

Medicated Chewing Gum- A Mobile Oral Drug Delivery System

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Abstract: Oral drug delivery system is highly accepted amongst patients. In present era many research and technological advancements are made in novel oral drug delivery. Chewing gum incorporated with various types of active ingredient is one of such example of novel drug delivery. Medicated chewing gum (MCGs) is effective locally as well as systemically in dental caries, smoking cessation, pain, obesity, xerostoma, acidity, allergy, nausea, motion sickness, diabetes, anxiety, dyspepsia, osteoporosis, cough, common cold etc. Medicated chewing gums are used not only for special population groups with swallowing difficulties such as children and the elderly, but also popular amongst the young generation. Thus chewing gum proves to be an excellent drug delivery system for self-medication as it is convenient and can be administered discretely without the aid of water. The present review article has nicely detailed on history, advantages, disadvantages, formulation, manufacturing process, limitation of manufacturing process, factors affecting release of active substance, quality control tests for chewing gum, significance, stability study and future trends, patent filled on MCGs

Keywords: Medicated chewing gum, gum base, conventional manufacturing method, dental caries.

INTRODUCTION

Chewing gum can be used as a convenient modified release drug delivery system. Medicated chewing gums (MGCs) are currently available for pain relief, smoking cessation, travel illness, and freshening of breath. In addition, a large number of chewing gum intended for prevention of caries, xerostomia alleviation and vitamin / mineral supplementation are currently available.

MGCs usually consists of a gum core, which may or may not be coated. The water content of chewing gum is very low and requires no preservatives. MGCs are defined by the European Pharmacopoeia and the guidelines for pharmaceutical dosage forms issued in 1991 by the Committee for Medicinal Products for Human Use (CPMP) as 'solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not to be swallowed, providing a slow steady release of the medicine contained¹. Generally, chewing gum is

a combination of a water-insoluble phase, known as gum base and some of their ingredients. These include powdered sugar whose amount and grain size determine the brittleness of the resulting gum, corn syrup and/or glucose which serve as humectants and coat the sugar particles to stabilize their suspension and keep the gum flexible, various softeners, food colorings, preservatives, flavorings etc.

The first Medicated chewing gum "Aspergum" was launched in 1928. This chewing gum is still available and contains acetylsalicylic acid. Another commercially available medicated chewing gum is dimenhydrinate – containing chewing gum for motion sickness. However, chewing gum did not gain acceptance as a reliable drug delivery system until 1978, when nicotine chewing gum became available. Today improved technology and extended know how have made it possible to develop and manufacture medicated chewing gum with pre-defined properties.

Consequently, today chewing gum is a convenient drug delivery system, which is appropriate for a wide range of active substances. MGCs offers advantages in comparison to conventional oral mucosal and oral dosage forms both for (a) local treatment (b) systemic effect after absorption through the buccal and sublingual mucosal and from the gastrointestinal tract. Drug released from chewing gum also has the potential to be absorbed through the oral mucosa into the systemic circulation and thereby give rise to a systemic effect. As medicated chewing gum can be retained in the oral cavity for a long period and, if the drug is readily absorbed across oral mucosa, chewing gum can provide a fast onset time for a systemic effect. Drug absorbed directly via the membranes lining the oral cavity avoids metabolism in the gastrointestinal tract and the first-pass effect of the liver since the oral veins drain directly into the vena cava. It might therefore be possible to administer a reduced dose of a drug that is subjected to these processes in chewing gum compared to when they are incorporated into peroral delivery systems.

Alternatively, drug released from medicinal chewing gum but not absorbed through the oral cavity membranes will be swallowed and enter the stomach in a dissolved or a dispersed form in saliva. The drug will thus be presented to the gastrointestinal tract in an easily available form and the potential for avoidance of gastrointestinal and hepatic first – pass metabolism of susceptible drugs.

