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Development of Medicated Chewing Gum Using Natural Gum Base

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ABSTRACT

The present study aimed to develop chewing gum formulation for Levocetirizine Dihydrochloride (Levocet) using natural gum base. The gum bases used were either combination of beeswax and polyvinyl pyrolidine or a combination of prolamin (gliadin) and polyvinyl alcohol. First, preliminary study of the suggested gum bases and softeners was done to determine the softener level needed to produce chewing gum with accepted physical and organoleptic properties. Then, these chewing gums were used to prepare medicated chewing gums containing Levocet. The developed medicated chewing gums were then evaluated for drug content and *in vitro* drug release. Results suggested that this dosage form offers delivery system that can deliver the drug to the oral cavity.

INTRODUCTION

Medicated chewing gum (MCG) is a novel drug delivery system that contains a masticatory gum base with pharmacologically active ingredient and is intended to be used for local treatment of mouth diseases or systemic absorption through buccal mucosa or GIT. MCG is considered as vehicle or a drug delivery system to administer active principles that can improve health and nutrition (1).

MCG has many advantages compared to other drug‑delivery systems, for example: it is easy to be used and requires no water which in turn, increases consumers' compliance, it is suitable for children and patients who have difficulty in swallowing tablets, it has rapid onset of action and presents less risk of overdosing because chewing is necessary to release the active substance from the chewing gums (2).

There are many factors which should be considered for this formulation like contact time of formulation with oral mucosa. Physicochemical properties of drug which plays major role in drug release from the chewing gum formulation. Formulation factors like composition, amount of gum base and even the type of the gum base affect rate of release of active ingredient (3).

Levocetirizine dihydrochloride is the active R (-) enantiomer of Cetirizine. It is an orally active and selective H1 receptor antagonist used medically as an anti-allergic (4).

The present work presented formulation of placebo chewing gums as a dosage form. Then, Levocet was incorporated into the most acceptable chewing gum formulations.

MATERIALS AND METHODS

MATERIALS

Levocetirizine Dihydrochloride (Levocet) and Sucralose were obtained as a gift sample (Global Marcyrl Pharmaceuticals, Cairo, Egypt. Beeswax and *T. aestivum* grain was purchased from local market. Glycerol and Menthol were obtained as a gift sample (Al Kahira Co., Egypt), Soy Lecithin and PVP K 25 were obtained as a gift sample (Epico Co., Egypt), HBβCD was obtained as gift sample (Roqutte, France), Poly vinyl alcohol (PVA) was obtained as a gift sample (Al Gomhoria Co, Egypt).

METHODS

1- Isolation and characterization of Prolamin (Gliadin) from Wheat

Accurately weighed 100 mg *Triticum aestivum* flour (wheat grain) was stirred for 2 hours with 300 ml ethanol 70 %. Marc was removed from solution by extraction through multilayer muslin cloth. The solution was concentrated to one fifth of its volume by heating at 50°C to get pure prolamin (gliadin). To this, equal amount of water was added and heated at 70°C until solid gum base was formed (5).

The isolated prolamin was subjected to Differential Scanning Calorimetry (DSC) analysis over the temperature range 25-250 ^{o}C in order to identify the Gliadin fraction from other wheat protein (Gluten and Glutenin) where the Gliadin fraction gives an endotherm at lower temperature compared to other wheat protein (6).

2- Preparation of chewing gum mass

Chewing gums were prepared according to the nature of gum base. Prolamin containing chewing gums (Table 1) were prepared by mixing accurately weighed quantities of Prolamin and calcium carbonate in a mortar. To this mixture, a water soluble phase of polyvinyl alcohol dissolved in 5 ml water was added and mixed. Then plasticizer, flavor and sweetener were added and mixed. The mixture was triturated and dried until solid mass was formed. Thin mass was then made and cut in the desired size. For uniform appearance of the prepared gum, the thin mass formed was cut, folded and compressed on a tablet compression machine (5, 7).

Beeswax containing chewing gums (Table 1) were prepared by first melting the required quantity of Beeswax. A blend of PVP and calcium carbonate was mixed in a mortar to which the previously melted beeswax was added and mixed. To this mixture, plasticizers were added and mixed well then the remaining ingredients were added and compressed (8).

Table No. 1: Composition of placebo chewing gums

Formula	Gum base 640 mg	Glycerol (mg)	Soy Lecithin (mg)	Sucralose (mg)	Menth (mg)	Mg Stearate (mg)	Cal Carbonate (mg)
F1	Prolamin (580 mg)+ PVA (60 mg	32	-	24	8	8	88
F2		48	-	24	8	8	72
F3		64	-	24	8	8	56
F4		-	32	24	8	8	88
F5		-	48	24	8	8	72
F6		-	64	24	8	8	56
F7	240 mg Beeswax + 400 mg PVP	32	-	24	8	8	88
F8		48	-	24	8	8	72
F9		64	-	24	8	8	56
F10		-	32	24	8	8	88
F11		-	48	24	8	8	72
F12		-	64	24	8	8	56

3- Physical and organoleptic evaluation of the prepared chewing gums

The developed chewing gums were subjected to physical and organoleptic evaluation. Physical evaluation included gum mass, hardness, friability and stickiness to surface while hardness feel and stickiness to hands and teeth were reported based on mastication by human volunteers (7).

