REVIEW ARTICLE

Medicated Chewing Gum: A Review

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ABSTRACT

Medicated chewing gum (MCG) consider as a mobile system for drug delivery. It consists of a gum base, active ingredient, and other substances such as sweeteners and plasticizers. It can be taken without water and used for improved patient compliance, especially in children and geriatric patients. It can be utilized for drug administration locally, such as fluoride-containing gum for dental carries prophylaxes or systemically such as silver acetate and nicotine gum for smoking cessation. Many methods are used for chewing gum manufacture, such as fusion method, cooling, grinding and tableting method, and direct compression with a different evaluation method like weight variation, hardness test, surface pH, drug content, and in vitro release study**.**

Keywords: Chewing gum, Direct compression, *In-vitro* evaluations, Therapeutic uses.

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INTRODUCTION

Medicated chewing gum (MCG) considers a novel system for drug delivery consisting of an elastic gelatin base mixed with binding substances, sweeteners, and active therapeutic agents. MCG is intended for locally mouth disease treatment or systematic absorption throughout the mucosal of the oral cavity.[1] MCG is a semisolid or solid dosage form consisting of one or more active pharmaceutical agents (insoluble or water-soluble) that are incorporated into a lipophilic base.[2] The oral dosage form for many substances that have desirable function and characterization may consider a problem when delivered in a solid dosage form like tablet and multi particulates because of the unpleasant taste of these substances. The bitterness of some pharmaceutical agents considers a problem for acceptance and treatment effectiveness, so taste masking of the product is necessary to enhance patient compliance. Therefore chewable dosage forms (chewing gum, chewable tablet) are designed for mechanically processing within the mouth for enhancement disintegration and or dissolution of pharmaceutical substances.[3]

Advantages of MCG[4,5]

- Can be taken without water
- Improvement patient compliance, specially children and geriatric patients
- Increasing drug bioavailability by avoiding the first-pass effect
- It can be used for acute medication
- Rapid onset of action due to rapid drug release in buccal cavity which lead to systemic absorption enhancement.
- Gum can be removed at any time so that 'drug termination is possible
- Provided both local and systemic drug delivery.

Disadvantage[6,7]

- Drug disappearance in oral cavity due to saliva dilution.
- Drinking, speaking and eating lead to short administration time.
- Difference in chewing style lead to release profile variation.
- Allergic reaction may occur due to the use of some artificial sweeteners
- Chocking due to the swallowing of the gum by children of under-aged.

COMPOSITION OF MCG

Gum Base

It's a mixture of naturally occurring gum, bee wax, and solid paraffin. Its non-nutritive, inert portion of gum doesn't dissolve while the patient is chewing.[8]

Elastomer

It's a polymer (synthetic or naturally) with high elasticity and elongation properties, making them highly flexible towered cracking or breaking, such as latex and polyvinyl acetate.[9]

Plasticizer

These substances softened gum composition by promoting plasticity, decreasing brittleness, and making the elastomer

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more softy. It's either natural or synthetics such as glycerol and propylene glycol.[10]

Filler or Texturizer

Used for chewability improvement provided acceptable gum size with low drug dosing, the widely used substances like magnesium and calcium carbonate.[8]

Sweeteners

These substances used for taste improvement , providing the sweetness to the formulation, help for softening the ingredients blend and maintain the moisture. They are of two types of bulk and aqueous sweeteners, for example, a bulk sweetener such as sucrose, fructose, and artificial sweetener, while for the aqueous sweeteners like corn syrup and hydrogenated starch.[11]

Flavoring Agent

These substances are used as a taste masking agent for the bitter drug, so that they provide an acceptable product flavor such as essential oil (peppermint and citrus oil) and artificial oil.[8,12]

Antioxidant

Used to inhibit microbial growth by preventing oxidative processes such as propyl gallate and butyl hydroxyanisole.[13]

Active Pharmaceutical Agent[14]

The Active pharmaceutical agent may be found within the gum core or coat or in both of them in a percentage range from 0.5–30% of the final weight of gum, and the active pharmaceutical agent should have the following properties:

- Tasteless, highly soluble in saliva, does not affect the saliva flow rate and has pH-independent solubility.
- Not carcinogenic or cause tooth decay and staining.

METHOD OF PREPARATION OF MCG.[15]

- Fusion method
- Cooling, grinding, and tableting method
- Direct compression process

Fusion Method

In this method, the gum components are melted and put in a Kettle mixer in which the active ingredients and other additives are added at a definite period following the gum sent to a series of rollers. During these processes, sugar substitutes are used to prevent the gum from sticky and enhance the flavoring effect; after that, the gum cooled for 2 days. Finally, the gum is cut to the required size and shape and cooled at a certain temperature and humidity.[16]

Limitation[17]

- Temperature elevated during the melting process make restriction to the use of heat-sensitive drug
- Un precise shape, weight of the resulted dosage form
- Difficult control of uniformity and accuracy of drug dosing due to highly viscous gum use.
- Due to high moisture content, 2–8% of chewing gum is difficult to formulate to the tablet because its composition would sticky to the grinding machine with difficulty to compress.

