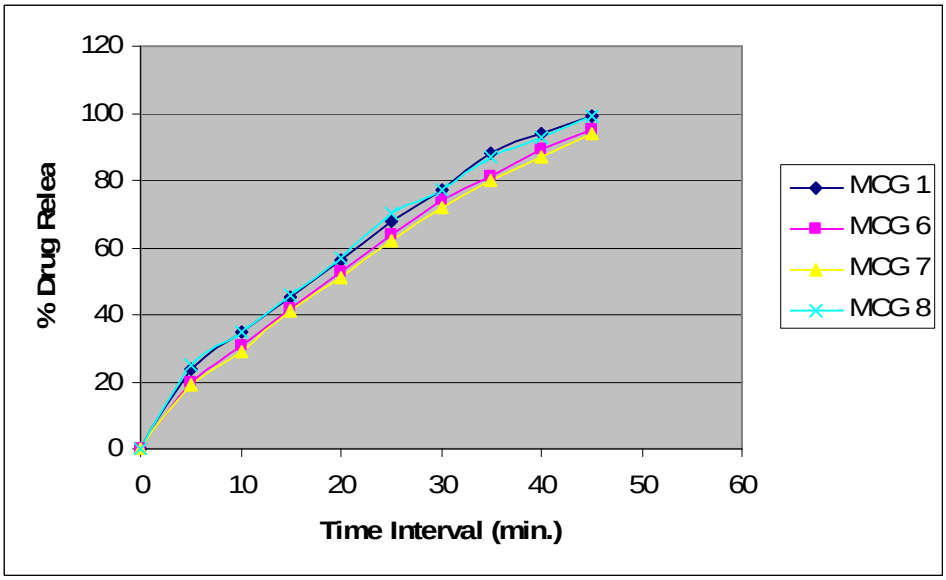

Fig 2: Percentage drug release with chewing frequency 60 Strokes/min

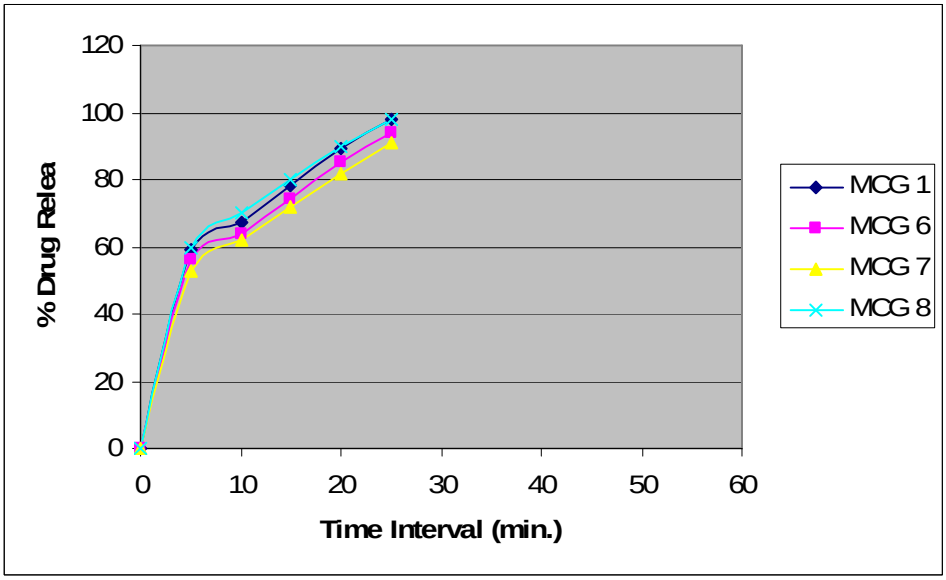

Fig 3: Percentage drug release with chewing frequency 120 Strokes/min

Table 3: *In vitro* drug release with setting of distance between the Jaws 1.5mm

S. No.	Distance between Jaws (mm)	Time Interval (min.)	% Drug Release (Formulation Code)			
			MCG 1	MCG 6	MCG 7	MCG 8
1.	1.5	0	0	0	0	0
2.	1.5	5	24	20	19	25
3.	1.5	10	35	31	29	35
4.	1.5	15	45	42	41	46
5.	1.5	20	56	53	51	57
6.	1.5	25	68	64	62	70
7.	1.5	30	77	74	72	77
8.	1.5	35	88	81	80	87
