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FORMULATION AND EVALUATION OF MEDICATED CHEWING GUM OF DOLASETRON AS AN ANTIEMETIC AGENT

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ABSTRACT

An attempt has been made to formulate new chewing gum for Dolasetron. The new drug delivery system was obtained, at room temperature conventional pharmaceutical equipment. The resulting chewing gum comprises a gum core combined with fillers, antioxidants, coloring agent and plasticizers, which provide smooth appearance and flexibility during storage and chewing. Drug release from a dosage form is the critical step in drug absorption and bioavailability, thus an experimental work has been designed to evaluate the efficiency of this kind of therapeutic system by verifying its capability to release the drug dose and by assessing the delivery of Dolasetron for bypassing the hepatic first pass effect. Simple diffusion into the medium causes the release of only a small percentage of the drug contained in the medicated chewing gum, while the delivery of the major part of the dose occurs during mastication. In the present study, an attempt has been made to formulate the chewing gum of Dolasetron. Different formulations of chewing gum with varying concentration of plasticizers like glycerol and castor oil were formulated. MCG II formulation was considered to be the best-optimized formula which consists of synthetic gum base (45%), Sorbitol (14.6%), sucrose (46%) etc. which shows first slow release the fast release in the phosphate buffer saline (ph 6.8). The cumulative drug release of MCG II formulation was found to be 99.43 %. From this study, we can conclude that the medicated chewing formulation can be a better choice in the coming years which provides several benefits and also benefits commercially.

Keywords: Medicated Chewing Gum, Dolasetron, Hepatic First Pass Metabolism.

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INTRODUCTION

Drug can be administered via different routes of administration to produce a systemic pharmacologic effect. The most common method to administer drug is oral route, in which the drug is swallowed and it enters the systemic circulation. There are various dosage forms those can be administered orally. Out of which, chewing gum is most popular. It is a potentially useful means of administering drugs locally and systemically. Chewing gum has been used for centuries to clean the mouth as well as fresh the breath. The advantage of buccal route is administration has direct access to systemic circulation. This avoids first pass hepatic metabolism and local loss of the drug at site. In the present work non toxic synthetic gum base has been used in the formulation of medicated chewing gum (MCG) containing an Dolasetron as an Antiemetic Agent.[1, 2]

Dolasetron is suitable drug to prepare MCG. Dolasetron is a selective serotonin 5-HT_3 receptor antagonist. In vivo, the drug is rapidly converted into its major active metabolite, hydrodolasetron, which seems to be largely responsible for the drug's pharmacological activity. The antiemetic activity of the drug is brought about through the inhibition of 5-HT_3 receptors present both centrally (medullary chemoreceptor zone) and peripherally (GI tract).Glycerin, Castor oil and Dibutyl phthalate were used as plasticizer in varying amount. Sucrose coating was given to the chewing gum pieces. Trial runs were performed using plasticizers in combination. When plasticizers were used in combination, it was observed that the gum formulations formed were very sticky.[3, 4]

MATERIALS AND METHODS

Dolasetron was gift sample of Manus Aktteva Biopharma LLP, Ahmedabad, India and synthetic gum base from Amber Confectionaries Pvt. Ltd. Sucrose, sorbitol, magnesium stearate, talc, flavor and color were purchased from Lobachemi chemicals Pvt. Ltd, India. All other chemicals/solvents used were of analytical grade.

Preparation of Medicated Chewing Gum

All ingredients were weighed accurately as shown in formulation table 1. Molten mass of synthetic gum base was prepared and plasticizer was mixed thoroughly in porcelain dish. The dish was kept on water bath and temperature was maintained at about 35-45^{o} C. Drug Dolasetron was then added to above mass. Corresponding amount of Sucrose and mannitol was added to above mixture with continuous stirring up to 30 min. Finally the adequate amount of flavor was incorporated in the mixture. The mass was poured in to the mould and was allowed to cool at room temperature. The gum pieces were removed.[4, 5, 8]

Coating of MCG was done by liquid coating solution of sucrose. The coating solution was sprayed uniformly. Coating was dried in hot warm air in temperature range 27^{0}C to 38^{0}C. After cooling chewing gum pieces were wrapped properly.