3-1- Physical evaluation of the prepared chewing gums.

Weight Variation

Twenty CGs were taken randomly and weighed individually on analytical balance; the average weight and standard deviation were calculated. The formulation complies with the test; if not more than two of the individual masses deviate from the average mass by more than 5% (9).

Friability

Friability is a measure of the resistance of the chewing gum to abrasion (10). Ten chewing gums were randomly taken and weighed carefully then placed in the Friabilator (VEEGO, model: FT-2D, India) which was rotated for 100 revolutions at 25 rpm. The medicated chewing

gums were then dedusted and reweighed (11). Percent friability was calculated according to the following equation:

$$\% F = (\text{loss in weight} / \text{initial weight}) \times 100$$

Where F is the loss in weight in terms of percent. Ideally there should not be more than 1% weight loss (3).

Hardness

Hardness or crushing strength is the force required to break a tablet in diametric compression. Hardness is determined by a Pharmatest Tablet Hardness Tester, (Germany). Three chewing gums from each batch were taken randomly and their hardness was determined. The mean hardness and standard deviation were calculated (12).

Stickiness

The chewing gum was placed on a plain surface. A mass of 250 gram was 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 as sticky or non sticky (13).

3-2- Organoleptic evaluation of the prepared chewing gum

Consumer acceptance is prerequisite for development and commercialization of chewing gums. So, the developed chewing gums were subjected to sensory evaluation using six human subjects. Before starting the experiment, all volunteers were instructed to rinse their mouth thoroughly (11, 14).

Subjects were asked for their opinion about organoleptic properties (properties that individuals experience by the senses) such as hardness/softness and gritty or sandy effect since chewing gum is a material which does not break up into particles during mastication. Volunteers were allowed to give their opinion according to the Likert scale of 1 to 5 (very poor = 1, poor = 2, average= 3, good = 4, and excellent = 5) (2).

Also, stickiness to hands and teeth was reported by the volunteers. The chewing gum should provide the good mouth feel and comfort during chewing without sticking to the teeth. Stickiness to hands (texture feels) was performed manually by pressing the gum between the

thumb and the finger. The texture feel was characterized into very sticky, sticky or non-sticky. While stickiness to teeth was assessed by asking subjects to categorize chewing gums as very sticky, sticky and non-sticky after chewing the gums (5).

4- Preparation and evaluation of Levocet containing MCGs

Based on the results obtained from physical evaluation and organoleptic study, formulations with accepted results were further chosen to be medicated with Levocetirizine Dihydrochloride.

Levocet is an extremely bitter drug, which is not suitable for oral administration. Therefore, inclusion complex of Levocet with HBβCD was prepared at 1: 3 drug: HBβCD molar ratio. Components were weighed and dry triturated in a mortar for 15 min. The mixture was then kneaded with 50% (v/v) Ethanol for about 45 min. During this process, an appropriate quantity of the solvent was added in order to maintain a suitable consistency required for kneading. The product was dried at 50 °C and kept under vacuum for 24 h. The dried mass was then passed through sieve no. 30 (15).

MCGs were formulated using the previously selected chewing gums according to the methods previously discussed. Drug was added in replace of part of the calcium carbonate.

Table No. 2: Composition of medicated chewing gums

Formula	Gum base	Glycerol (mg)	Soy Lecithin (mg)	Sucralose (mg)	Menthol (mg)	Mag St. (mg)	Drug complex (mg)	Cal Carb. (mg)
F3	Prolamin (580 mg)+ PVA (60 mg	64	-	24	8	8	53	3
F5		-	48	24	8	8	53	19
F7	Beeswax (240 mg)+ PVP (400	32	-	24	8	8	53	35
F8		48	-	24	8	8	53	19

The developed MCGs were evaluated for:

4-1- Drug Content

Three chewing gums from each formulation were selected randomly. Each gum was dissolved in 100 ml phosphate buffer pH 6.8. The amount of Levocet was analyzed by measuring the drug absorbance at 231 nm using UV spectrophotometer. The formulation complies with the test if the individual content is between 85 % and 115 % of the average content (5, 11).