9.	1.5	40	94	89	87	93
10.	1.5	45	99	95	94	99
11.	1.5	50	-	-	-	-

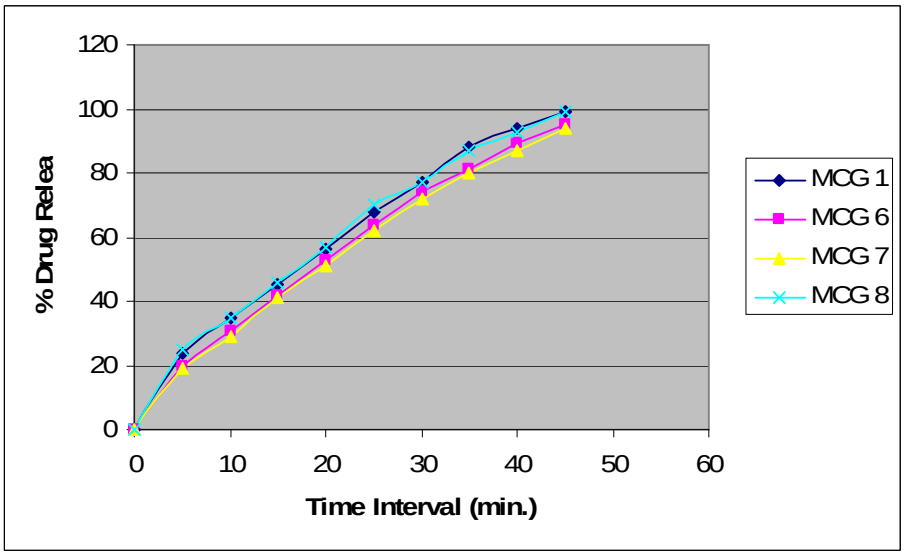

Fig 4: Percentage drug release with distance between the Jaws 1.5mm

Table 4: *In vitro* drug release with setting of twisting angle at 20^0

S. No.	Twisting Angle (degrees)	Time Interval (min.)	% Drug Release (Formulation Code)			
			MCG 1	MCG 6	MCG 7	MCG 8
1.	20	0	0	0	0	0
2.	20	5	10	8	9	11
3.	20	10	18	15	16	15
4.	20	15	29	26	23	25
5.	20	20	40	37	33	38
6.	20	25	52	48	40	49
7.	20	30	60	54	45	57
8.	20	35	70	60	51	65
9.	20	40	74	69	60	69
10.	20	45	84	77	71	79
11.	20	50	93	86	84	89