HISTORY

From thousand of years chewing gums are highly enjoyed by people as confectionery preparation. it has an ancient history in 50 AD of Greeks sweetening their breath and cleaning their teeth by using mastiche, a resin from the bark of mastic tree. Mayan Indians of Yucatan chewed chicle from the sapodilla tree. Shortage of natural gum bases during World War II enhanced development of the synthetic gum bases that are used today. Spruce gum, which was manufactured in 1848, became the first chewing gum product to be manufactured commercially Called "STATE OF MAINE PURE SPRUCE GUM." However, its use was eventually replaced by paraffin, which is still being chewed in some areas. During the 1860's, a New York photographer named Thomas Adams, realized the potential market for chewing gum products. He wrapped pieces of pure, flavorless chicle in colored tissue paper, packaged them in boxes, and left them on consignment with numerous drugstore owners. The gum was named Adams New York No.1. Public response to the product was very favorable.

The first patent for chewing gum, U.S. number 98,304 was filed on December 28, 1869 by Dr. William F. Sample, a dentist from Mount Vernon, Ohio. This product, consisting of liquorice and rubber dissolved in alcohol and naphtha, was initially intended to be used as a dentifrice. In 1891, William Wrigley Jr., arrived in Chicago with \$32 in cash with a desire to market his special variety of soap. Eventually, he switched from soap to baking powder sales and offered chewing gum premiums to merchants who became his customers. By 1892, when the premiums had become more popular than the baking powder, Wrigley launched his first chewing gum products, LOTTA and VASSAR. A year later, he developed JUICYFRUIT, and shortly thereafter, WRIGLEY'S SPEARMINT gum.

Sugarless gum made its debut in the early 1950s, generally used sorbitol as a sugar substitute. The first brand to be marketed was Harvey's followed by Trident and Carefree. In 1975, the Wm. Wrigley Jr. Company introduced the arrival of a new chewing gum product, Freedent, designed especially for denture wearers, which did not stick to most dentures as ordinary gum did.

Table 1: Constituents of MCGs^{11,12,13}

Ingredients	Characteristics	Proportion Used
Active pharmaceutical ingredient	Vitamins, oral contraceptive, nicotine, minerals, analgesic, antacids, muscle relaxants, antihistamic, decongestants, anaesthetics, antitussive, antibiotics, etc.	Maximum approx. 50%
Masticatory gum base (elastomers)	It provides elasticity and controls gummy texture.	15-45%
Natural gums		
Chile gum	Latex of Manilkara zapotilla Family : Sapotaceac	
Nispero	Latex of Manilkara huberi Family : Sapotaceac	
Gutta hang kang	Latex of Palaquium leiocarpum Family : Sapotaceac	
Rosidinha (rosadinha)	Latex of Micropholis spp. Family : Sapotaceac	
Jelutong	Latex of Dyera costulata Family: Apocynaceae	
Leche caspi(sorva)	Latex of Couma utilis Family: Apocynaceae	
Perillo	Latex of Couma macrocarpa Family: Apocynaceae	
Niger gutta	Latex of Ficus platyphylla Family: Moraceae	
Natural rubber	Smoked sheet and latex solids of Hevea brasiliensis Family: Euphorbieaceac	
synthetic gum		
Butadiene- styrene rubber, polyisobutylene, polyvinyl alcohol, polyisoprene, polybutadiene	They are polymer prepared by Ziegler- Natta polymerisation.	
Elastomer solvents :	It provides softening to the elastomer base component.	45-70%
Terpinene resins	Polymers of alpha-pinene or beta-pinene, methyl, glycerol or pentaerythritol esters of resins	
Modified resins or gums	Hydrogenated, dimerized or polymerized resins or mixtures	
Plasticizers	They are to provide a variety of desirable textures and consistency properties. Examples : Lanolin, palmitic acid, oleic acid, stearic acid, glyceryl triacetate, propylene glycol monostearate, glycerine, natural and synthetic waxes, hydrogenated vegetable oils, paraffin waxes, fatty waxes, sorbital monostearate, propylene glycol	0.5-15%
Fillers or texturizers or mineral adjuvant	It provide texture, improve chewa-bility, provide reasonable size of the gum lump with low dose drug. Examples: Calcium carbonate, magnesium carbonate, aluminum hydroxide, talc, aluminum silicate	Provide reasonable size of gum lump with low dose drug up to 50%
Colorants and whiteners	It gives the formulation soothing color and improves acceptability of the formulation. Examples: Titanium dioxide, natural food colors and dyes suitable	<0.1%
Sweeteners	It provide the desired sweetness of the product	Upto 60%
Water soluble sweetening agents	xylose, ribulose, glucose, mannose, galactose, sucrose, fructose, maltose, monellin, sugar alcohols like sorbitol, mannitol etc.	
water soluble artificial sweeteners	sodium or calcium saccharin salts, cyclamate salts etc	
protein based sweeteners	thaumatin I and II	
dipeptide based sweeteners	aspartame, alitame etc.	
chlorinated derivatives of ordinary sugar	Sucralose	
Antioxidants	It prevents any possible microbial growth. Examples: Butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate	0.02% of gum base
Flavoring agents	It enhance consumer acceptability.	0.01-1%
Bitter taste of drug	Wild cherry , raspberry, coffee, chocolate, mint, grapefruit, peach, orange, lemon	
Sweet tasting drug	Fruit and berry, honey, vanilla, bubble gum	
Acidic sour tasting drug	Lemon, orange, cherry, grapefruit, liquorice,	
Alkaline tasting drug	Mint, chocolate, cream, vanilla	
Metallic	Burgundy, berries, grape, marshmallow, Guyana	
Salty tasting drug	Butterscotch, maple, apricot, peach, melon, vanilla, wintergreen, mint	
Compression adjuvant: lubricant, glidant and antiadherent	It ease the compression process. Examples: Silicon dioxide, magnesium stearate, calcium stearate, talc	0.2-1%