4-2- *In vitro* Drug release

The dissolution study of the chewing gum is relatively different than the conventional dosage forms. The mechanical force is required to release the drug from the chewing gum. After extensive literature survey, disintegration apparatus was slightly modified for this study. The disintegration apparatus was modified in such a way that the formulation was compressed or crushed as like our mastication activity in the mouth resulting in drug release. In this test, the MCG was placed in 500 ml of 6.8 pH phosphate buffer and samples were collected periodically for each time interval of 5, 10, 15, 20, 25 and 30 min and absorbance was measured at 231 nm. Measurements were carried out in triplicates and mean ±SD values are recorded (5, 8, 12).

RESULTS AND DISCUSSION

1- Isolation and characterization of Prolamin (Gliadin) from Wheat

The DSC thermogram of Prolamin (Figure 1) shows an endotherm at 59.8 ^{o}C corresponding to the Gliadin fraction of the wheat protein since the Gluten and Glutenin fractions fraction experience endotherms at relatively high temperatures (64 and 84 ^{o}C) (6).

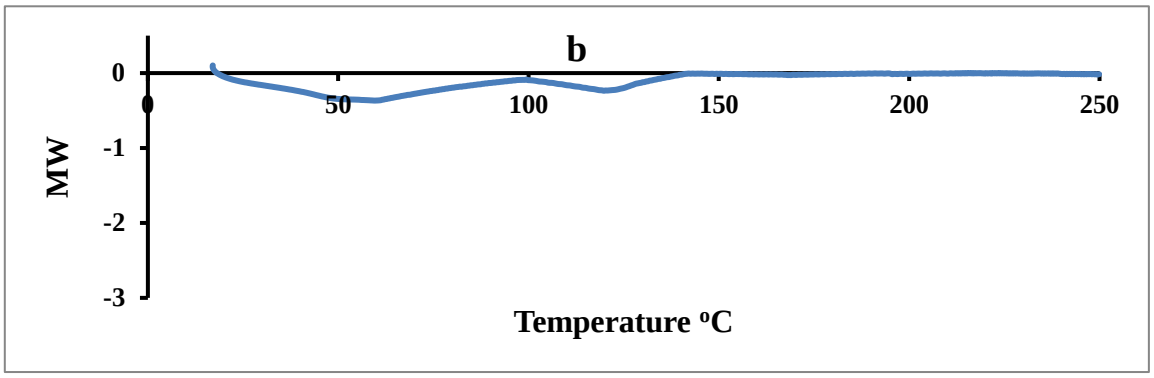

Figure No. 1: DSC thermogram of prolamin

2- Preparation and evaluation of chewing gum mass

The prepared CGs showed satisfactory weight variation (Table 3). None of the chewing gums deviated by more than 5% from the mean weight, indicating that all the formulations fulfilled the pharmacopeial limits for weight variation.

The % friability (Table 3) was less than 1% in all the formulations which complies with the requirements ensuring that the CGs were mechanically stable (11, 13).

Hardness of the prepared chewing gums was decreased with increased softener conc. Softener makes materials softer and more flexible. This could explain the observed decrease in hardness with increased plasticizer conc. The majority of the prepared chewing gums possessed good mechanical strength with sufficient hardness in the range of 2 to 3 kg/ cm^2 (Table 3). Hardness within this range ensures good handling characteristics of MCG (11, 16, 17).

CGs of F1, F2, F4, F10 and F11 were found to be hard compared to other formulations. This could be due to decreased softener level in these preparations.

All formulations except F9 and F12 were suitable in terms of stickiness. The observed stickiness could be due to increased softener level which led to decreased glass temperature and increased stickiness. The glass transition temperature (Tg); an important characteristic for amorphous materials like gum base is the temperature at which transition from a glassy solid state to a gummy (rubbery) state or from the rubbery state to the glassy one occurs. If the glass transition temperature of a material is lower than the storage temperature, the phenomena of stickiness, caking, and unwanted agglomeration becomes unavoidable. So, stickiness behavior can be explained by the fact that, polymers which are handled closely to their glass transition temperature (which is decreased by plasticizer addition), are sticky materials (18, 19).

Organoleptic properties of the prepared chewing gums showed that formulations F1, F2 and F10 were hard in chewing as reported by volunteers. CGs F9 and F12 were found to be sticky to hands and teeth (Table 4). Chewing gums F1, F4, F6, F10 and F11 showed gritty effect during chewing. These gums were brittle in nature and not suitable for use as gums. Chewing gum is a material which does not break up into particles during mastication.

According to physical and organoleptic results, F3, F5, F7 and F8 earned most points and thus were selected for further study.