Physical evaluation of drug and synthetic gum base

Preliminary studies

Physical evaluation of medicated chewing gum

The formulated chewing gum were evaluated for various physicochemical parameters including color, softening point, stickiness, weight variation, plasticity/hardness, percentage drug content and percentage cumulative in-vitro drug release.

RESULTS AND DISCUSSION

Physical evaluation of gum base

1. **Color:** Color of synthetic gum base is Pale yellow observe visually**.**
2. **Softening point:** Softening point of synthetic gum base was observed by heating the base in Petri dish. The temperature at which it starts melting is the softening point of that base. It was found to be 55-60^{0}C.
3. **Solubility studies of synthetic gum base**

As the gum has showed very negligible solubility in artificial saliva and phosphate buffer, it can be concluded that the procured synthetic gum base was the best for use as base for medicated chewing gum preparation.

Table 1: Solubility studies

Sr. no.	Solvent	Solubility(gm) / 10 ml
1	Alcohol	Up to 2 gm
2	Chloroform	Up to 17 gm
3	Acetone	Soluble
4	Water	Slightly soluble
5	Artificial saliva	Up to 1 gm

Physical evaluation of medicated chewing gum

The formulated medicated chewing gum was evaluated physically for following parameters and is mentioned.

1. **Color:** The color of MCG formulation was observed visually and all the batches were light brown in color which in acceptable limit.
2. **Melting point:** Melting point of drug was found to be 276-279°C which is in standard range of 276-278°C.
3. **Stickiness:** The formulated medicated chewing gum was placed on plain surface. A mass of 250 gm was hammered on it up to 10 min. the frequency of hammering was about 30/min. None of the batch stuck to hammer or surface.
4. **Weight variation:** Chewing gum from each batch was individually weighed on analytical balance, the average weight and standard deviation were calculated which was found in acceptable limit.[3]
5. **Plasticity/hardness:** Hardness of chewing gum was determined by Monsanto hardness tester and the average hardness and standard deviation were reported.[3]

Percentage drug content: Chewing gum was manually divided in to pieces and transferred into separating funnel containing 10 ml of dichloromethane. Separating funnel was shaken for 10 – 15 minutes so as to disperse the chewing mass. The turbid solution was shaken simultaneously with 50 ml distill water for 15 minutes for dissolving the drug in to it. Separating funnel was kept undisturbed for 15 minutes for separation of the two phases. The aqueous phase was collected and filtered through whatman filtered papers grade 41. Filtrate was sufficiently diluted and estimated for the drug content at 285 nm in UV spectrophotometer. Same procedure was repeated for three times.

Stability Studies of synthetic gum base

Stability studies of synthetic gum base: 10 gm of synthetic gum base was stored in bottle at 50^{o} C for 30 days. After 30 days the gum was examined for natural ageing and physical nature.

Table 2: Stability Studies of Synthetic Gum Base

S. No.	Properties	Observations
1	Color (before ageing)	Off white- pale yellow
2	Color (after ageing)	Pale yellow
3	Softening range (before ageing)	85- 90°C
4	Softening range (after ageing)	86- 88°C

UV Spectroscopy

λmax of Dolasetron was found to be 285 nm in artificial saliva solution having pH 6.4.