MERITS OF MGCs

1. Does not require water to swallow. Hence can be taken anywhere².
2. Advantageous for patients having difficulty in swallowing³.
3. Excellent for acute medication.
4. Counteracts dry mouth, prevents candidiasis and dental caries².
5. Highly acceptable by children.
6. Avoids First Pass Metabolism and thus increases the bioavailability of drugs³.
7. Fast onset due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation
8. Gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients.
9. Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa³.
10. Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased.
11. Aspirin, Dimenhydrinate and Caffeine⁴ shows faster absorption through MCG than tablets.
12. As a delivery systemic administration of drug via the oral mucosa it has the potential to overcome the problems of short lived action and variations in drug release and retention times.
13. It may prove to be particularly suitable for the systemic delivery of drugs, which are susceptible to metabolism in the gut wall or liver.
14. The treatment can, if required, be terminated at any time.
15. In addition, the 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.

DEMERITS OF MCGS

1. 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 time⁵.
2. Sorbitol present in MCG formulation may cause flatulence, diarrhea⁶.
3. Additives in gum like flavoring agent, Cinnamon can cause Ulcers in oral cavity and Licorice cause Hypertension.
4. Chlorhexidine oromucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue⁷.
5. Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers⁸.
6. Prolonged chewing of gum may result in pain in facial muscles and ear ache in children⁹.

COMPOSITION OF MGCs

Chewing gum consists of a neutral, tasteless and inert masticatory gum base and several non masticatory ingredients such as fillers, softeners, sweetener, flavour and texture regulating agents¹⁰. Gum base is an inert and insoluble nonnutritive product used as a support for the edible and soluble of the chewing gum (sugar, glucose, poly oils and flavors). The medicated chewing gum consist of core made up of various constituents as shown in Table 1. The optimal properties of active ingredient in MCG are shown in Table 2.

