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FORMULATION DEVELOPMENT AND EVALUATION OF MEDICATED CHEWING GUM OF DOMPERIDONE MALEATE

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ABSTRACT

The present study was aimed to develop the chewing gum as drug delivery system for Domperidone maleate with fast onset of action and to avoid first pass metabolism. Chewing gum formulations were prepared in the tablet form as well as pieces form by using lactose, glycerin and PEG 400 in different concentration. For both type of formulations all studies were performed like hardness, stickiness, weight variation, friability and in vitro release test. The results were within the range according to pharmacopoeial specification. The test for chewing gum pieces stickiness; hardness and *in-vitro* release were performed. It was concluded that hardness was less than tablet form and they were slightly sticky in nature. From the in vitro drug release data it was observed that drug release from the chewing gum in tablet form was less as compared to pieces of chewing gum containing glycerin and PEG 400. From the drug release study in saliva it is concluded that drug release was fast and in higher percentage as compared to in-vitro study because release is totally depends on the chewing process.

KEYWORD: Medicated chewing gums, Domperidone maleate, Gum base, *In-vitro* dissolution.

INTRODUCTION

Pharmacological active agents or drugs are formulated into variety of dosage forms like tablets, capsules, injectable, inhalers, ointments etc. considering physicochemical properties, pharmacokinetic &pharmacodynamics parameters and biopharmaceutical aspects of drugs. In addition to its confectionary role, Chewing gum also has proven value as a delivery vehicle

for pharmaceutical and nutraceutical ingredient. Today chewing gum is convenient drug delivery system which is appropriate for a wide range of active substances. Many therapeutic agents are absorbed in the oral cavity. For the drugs having significant buccal absorption, dosage forms such as lozenges, chewable tablets and chewing gum permits more rapid therapeutic action compared to per-oral dosage forms. Chewable tablets and chewing gum have been very well received by the parents for use in children with full dentition. Children in particular may consider chewing gum as a more preferred method of drug administration compared with oral liquids and tablets. The use of medicated chewing gum is feasible in local treatment of diseases of oral cavity as well as treatment of systemic conditions.[1]Medicated chewing gums are solid, single dose preparations with a base consisting mainly of gum that is intended to be chewed but not swallowed. They contain one or more active substances which are released by chewing and are intended to be used for local treatment of mouth diseases or systemic delivery after absorption through the buccal mucosa.[2, 3]

Domperidone maleate is selective peripheral dopamine antagonist with antiemetic properties. The human D_2 receptors located on chromosomes II and belongs to the class of G- protein coupled receptors. It acts principally at receptors in the chemoreceptor trigger zone and stomach. It does not readily enter the central nervous system. The chemoreceptor trigger zone is considered to lie outside the blood brain barrier.[4]

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.

METHOD AND MATERIALS

Materials

Domperidone maleate was received as gift sample from Flemingo Pharma. Ltd, Mumbai. Synthetic gum base was received as gift sample from Candigo, Nagpur. All other ingredients and solvents used were of analytical grade.

CHARACTERIZATION OF GUM BASE

Determination of color

The color of gum was observed visually and reported.[5]

Determination of softening point of gum base

The sufficient quantity of gum base was taken in porceline dish and heat at the lowest temperature on heating mantle. Softening point was determined by thermometer. At which temperature gum was started to soft be measured.[6]

Determination of acid value of gum base

Accurately weigh, 10 mg gum base dissolved in 50 ml of mix of equal volumes of ethanol (95 %) and ether previously neutralize with 0.1 M potassium hydroxide to phenolphthalein solution. Warm the flask containing sample to dissolve the gum base. Add 1 ml of phenolphthalein solution and titrate with 0.1 M KOH until the solution remains faintly pink after shaking for 30 minutes. Calculate the acid value from following formula:

$$\text{Acid value} = 5.61\ n / w$$

Where n = the no. of ml 0.1M KOH

w = the weight in gram of the substance.

Determination of solubility of gum base

For determination of solubility of gum base 1 gram of gum base dissolved in 10 ml of different solvents like diethyl ether, ethanol, chloroform, acetone, pH 6.4 buffer solution and water. Each solvent containing gum base kept in sonicator for 24 hours. After 24 hours solvent was filtered and determine the solubility.[7]

Formulation of Chewing Gum Tablet By Compression.

Each ingredient was weight accurately. Synthetic gum base was molten slowly with constant stirring in porcelain crucible at 50^0-55^0 then physical mixture of domperidone maleate and sucrose was added to it with constant stirring until even distribution of mixture. After lactose was added as diluents the mixture was allowed to cool at room temperature. After cooling the mixture it was triturated in the mortar and pastel. Then triturated mass was passed from sieve no. 22 # to obtained uniform granules and talc was added as glident and compressed the tablet on single rotatory punching machine by using round shape and 14 mm punch.[8,9]

Table No: 1 Formula for chewing gum tablet by compression method.