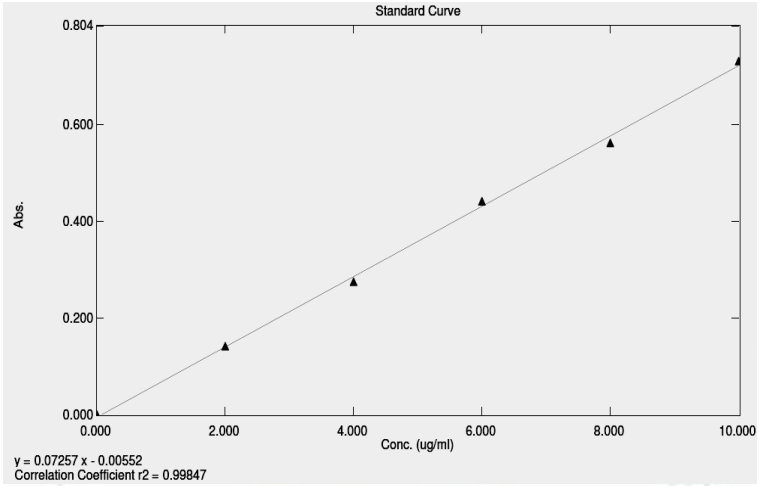

Figure 1: Calibration curve of Dolasetron.

In vitro dissolution studies

In order to study the in vitro dissolution pattern from chewing gums, it was necessary to design an apparatus, which could give same impact of mastication on MCG. This was necessary in order to mimic the human mastication. After an extensive literature survey and discussion with guide it was decided to modify the disintegration test apparatus and fabricate suitable chewing gum apparatus. Release measurements were performed using Lab fabricated medicated chewing gum test apparatus at 50 rpm. In each flask a 900 ml of artificial saliva pH 6.4 was filled. The temperature was maintained at 37±0.5°C. At predetermined time intervals (5, 10, 15, 20, 25, 30 and 35 min) absorbance were recorded spectrophotometrically at 285 nm and the percentage of drug released was determined as a function of time.

Figure 2: Lab fabricated Medicated Chewing Gum apparatus with Die and punch.

Table 3: Formulation Table.

S. No	Ingredients	Percentage (%w/w)			
		MCG I	MCG II	MCG III	MCG IV
1	Synthetic gum base	25	35	45	55
2	Drug	1%	1%	1%	1%
3	Sorbitol	14.6	14.6	14.6	14.6
4	Sucrose	56	46	36	26
5	Flavor	0.6	0.6	0.6	0.6
6	Magnesium stearate	0.2	0.2	0.2	0.2
7	Talc	2.364	2.364	2.364	2.364
8	Color	Q.S	Q.S	Q.S	Q.S

Table 04: Cumulative % Drug Release.

S. No.	Time(min)	% CUMULATIVE DRUG RELEASE± SD			
		MCG I	MCG II	MCG III	MCG IV
1	0	0	0	0	0
2	2	30.2±0.90	23.4±0.29	28.8±0.16	32.4±0.40
3	4	50.41±0.53	36.78±0.32	42.12±0.35	42.54±0.24
4	6	57.51±0.20	45.36±0.35	50.62±0.20	48.12±0.32
5	8	66.07±0.17	53.67±0.32	57.43±0.33	59.03±0.17
6	10	69.56±0.28	62.34±0.57	65.36±0.47	66.23±0.03
7	12	73.74±0.27	74.62±0.42	69.32±0.17	70.50±0.26
8	15	78.98±0.53	86.34±0.35	72.33±0.33	74.06±0.41
9	20	83.28±0.20	90.08±0.15	79.66±0.27	82.43±0.06
10	25	89.12±0.16	96.34±0.24	88.64±0.34	85.21±0.36
11	30	94.56±0.31	99.43±0.32	96.45±0.36	92.45±0.12

CONCLUSION

Medicated chewing gum (MCG) is 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.

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.

Antiemetic drug Metoclopramide, Domperidone, Cisapride (prokinetic drug), Neuroleptic drug, Chlorpromazine, Prochlorperazine, Haloperidol, 5-HT3 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. Diphenhydramine 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.

MCG II formulation was considered to be best optimized formula which consists of synthetic gum base (45%), sorbitol (14.6%), sucrose (46%) etc. which shows first slow release the fast release in the phosphate buffer saline (pH 6.8). The cumulative drug release of MCG II formulation was found to be 99.43 %. From this study we can conclude that the medicated chewing formulation can be better choice in the coming years which provides several benefits and also benefits commercially.

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