MANUFACTURING PROCESSES

Different methods employed for the manufacturing of MGCs can be broadly classified into three main classes namely:

1. Conventional/ traditional Method (Melting).
2. Freezing, grinding and tableting Method.
3. Direct Compression Method.

Table 2: Optimal properties of drug

Physicochemical Properties of Drug	pH independent solubility
	High Salivary Solubility
	Tasteless
Patient Related Factors	Non-toxic to oromucosa and salivary ducts
	Non-carcinogenic
	Should not cause tooth decay
	Should not cause oromucosa and teeth staining
	Should not affect salivary flow rate

1. Conventional/Traditional method (Melting)^{14,15}

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 carefully controlled room, the gum is cooled for upto 48 hours. This allows the gum to set properly. Finally the gum is cut in desired size and cooled at a carefully controlled temperature and humidity.

Limitation:

- Manufacturing of thermolabile may become challenging as elevated temperature is required during melting
- If the gum is highly viscous, accurate dosing is not possible
- Lack of precise form, shape, weight of dosage form
- Grinding and compression: difficult to formulate chewing gum as tablets due to high moisture content.

2. Freezing, grinding and tableting method¹⁶

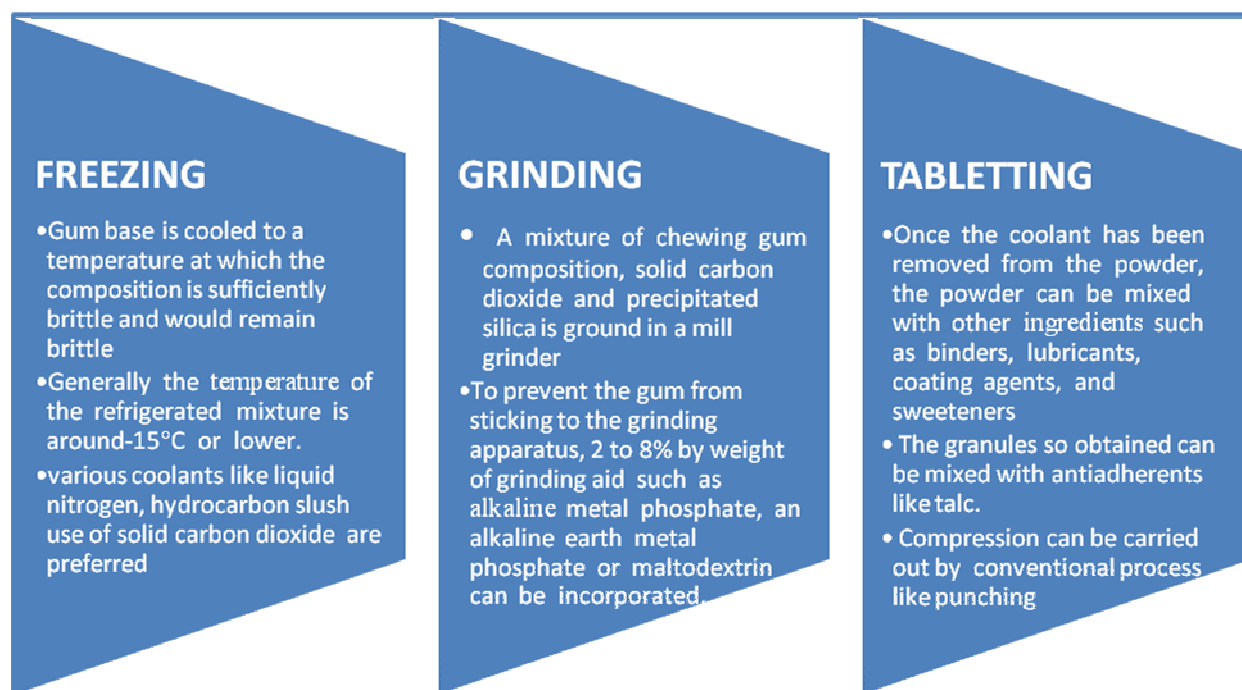


Figure 1: Steps of manufacturing by freezing, grinding and tableting

Limitation:

- High-tech, expensive equipments are required;
- Careful monitoring of humidity during manufacturing process becomes a challenge.