Cooling, Grinding, and Tableting Method

The composition of chewing gum is cooled to a temperature -15°C, at which it maintains brittle throughout the grinding next step. After that, the refrigerated composition is crushed to produce fine pieces of composition. To produce more efficient cooling, the mixture of chewing gum, silica, and solid carbon dioxide is grinding first in a mill grinder, then adding additional silica and solid carbon dioxide and grinding in the 2nd grinding process. These two grinding steps keep the composition of chewing gum at a low temperature, and the presence of solid carbon dioxide enhances the grinding process efficiency. Also, anticaking like precipitated silica dioxide can blend with solid carbon dioxide and chewing gum composition before the grinding step to prevent agglomeration of product[18] and a fluidized bed reactor (FBR) is used for gum tableting by removal the coolant from the powder mixture, then these powder mixed with lubricant, binder, sweeteners in high shear mixer. The use of FBR rebuilds the powder in the granules and provides coating the granule with a coating agent so that it reduced the undesired agglomeration of particles.[19]

Direct Compression

To avoid the limitation of freezing and melting method, direct compression is used in which Pharmgum®, a compactable gum system produced by SPI Pharma. It's a mixture of sugars and polyols mixed with a chewing gum base. Pharmgum® was found as a directly compressible powder with free-flowing properties that enables it to be compatible with a gum tablet by using classical tab press to provide low cost and rapid gum delivery system development.[20]

Problems associated with the Manufacturing of MCG[21]

- Capping, sticking, and picking are widely occurring during processing.
- Heating followed by melting affecting on the accuracy and uniformity of dosage form
- Using of high temperature during the gum base mixture may produce spoiling of another component
- Appearing of sugar lumps or spot IN in the final texture causing unacceptable feeling
- Prevent gum fragments formation due to balling and caking of the gum.
- Gum with a low calorie produces a bad taste, poor texture, and hard chew.

Formulation Techniques for Preparation of Sustained-release MCG[22]

1. Drug -ion-exchange Complex

The use of ion-exchange resin with drugs produces a complex that slows drug release from the gum base.

2. Adsorption

Flavoring material adsorption onto a silica gel will decrease the drug release rate from the dosage form.

Coating and Embedding

Drug coating with a different coating agents such as cellulose or PVP and drug embedded within synthetic waxes such as

Table 1: Therapeutic uses of MCG

Uses	*Example*
Orally antifungal treatment	Miconazole , Econazole, and Nystatine
Cessation for smoking	Silver acetate and nicotine
Relief in pain	Lobeline, aspirine, Silver acetate, and Methadone
Memory improvement for CNS stimulation	Caffeine
Otitis media treatment	Chlorhexidine, Xylitol, Salvadorapersica
Tooth decay and caries treatment	Chlorhexidine
Motion sickness management and treatment	Ginger, Nicotine, Diphenhydramine hydrochloride
Notarization of acid	Antacid
Treatment of the deficiency of vitamin C	Vitamin C
Antioxidant	Green tea
Antiseptic, anti-inflammatory, healing agents	Aloe Vera

lecithin or hydrophobic matrix will decrease the drug release rate from chewing gum.

EVALUATION OF MCG

Visual Appearance

All the prepared MCG were inspected visually for their taste, homogeneity, color, smoothness, and transparency.[23]

Thickness Measurement

The mean thickness was determined for each prepared gummy by using a digital venire caliper (screw gauge in milliliter).[24]

Weight Variation

The weight of each prepared gummy was determined by using a digital electrical balance followed by calculating the mean and the standard deviation for each gummy.[25]

Percentage Moisture Loss and Moisture Content

Each gummy was weighted and put in a desiccator containing about 1-g of anhydrous $cacl_2$ for three days, after that it was removed from the desiccator and re-weight again. The Percentage moisture loss and moisture content were determined by using the following equation.[26]

Percentage moisture loss = initial weight – final weight/ initial weight … eq 1

Percentage moisture content = initial weight – final weight … eq 2

Hardness Test

The hardness of the gummy was obtained by calculating the forces which is required for crushing the gummy by using the Monsanto hardness tester.[27]

Surface pH

This test is done by cutting the gum into four pieces and putting them in 50ml DW following recording the pH by digital pH meter after 10 minutes.[28]

Drug Content

The gummy was put in a beaker containing a solution of 50 mL 0.1 N HCL under a magnetic stirrer for 2 hours. The solution was filtered by using Millipore filter paper and the drug content was determined by using UV-visible Spectrophotometer.[19]

In vitro Drug Release Study

This test is performed by using a suitable volume of 0.1 N HCL at 37°C and at rotation 50 rpm of dissolution apparatus type ll. At regular time intervals, the sample withdrew from the jar and replaced with the same dissolution media volume following filtration and analyzed the sample at its max by using UV-visible Spectrophotometer.[30]

Therapeutic Uses

Prevent and treatment of oral disorders are the main targeting for MCG formulation. Also, this gum can release the drug at a controlled rate and extended time to provide a local and prolonged effect. Sugar-free MCG is used for dental health because these gums consider as a supplement for brushing the tooth after snacks and meals. MCG is used in drug delivery for systemic effect as seen in Table 1, especially when the drug is absorbed throughout the mucosal of the buccal cavity to provide acute and fast treatment and reduce the risk of GIT adverse effects. In addition, drug absorption from MCG is faster than from tablets so this formulation provided fast relief for the pain.[31]

CONCLUSION

Chewing gum is considered an excellent system for drug delivery because of self-administration and can be taken without water. It provided many advantages compared to lozenges and chewable tablets; they contain one or more pharmaceutical agents released from the gum by chewing and used for local mouth disease treatment or systemically after the buccal mucosal absorption.

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