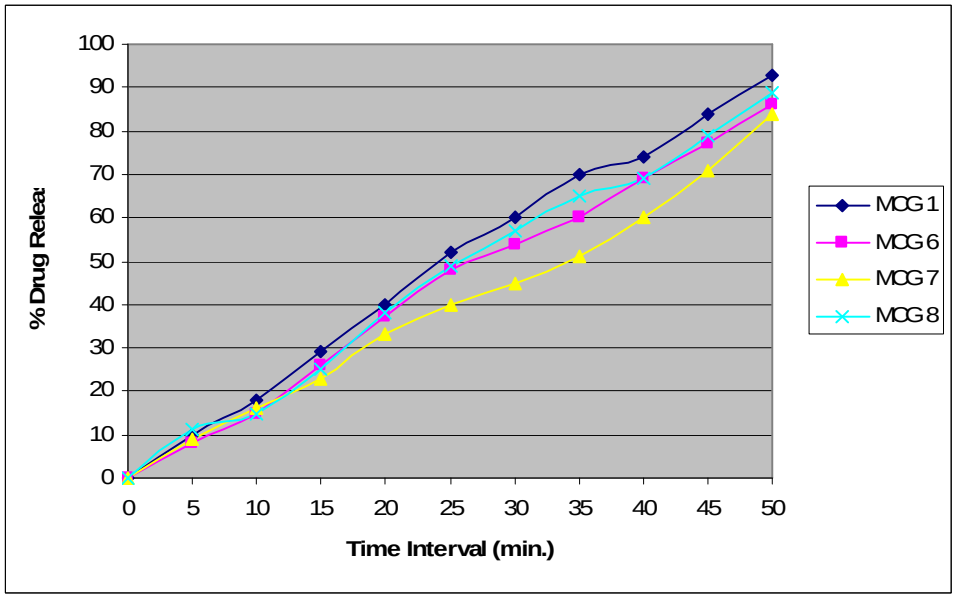

Fig 5: Percentage drug release with twisting angle 20^0

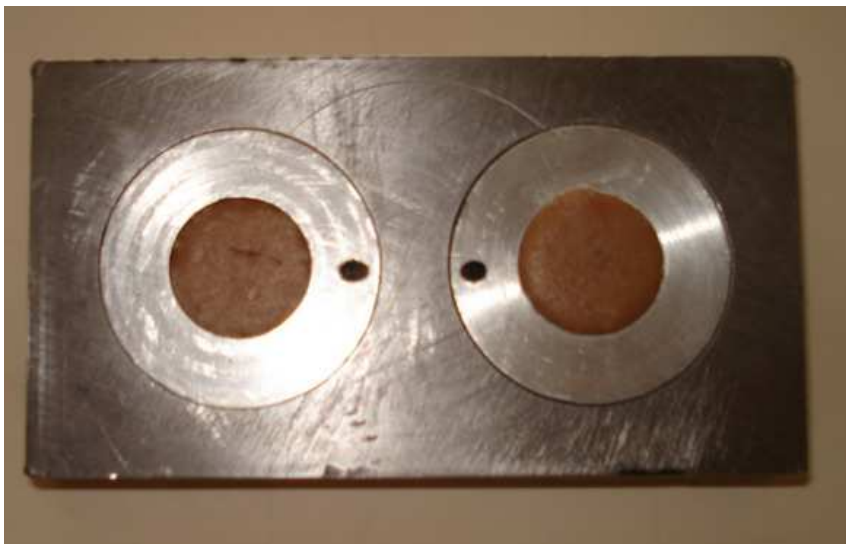

Fig 6: MCG poured in mould

Table 6; Different formulation and ratio of ingredient %w/w

S.no	Ingredients	MCG-1	MCG-6	MCG-7	MCG-8
1	Polyisobutylene	10	10	10	10
2	Glycerol	30	30	30	25
3	Calcium carbonate	35	35	35	30
4	Paraffin wax	15	7	15	15
5	Lipid	7	15	4	7
6	Emulsifier	3	3	6	3

Table 7: Showing coating formulation composition

S.no	Ingredients	Weight (%)
1.	Gum base	25
2.	70% Sorbitol	15
3.	Glycerin	6
4.	Sorbitol	51
5.	Peppermint	3

Table 8; Physiochemical properties of synthetic gum base after stability studies

S.NO	Properties	Observations
1.	Color(before ageing)	Off yellow to dark brown
2.	Color(after ageing)	Off yellow to dark brown
3.	Softening range(before ageing)	60 to 70^0C
4.	Softening range(after ageing)	57 to 68^0C
5.	Texture(before ageing)	Chewee
6.	Texture(after ageing)	Chewee

CONCLUSION

Medicated chewing gum (MCG) are solid, single dose preparations with a base consisting mainly of gums that are intended to be chewed but not swallowed. Medicated chewing gum (MCG) is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. MCG is considered as vehicle or a drug delivery system to administer active principles that can improve health and nutrition.