3. Use of Directly Compressible Chewing Gum Excipients:^{17,18}

The manufacturing process can be made easier and faster if a chewing gum is prepared by directly compression. Gums formed using compressible formulation are 10 times harder and crumble when pressure is applied resulting in faster release than conventional methods. The limitations of conventional manufacturing methods for medicated chewing gum such as melting & freezing can be overcome by the use of directly compressible gums. Pharmagum is one such compactable gum system developed by SPI Pharma. Pharmagum is a mixture of polyol(s) & 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). Pharmagum® is available in three forms namely S, M and C. Pharmagum® M has 50% greater gum base compared to Pharmagum®S. Pharmagum®S consists primarily of gum base and sorbitol. Pharmagum®M contains gum base, mannitol & Isomalt. Also another directly compressible gum which has made the production of medicated chewing gum easier is the Cafosa's Health in Gum (HIG), an innovative concept for the pharmaceutical industry. Health in Gum is an excipients, a directly compressible powder gum containing a mixture of ingredients, to which you only need to add APIs. Health in Gum is specially designed for in-house use in pharmaceutical facilities and does not require specific chewing gum production equipment. It can be compressed easily using standard tablet press. Health in Gum offers an innovative drug delivery system that benefits from all the advantages of chewing gum and also contributes to improved compliance. It has been created to simplify the manufacturing process of chewing gum in a quick and cost-effective way. It is directly compressible and works at room temperature, which allows the use of thermo-sensitive APIs. It is also available in three grades HIG 01, 02 and 03. HIG 01 and HIG 02 have same composition i.e.gum base, sorbitol, xylitol, and caking agent and plasticizer; only difference is that concentration of gum base in HIG 02 is slightly more than HIG 01. HIG 03 contains higher percentage of gum base than HIG 01 and 02 and also contains isomalt, sorbitol and anticaking agent.

SOME IMPORTANT FORMULATION ASPECT

1. Increased amount of softeners and emulsifiers in gum base fasten release whereas hard gum may retard.¹⁹
2. Cyclodextrin complexation or solubilisation technique increases aqueous solubility of drugs that are poorly water soluble.^{20,21}
3. A solid system of lipophilic active ingredients bound to the cation exchange resin permits a sustained drug delivery system.
4. Microencapsulation or agglomerations are the methods to modify and control the release of active ingredient^{22,23}.

FACTORS AFFECTING RELEASE OF ACTIVE INGREDIENT

1. **Contact Time:** The local or systemic effect is dependent on time of contact of MCG in oral cavity. In clinical trial chewing time of 30 minutes was considered close to ordinary use.
2. **Physicochemical properties of active ingredient:** Physicochemical properties of active ingredient plays very important role in release of drug from MCG. The saliva soluble ingredients will be immediately released within few minutes whereas lipid soluble drugs are released first into the gum base and then released slowly.
3. **Inter individual variability:** The chewing frequency and chewing intensity which affect the drug release from MCG may vary from person to person. In-vitro study prescribed by European Pharmacopoeia suggest 60 cycles per minute chewing rate for proper release of active ingredient²⁴.

4. **Formulation factor:** Composition and amount of gum base affect rate of release of active ingredient. If lipophilic fraction of gum is increased, the release rate is decreased.

EVALUATION OF MGCs

Uniformity of content²⁴

Unless otherwise prescribed or justified and authorised, MGCs with a content of active ingredient less than 2 mg or less than 2 per cent of the total mass comply with test A for uniformity of content of single-dose preparations. If the preparation contains more than one active substance, the requirement applies only to those active substances which correspond to the above conditions.

Uniformity of mass²⁴

Uncoated MGCs and, unless otherwise justified and authorised, coated medicated chewing gums comply with the test for uniformity of mass of single-dose preparations. If the test for uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required.

In-vitro drug release

It has been reported commercially that the drug release from MGCs 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.