Table No. 3: Results of physical evaluation of the prepared chewing gums

Formula	Weight (mg)	Friability (%)	Hardness (kg/ cm^2)	Stickiness
F1	793.90±2.651	0.140±0.006	3.90±0.150	NS
F2	790.87±3.592	0.230±0.020	3.79±0.060	NS
F3	791.93±0.902	0.110±0.041	2.50±0.240	NS
F4	800.50±0.954	0.130±0.0150	3.14±0.130	NS
F5	797.85±1.015	0.220±0.009	3.02±0.164	NS
F6	800.60±2.152	0.350±0.027	3.07±0.6.4	NS
F7	801.03±0.643	0.200±0.020	2.94±0.06	NS
F8	801.80±0.917	0.096±0.012	2.55±0.148	NS
F9	796.58±0.865	0.122±0.015	1.78±0.250	S
F10	801.40±0.529	0.147±0.035	3.70±0.140	NS
F11	801.57±0.351	0.363±0.032	3.39±0.115	S
F12	796.50±1.00	0.106±0.005	3.93±0.416	S

Table No. 4: Results of organoleptic evaluation of the prepared chewing gums

Formula	Hardness feel X of 5	Gritty/Sandy effect X of 5	Stickiness to teeth	Stickiness to hands
F1	2	1	NS	NS
F2	2	3	NS	NS
F3	4	4	NS	NS
F4	3	2	NS	NS
F5	3	3	NS	NS
F6	4	1	NS	NS
F7	3	4	NS	NS
F8	4	5	NS	S
F9	1	2	S	S
F10	3	1	NS	NS
F11	3	1	NS	NS
F12	4	2	S	NS

3- Levocet containing MCGs

The prepared MCGs met the requirement for content uniformity since the drug content ranged from 97.40 ± 0.56 to 100.1 ± 0.23 %.

Levocetirizine is a drug with high water solubility so, it is supposed to have fast release profile. Water soluble substances are released from medicated gums completely and rapidly. On the contrary, substances that are less soluble in water will dissolve in the gum base and therefore are released from medicated gums incompletely and slowly. This is mainly due to high solubility of water soluble drugs in the aqueous medium and the interaction (binding) of hydrophobic drugs with the gum matrix which is a complex mixture of hydrophobic polymers (2, 20).

Softener level and nature affects drug release from the prepared MCGs (Figure 2). Glycerol was more efficient softener due to its small molecular weight and liquid status. The low MW of Glycerol enables it to creep within the polymer chain intermolecular spaces, reducing the intermolecular hydrogen bond strength, hence, increasing the molecular mobility which in turn decreases hardness and increases flexibility (21, 22).

Drug release was increased proportionally with increasing softener level (F7, F8). Softener level also affects drug release by rendering formulations soft. Softener type and concentration influence the drug release since softener reduces polymer-polymer chain secondary bonding, and provide more mobility for the drug. In addition, softener can leach of the polymer resulting in pore formation for early drug release stage (5, 16).

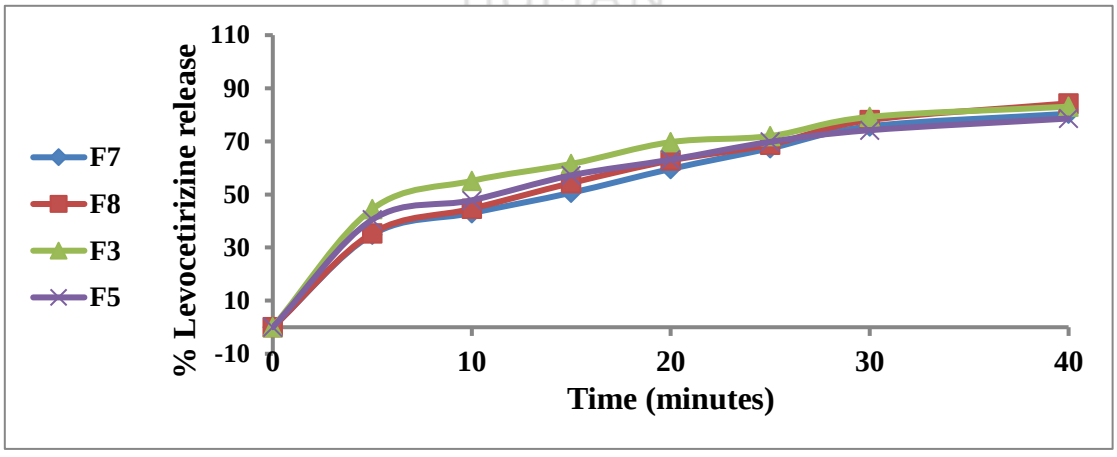

Figure No. 2: Cumulative % drug release from medicated chewing gums

CONCLUSION

The present study discussed the probability of formulating medicated chewing gum using natural ingredients. According to our findings, formulations with suitable physical and organoleptic properties were prepared (F3, F5, F7 and F8). The formulated medicated chewing gum possessed desirable drug content and release behavior. Consequently, our study confirmed that chewing gums provide suitable dosage forms for drug delivery.

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