Ingredients (mg)	Formulation Batches				
	F1	F2	F3	F4	F5
Drug	10	10	10	10	10
Gum base	300	350	400	300	300
Sorbitol	----	----	----	50	100

Sucrose	600	650	700	600	600
Lactose	50	50	50	50	50
Talc	1%	1%	1%	1%	1%

Formulation of Chewing Gum by Molding Method

Each ingredient was weight accurately. Synthetic gum base was molten slowly with constant stirring in porcelain crucible at 50^0-55^0 c. Then previously weighed quantities of glycerin was added to it and mixed thoroughly. Then physical mixture of domperidone maleate, sorbitol and sucrose was added to it with constant stirring until even distribution of mixture. The mixture was allowed to cool at room temperature. After cooling, the mass was rolled and cut into pieces of uniform size and weight. These pieces were scraped with spatula and wrapped in butter paper.

Table No: 2 Formula for chewing gum by Molding method.

Ingredients (mg)	**Formulation Batches**			
	F6	**F7**	**F8**	**F9**
Drug	10	10	10	10
Gum base	300	300	300	300
Sorbitol	100	100	100	100
Sucrose	400	400	400	400
Glycerine	40	80	--	--
PEG 400	--	--	40	80

Pre-compression study of chewing gum Tablet granules.

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

Post-compression studiesof chewing gum Tablet.

Stickiness

The stickiness of each formulation was tested by method mentioned below:

The chewing gum was placed on a plain surface. A mass of 250 gm. hammered on it for a period of ten minutes. The frequency of the hammering was about 30/min. After 10 min. sticking of the gum to the surface was manually observed and reported.

The stickiness of all the formulation was studied in human volunteers also to chew the dummy chewing gum for 5 minutes and then reported about stickiness of each formulation.[10]

Friability

Tablets have a tendency to cap during handling and transportation which affects the quality, appearance, drug content, coating requirements and hence friability test is carried out. The apparatus used is Roche friabilator, which consists of a rotating disk 12 inch in of diameter; rotating at speed 100r.p.m. Tablets to be evaluated are added into disc and rotated for 100 revolutions.

Hardness

For each type of formulation the hardness values for 3 tablets were determined using Monsanto tester and average values were calculated.[11]

Weight variation test.

To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.[12]

Uniformity of content of Domperidone maleate.

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 to10 mg of DM was taken. The powder was dissolved in100 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.

***In-vitro* release test**

The basket assembly of the I. P. disintegration test apparatus was replaced with a tephlon piston. The weight of the tephlon piston was approximately equal to that of the basket assembly in the original apparatus. This heavy piston was necessary to give impaction and exert pressure simulating the human mastication. The drug from the gum slowly gets released with each impact of the piston. The piston also serve a stirring purpose due to its up and down movement. The drug, which was released with each impact of the piston in the phosphate buffer (pH 6.4) medium surrounding it. The piston showed a frequency of between 28-32 cycles per minute.

Figure No.1: Front view of modified drug release apparatus.

The vessel was filled with 800 ml. phosphate buffer (6.4) and the gum was placed in the inner perforated vessel. The metal tephlon piston was attached to the rod, the height of the rod and bob was previously adjusted so that the bob completely touches the bottom of the perforated vessel.

The apparatus was switched on and the tephlon piston was allowed to impact on the chewing gum. This process was continued for the period of 20 minutes and 5 ml sample of the buffer solution was withdrawn at a regular interval of 2 minutes and every time this was replaced with equal amount of phosphate buffer. Thus, the samples were collected at 0, 2, 4, 6….20 minutes intervals. The cumulative amount of drug released Vs time was plotted graphically. The test was repeated for 3 chewing gum tablets of each types and statistical mean of 3 reading is reported.[13,14]

RESULT AND DISCUSSION

Characteristic of gum base.

The color of gum was observed yellowish, acid value was found to be 1.683 n/w and softening point for gum was found 50^0C-55^0C.solubility of gum was carried out and gum was soluble in chloroform, methanol whereas it is insoluble in water and Buffer pH 6.4.

Characterization of granules

The loose bulk density and tap bulk density were in the range of 0.62 - 0.68 and 0.70 - 0.78 respectively. The Carr's compressibility indexes were in the range of 11.42 - 13.33 % and angle of repose were in the range of 20.63 - 25.15. It indicates excellent and good to acceptable flowability of granules.

Table No.3: Results of granules characteristics.