Though chewing gum as a drug delivery system has gained wide acceptance only within smoking cessation and oral health care, clinical trials have proven that there are therapeutic advantages to be gained by using chewing gum as a drug delivery system through exploiting the effects achieved by chewing gum per se, the convenience of the delivery system, and the possibilities of having buccal absorption or local effect of an active substance. Furthermore, one of the trials has indicated that chewing gum as drug delivery systems are possibly safer for active substances that are susceptible to abuse. Chewing gum formulations may also be less prone to accidental overdose.

The development costs of new active pharmaceutical ingredients have increased dramatically and thus the pharmaceutical companies are now more and more focusing on new initiatives to achieve maximum commercial advantage from their current products and brands.

A Medicated Chewing gum formulation is easy to take as no water or swallowing is required. This makes it especially beneficial for patients with nausea or persons who experience swallowing problems. Additionally, chewing gum enhances motility of the GI-tract which could be helpful in overcoming nausea. Compared to injections and suppositories, medicated chewing gum are highly preferred by the patients. Furthermore, as chewing is required to have the active substance released, the risk of overdose will be diminished.

Fast onset of action is one of the most desirable effects to be obtained from the treatment when suffering from nausea. A Medicated Chewing gum formulation can facilitate fast onset of action. If the active substance is absorbed buccally, onset of action will occur fast – without being delayed by passing through the gastrointestinal tract and liver. Fast onset of action can also be expected if the active substance is not absorbed buccally, as the active substance will be dissolved before reaching the gastrointestinal tract and, therefore, be readily absorbed. Furthermore, in case of buccal absorption, it is likely that the dose could be decreased due to the avoidance of first pass metabolism, and thus, fewer side effects will be seen. As the fear of side effects is predominant among patients, a Medicated Chewing gum formulation with lesser amount of active ingredient is likely to be favored by the patients.

Children do not like to take tablets or suppositories nor do they like to have injections. Any improvement in the formulation which could diminish the discomfort and battle in connection with taking the medication would be appreciated by children and their parents and thereby leading to increased acceptance and compliance.

Antihistamines are suitable candidate for motion sickness; their antiemetic effect appears to be based on anticholinergic, antihistaminic & sedative properties.Chemoreceptortrigger zone (CTZ) located in area postrena & the nucleus tractus solitarius (NTS) has variety of receptor H_1, D_2 serotonim 5-HT_3, cholinergic M & Opioid μ through which emetic signal are relayed which are possible target for antiemetic drug.

Antiemetic drug metoclopramide, domperidone, cisapride (prokinetic drug), neuroleptic drug, chlorpromazine, prochlorperazine, haloperidol, 5-HT_3 antagonists ondansetron are less suitable for treatment of motion sickness, they are more suitable for emesis induced by cytotoxic drug or emesis caused due to post operative vomiting. Dimenhydrinate Hydrochloride based on its higher salivary solubility and fewer side effects (no extra pyramidal effect) is the suitable candidate for formulation of MCG for prevention of motion sickness.

Chewing gum is no longer seen simply as confectionary. Wrigley have recently created a healthcare division to use chewing gum as a delivery system for active ingredients that provide health benefits dental health chewing gum is here to stay, as is medicated gum for smoking cessation A bright future for a preparation with a long history.

Nausea can occur acutely or with a very short warning. Thus, the patient requires not only fast onset of action, but also a product that can be taken anywhere without too much difficulty. A medicated chewing gum formulation addresses these concerns perfectly.

Patients value benefits that are easily understood. Patients will favour products that are convenient and will help them carry on with their daily lives without betraying outward signs of illness or disease. Consequently, a medicated chewing gum formulation is ideal.

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