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Recently Developed Novel Drug Delivery System: Medicated Chewing Gum: An Overview

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Abstract

The medicated chewing gum (MCG) is one of the very popular oral confectionery products. It is mobile drug delivery system. It is a potentially useful means of administering drugs either locally or systemically via, the oral absorption. MCG offers various advantages over conventional drug delivery systems. It is a potentially useful means of administering drugs either locally or systemically via, the oral cavity. The medicated chewing gums are solid, single dose preparations with a base consisting mainly of gums that are intended to be chewed but not swallowed. The medicated chewing gum has through the years gained increasing acceptance as a drug delivery system. Chewing gum known as gum base (insoluble gum base resin) contains elastomers, waxes, emulsifiers, fillers, antioxidants, food colorings, softeners, sweeteners, flavoring agents, and in case of medical chewing gum, active substances. 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 and improve the oral bioavailability of drugs undergoing first pass metabolism. It was concluded that chewing gum is an excellent drug delivery system for self-medication as it is convenient and can be administered discretely without water.

Keywords: Medicated Chewing Gum, Oral, Dental Caries, Mouth Diseases

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1. Introduction

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[1]. Today MCG is convenient drug delivery system which is appropriate for a wide range of active substances. MCG is considered as vehicle or a drug delivery system to administer active principles and nutrition that can improve health, and creates additional patient benefits that will add new competitive advantages

for a drug and thus increase revenue [2]. Chewing gum has been used for centuries to clean the mouth and to fresh the breath[3]. The first patent for the production of chewing gum was filed in 1869 and was issued to Mr. W. F. Semple in Ohio under U. S. Patent No. 98,304. A MCG containing Acetyl Salicylic Acid was commercially introduced in 1928 [3, 4]. Now a days, MCG meets the same superior quality of standards as tablets as per current good manufacturing practice (cGMP) guidelines and it can be easily formulated to obtain different release rates of active pharmaceuticals which enabling distinct patient group targeting. Particularly in children, MCG may be a more favored method of drug administration compared with oral liquids or tablets [5].

Advantages of MCG

1. Fast onset due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation.
2. Does not require water to swallow, hence can be taken anywhere.
3. Excellent for acute medication.
4. The treatment can, if required, be terminated at any time.
5. Highly acceptable by children
6. Pleasant taste
7. Caffeine, Aspirin and Dimenhydrinate shows faster absorption through MCG than tablets.
8. Drugs that are released from chewing gum and swallowed, will be introduced in the gastrointestinal tract either dissolved or suspended in saliva and thus the drug will be presented in a readily bioavailable form
9. Avoids First Pass Metabolism and thus increases the bioavailability of drugs
10. Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased
11. Gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients [1, 4, 6]

Disadvantages

1. Additives in gum like flavoring agent, Cinnamon can cause Ulcers in oral cavity and Liquorice cause Hypertension.
2. Prolong chewing on gum may result in pain in facial muscles and earache in children.
3. Risk of over dosage with MCG compared with chewable tablets or lozenges that can be consumed in a considerable number and within much shorter period of time.
4. Sorbitol present in MCG formulation may cause flatulence, diarrhea.
5. Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers[3, 7].

Characteristic of Ideal Medicated Chewing Gums

1. They should not require water for administration and should not disintegrate with in the mouth.
2. They should allow high drug loading.
3. They should be compatible with taste masking
4. They should exhibit low sensitivity to environmental condition such as humidity and temperature.
5. They should be manufactured and processed easily.
6. They should have a pleasing mouth feel [1, 8].

Composition of Mcgs

Chewing gum is a mixture of natural or synthetic gums and resins, sweetened with sugar, corn syrup, artificial sweeteners and may also contain coloring agents and flavor. The basic raw material for all chewing gum is natural gum Chicle, obtained from the sapodilla tree. Chicle is very expensive and difficult to procure therefore other natural gum or synthetic materials like polyvinylacetate and similar polymers can be used as gum base.