Formulation Code	Average Bulk Density (g/ml)	Average Tap Bulk Density (g/ml)	Carr's Compressibility Index (%)	Angle of Repose (θ)
F1	0.65±0.03	0.75±0.04	13.33	21.23
F2	0.64±0.01	0.73±0.01	12.32	24.45
F3	0.62±0.04	0.70±0.05	11.42	22.45
F4	0.68±0.01	0.78±0.09	12.82	20.63
F5	0.65±0.05	0.74±0.01	12.16	25.15

* n= 3

Evaluation of chewing gum tablet

All formulations were off white in color and non-sticky in nature. Formulations were contain weight uniformity within the range as per Indian pharmacopoeia. The thickness, friability and hardness were in the range of 5.12 - 6.28 mm, 0.010 - 0.022 % and 3.8 - 4.3 kg/cm^2.The drug content of each formulation was found to be uniform in the range of 91.60 - 94.20 % which passes the pharmacopoeia limit from 85 - 115 %.respectively.

Table No: 4 Physical characterization of Chewing gum Tablet.

Formulation	Color	Weight uniformity (mg)	Thickness (mm)	Stickiness	Friability (%)	Hardness (Kg/cm^2)
F1	Off white	969.35 ± 1.22	5.12±0.45	Non sticky	0.022	4.0 ± 1.58
F2	Off white	1070.50 ±2.00	5.75±1.24	Non sticky	0.021	4.3 ± 1.15
F3	Off white	1171.05 ± 1.40	6.28±0.67	Non sticky	0.010	4.1 ± 1.12
F4	Off white	1020.15 ± 1.80	5.45±1.69	Non sticky	0.014	3.9 ± 0.86
F5	Off white	1070.30 ± 1.65	5.72±1.44	Non sticky	0.010	3.8 ± 0.66

Evaluation of chewing gum

Formulations F6-F9 were off white in color and slightly sticky in nature. The hardness was in the range of 2.0 - 2.3 kg/cm^2 respectively.

In-vitro drug release study

In-vitro release study was carried out and revealed that cumulative % drug release in chewing gum formulations were decreases with increases concentration of gum base. From above formulations F1 contain less amount of gum base so cumulative % drug release increases. So, release rate of drug from formulations wasF1 > F2 > F3.cumulative % drug release was increased with increase concentration of sorbitol. So drug release from formulation F5 was significant than F4. The sorbitol was used as sweetening and softening agent. When it was added in chewing gum formulations, it acts like softener for gum base. So concentration of sorbitol increased release from formulation was significant. Release from the F3 and F5 was better from F1 - F3 and F4 - F5 respectively like from *in-vitro* release. So, increase in concentration of gum base decrease the drug release and increase in sorbitol increase the drug release. The formulation F6 and F7 contain glycerin and formulation F8 and F9 contain PEG 400. Shows that cumulative % drug release was significant if the concentration of glycerin and PEG 400 was increased.

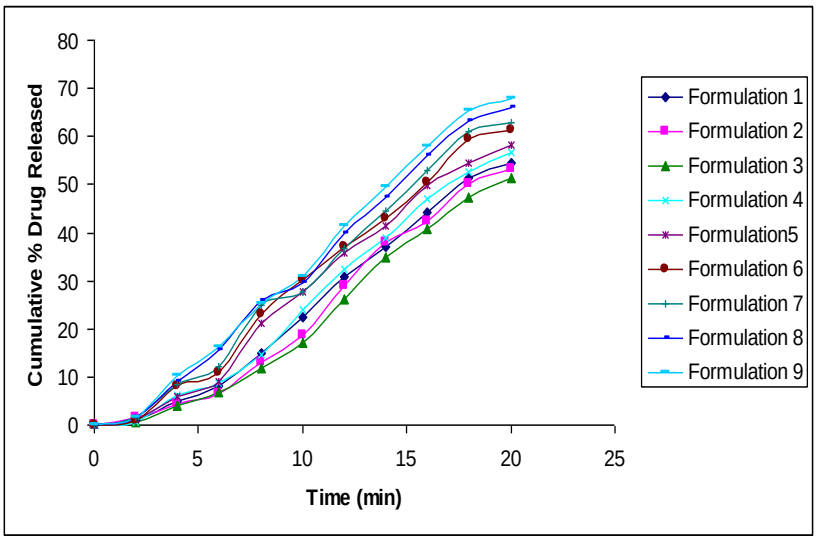

Figure No: 2 Drug Dissolution profile of Chewing gum.

CONCLUSION

The synthetic gum base is insoluble on salivary pH (pH 6.4). This property is essential for the chewing gum base because it eliminates the possibility of dissolution of gum base in saliva. From the results obtained in this work, it can be concluded that synthetic gum base used for formulation of chewing gum is excellent agent. From the in vitro drug release data it was concluded that drug release from the chewing gum in tablet form was less as compared to pieces of chewing gum containing glycerin and PEG 400. In the formulation sorbitol was

used as a softener and it act on the drug release in some extent. If concentration of sorbitol increased than drug release was increased. In chewing gum pieces PEG 400 give better release than glycerin and if concentration of PEG 400 was increased, the drug release was increased.

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