Typically chewing gum comprises two parts:

A. Water-soluble bulk portion
B. Water insoluble chewable gum base portion

A. Water-soluble bulk portion

A water soluble portion contains Softners, Emulsifiers, Colourants, Sweetners, Sugarless Components, Bulking agents and Flavouring agents.

a) Softners and Emulsifiers:

These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. Softners include Glycerin, Lecithin, Tallow, Hydrogenated Tallow, Mono/ di/ tri-Glycerides, Fatty acids like Stearic acid, Palmitic acid, Oleic acid and Linoleic acid[9, 10].

b) Sweetners:

These are of two types, Aqueous and Bulk.

Aqueous Sweetners can be used as softners to blend the ingredients and retain moisture. These include Sorbitol, hydrogenated Starch hydrolysates and Corn Syrups. Corn syrup keeps gum fresh and flexible.

Bulk Sweetners include Sugar and Sugarless components. Sugar Components include Saccharides like Sucrose, Dextrose, Maltose, Dextrin, Fructose, Galactose, and Corn Syrup [10].

c) Colourants and Whiteners:
It may include FD & C type dyes and lakes, fruit and vegetable extracts, Titanium Dioxide [6].

d) Sugarless Components:
These include sugar alcohols such as Sorbitol, Manitol, Xylitol, hydrogenated Starch hydrolysate. High intensity artificial Sweetners can also be included to provide longer lasting sweetness and flavour perception e.g. Sucralose, Aspartame, salt of Acesulfame, Alitame, Saccharin, Glycerrhizin, Dihydrochalcones [3,9].

e) Flavouring Agents:
A variety of flavouring agents are used to improve flavour in chewing gum includes essential oils, such as Citrus oil, fruit essences, Peppermint oil, Spearmint oil, Mint oil, Clove oil & Oil of Wintergreen. Artificial flavouring agents can also be used [11].

f) Bulking agents:
These are used if low calorie gum is desired. Examples of low caloric bulking agents include Polydextrose, Oligofructose, Inulin, Fructooligosaccharides, Guargum hydrolysate, Indigestible Dextrin [3, 8].

B. Water insoluble chewable gum base portion
Water insoluble gum base generally comprises Elastomers, Resins, Fats and Oils, and Inorganic fillers.

a) Elastomers:
They provide elasticity, gummy texture and cohesion to the chewing gum. These are again divided into Natural and Synthetic elastomers.
Natural elastomer Natural rubbers like Latex or Natural gums such as Jelutong, Lechi Caspi, Perillo, and Chicle.
Synthetic elastomers like polyisobutylene and butyl rubber are used [12].

b) Fillers or Texturizers:
Provide texture, improve chewability, and provide reasonable size of the gumlump with low dose drug. Commonly used fillers are Magnesium and Calcium Carbonate, Ground Limestone, Magnesium and Aluminium Silicate, Clay, Alumina, Talc, Titanium Oxide & Mono/ di/ tri Calcium Phosphate[6, 9].

c) Plastisizer:
These are used to regulate cohesiveness of product. These are again divided into Natural and Synthetic Plastisizer.
Natural Plastisizers include Natural rosin esters like Glycerol Esters or partially hydrogenated Rosin, Glycerol Esters of Polymerized Esters, Glycerol Esters of Partially dimerized Rosin & Pentaerythritol Esters of Rosin.
Synthetic Plastisizers include Terpene Resins derived from α-pinene and or d-limonene [13].

Characteristic of Ideal Drug Candidates for Chewing Gum

1. The drug should not be have any type of disagreeable taste and it should not be irritant to oral mucosa this can affect patient compliance.
2. The drug should be water soluble and should have suitable pKa for mucosal absorption.
3. The particle size of the drug should be kept below approximately 100μm to avoid unpleasant gritty feeling during chewing [5, 14].

2. Manufacturing Process

Different methods employed for the manufacturing of chewing gum can be broadly classified into three main classes namely.

1. Conventional/ Traditional method (Fusion)
Components of gum base are softened or melted and placed in a kettle mixer to which sweeteners, syrups, active ingredients and other excipients are added at a definite time. The gum is then sent through a series of rollers that forms into a thin, wide ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavor. In a carefully controlled room, the gum is cooled for up to 48 hours. This allows the gum to set properly. Finally the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity.
Limitation:

1. Elevated temperature used in melting restricts the use of this method for thermo liable drugs.
2. Such a chewing gum composition is difficult to form into chewing gum tablets because often their moisture content (2-8%).
3. Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.

4. Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult [15-18].

2. Cooling, Grinding and Tabletting Method (Thermo liable)

This method has been developed with an attempt to lower the moisture content and alleviate the problems mentioned in conventional method.

Cooling and Grinding:

The CG composition (base) is cooled to a temperature at which the composition is sufficiently brittle and would remain brittle during the subsequent grinding step without adhesion to the grinding apparatus. The temperature required for cooling is determined in part by the composition of the CG and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperature of the refrigerated mixture is around−15°C or lower. Amongst the various coolants like liquid nitrogen, hydrocarbon slush use of solid carbon dioxide is preferred as it can give temperatures as low as−78.5°C, it sublimes readily on warming the mixture, is not absorbed by the chewing gum composition, does not interact adversely with the processing apparatus and does not leave behind any residue which may be undesirable or potentially hazardous. The refrigerated composition is then crushed or ground to obtain minute fragments of finely ground pieces of the composition.

Use of anti-caking agent:

An anti-caking agent such as precipitated silicon dioxide can be mixed with chewing gum composition and solid carbon dioxide prior to grinding. This helps to prevent agglomeration of the subsequently ground chewing gum particles.

Use of grinding agents:

To prevent the gum from sticking to the grinding apparatus, 2-8% by weight of grinding aid such as alkaline metal phosphate, an alkaline earth metal phosphate or maltodextrin can be incorporated.

Tabletting:

Once the coolant has been removed from the powder, the powder can be mixed with other ingredients such as binders, lubricants, coating agents and sweeteners etc, all of which are compatible with the components of the chewing gum base in a suitable blender such as sigma mill or a high shear mixer. Alternatively a Fluidized Bed Reactor (FBR) can be used. The use of FBR is advantageous as it partially rebuilds the powder into granules, as well as coats the powder particles or granules with a coating agent thereby minimizing undesirable particle agglomeration. The granules so obtained can be mixed with antiadherents like talc. The mixture can be blended in a V type blender, screened & staged for compression. Compression can be carried out by any conventional process like punching. It requires equipment other than conventional tabletting equipment and requires careful monitoring of humidity during the tabletting process which is the major limitation [18, 19].

3. Use of direct compression chewing gum excipients

The manufacturing process can be accelerated if a directly compressible chewing gum excipient is available. The limitations of melting & freezing can be overcome by the use of these. Pharmagum is a mixture of polyol(s) and/or sugars with a chewing gum base. It is available as directly compressible powder, free flowing powder which can be compacted into a gum tablet using conventional tablet press thus enabling rapid and low cost development of a gum delivery system. It is manufactured under CGMP conditions and complies with Food Chemicals Codex specifications as well as with FDA, so they can be considered as "Generally regarded as safe" (GRAS) [9, 20].

Evaluation [7, 9, 21, 22]

1. Weight variation:

Weight of the ten chewing gums is taken in a one batch then average weight is calculated from that standard deviation is calculated. As per individual monograph (According to USP).

2. Uniformity of mass:

Uncoated medicated chewing gum and unless otherwise justified and authorized coated medicated chewing gum comply with the test for uniformity of mass of single- dose preparations.

3. Hardness:

Hardness in simple term is the property of material by which it is able to hold all its constituents in an intact form. Hardness is amount of strength of chewing gum to withstand mechanical shocks of handling in manufacture, packaging and shipping and tablet should be able to withstand reasonable abuse when in the hand of consumer. Hardness of chewing gum will be evaluated by Monsanto hardness tester. Hardness is measured in kg/cm^2.

4. Stickiness:

The MCG placed on the plain surface, mass of 250 gm Teflon hammer collide on it for period of ten minute. The frequency of hammering was about 30 / minute. After 10 minutes, sticking of mass to the hammered surface was observed and reported.

5. **Test for Uniformity of Content:**
   Unless otherwise prescribed or justified and authorized medicated chewing gum with content of 2 mg or less than 2 percent of the total mass of gum comply with test.
6. **Drug release from medicated chewing gum:**
   It has been reported commercially that the drug release from medicated chewing gum as per the specification given in European Pharmacopoeia and is determined by applying a mechanical kneading procedure to a piece of gum placed in a small chewing chamber containing a known volume of buffer solution.

Applications of Medicated Chewing Gums

1. **Systemic therapy:**
   Chewing gum as a drug delivery system is beneficial to a number of indications, some of which are discussed below:
   a) **Obesity:** Active substances like chromium, guaran and caffeine are proved to be efficient in treating obesity. Chromium is claimed to reduce craving for food due to an improved blood-glucose balance. Caffeine and guaran stimulate lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger.
   b) **Pain:** Treatment of minor pains, headache, muscular aches can be successfully accomplished.
   c) **Smoking cessation:** Chewing gum formulation containing nicotine, lobeline and silver acetate have been clinically tested as aids to smoking cessation. Nicotine is a natural alkaloid occurring in the leaves of tobacco plant. It is a therapeutic agent intended to help smokers break the psychological habit of smoking by reducing the nicotine withdrawal symptoms normally experienced when smoking is stopped. The formulation nicoretteÒ available as mint and classic with different flavor and dosage, is developed with ion- exchange resin, released 90% of drug after 30 min chewing. The release rate was controlled by the rate and vigour of chewing. Thus the patient can control the drug intake to match his needs. Increasing the pH of the medium in which it is dissolved can enhance nicotine absorption.
   d) **Other indications:** Xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety etc are all indications for which chewing gum as drug delivery system could be beneficial[22, 23].
2. **Dental caries:**
   Prevention and cure of oral disease are obvious targets for chewing gum formulations. It can control the release rate of active substances providing a prolonged local effect. It also reelevates plaque pH which lowers intensity and frequency of dental caries. Fluoride containing gums have been useful in preventing dental caries in children and in adults with xerostomia. Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oral and pharyngeal infections. It can also be used for inhibition of plaque growth. Chlorhexidine chewing gum offers numerous flexibility in its formulation as it gives less staining of the teeth and is distributed evenly in the oral cavity. The bitter taste of chlorhexidine can be masked quite well in a chewing gum formulation [24, 25].

Marketed MCG Products [26-28]

Table 1: Marketed MCG Products

Marketed MCG	Active Ingredients	Therapeutic use
Aspergum	Aspirin	Pain relief
Endekay	Vitamin C (ascorbic acid)	Vitamin supplement
Orbit white, Happydent white, Trident white, Recaldent	Calcium as a tricalcium phosphate	Dental hygiene and tooth Whitening.
Fluogum, Fluorette,	Fluoride as a sodium fluoride	Prevention of dental caries
Zolf virility gum	Extract of Haw thorn Berry, Horny Goat Weed, Damiana Leaf, Muira Puama Leaf, Ginkgo Biloba Leaf, Catuaba Bark Extract, Saw Palmetto Berry	Increase male sexual Desire and Performance
Niquitin cq, Nicorette	Nicotine	Smoking cessation
Stay alert	Caffeine	CNS stimulant
Zolf stress gum	Extract of Ashwagandha, passion flower and jujube fruit and calcium carbonate	Reduce the symptoms associated with stress, anxiety and depression
Chew away gum, Slim n trim	Extract of Hoodia gordonni-nature's calcium channel blockers	Appetite supressant for weight loss
Travel gum	Dimenhydrinate	Motion sickness

3. Conclusion

Generally, it takes time for a new drug delivery system to establish itself in the market and gain acceptance by patients, however chewing gum is believed to manifest its position as a convenient and advantageous drug delivery system as it meets the high quality standards of pharmaceutical industry and can be formulated to obtain different release profiles of active substances. It can be concluded that the chewing gum can be used, as a carrier for vast categories of drugs where extended release and the local action is desired. Chewing gum can be used without water, at any time. Now a day, MCG is gaining more attention as a very good vehicle to administer active principles in pharmaceuticals and nutraceuticals. Since the development cost of a new chemical or a drug molecule is very high, the pharmaceutical companies are focusing on development of new drug delivery system for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects.

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