Apparatus I. Compendial chewing gum apparatus

The chewing apparatus for MGC was adopted by Ph. Eur. in 2000²⁵. Figure 2 shows the construction of the apparatus. The chewing apparatus comprises a chewing chamber, two horizontal pistons, and a third vertical piston (tongue). The vertical piston operates alternatively with the two horizontal pistons and makes sure the gum stays in the right place between chews. If necessary, it is feasible to construct the machine so that at the end of the chew the horizontal pistons rotate around their own axes in opposite directions to each other to obtain maximum chewing.

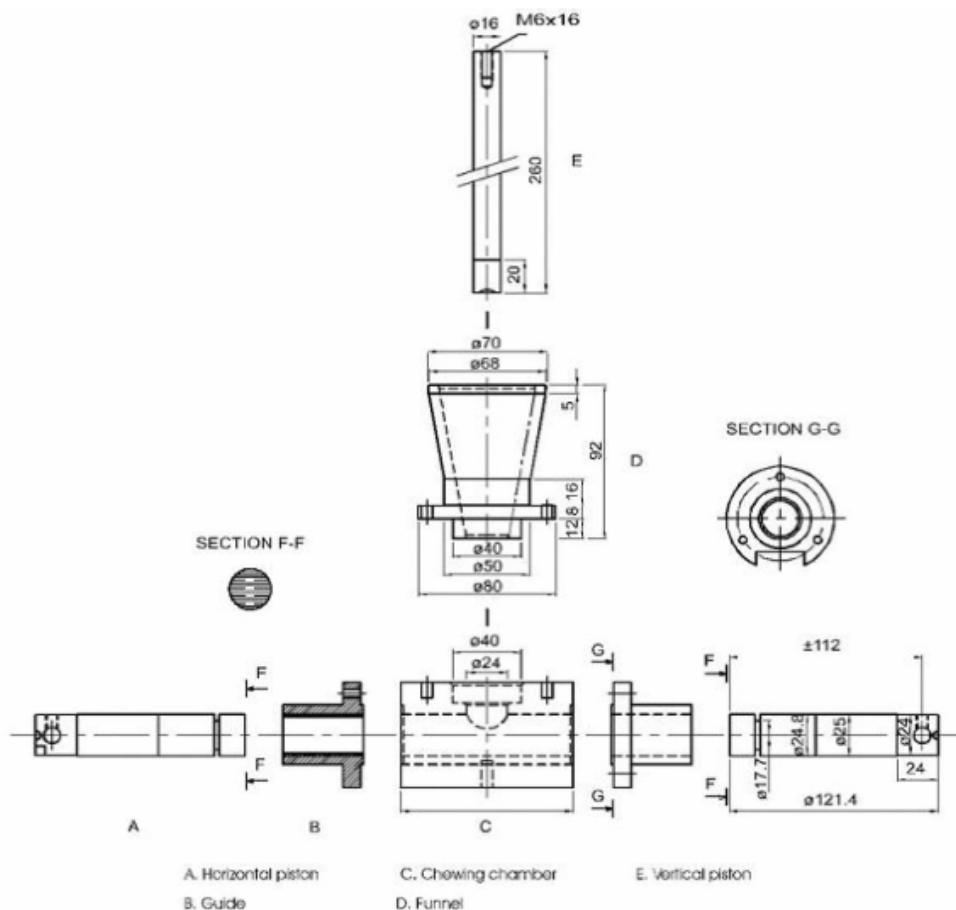


Figure 2: Construction of the Compendial chewing gum apparatus**Apparatus II Noncompendial chewing gum apparatus**

One of the noncompendial apparatus commercially available was designed by Wennergren²⁶. The schematic representation of the Wennergren chewing apparatus is shown in Figure 3. The chewing procedure consists of reciprocations of the lower surface in combination with a shearing (twisting) movement of the upper surface that provides mastication of the chewing gum and at the same time adequate agitation of the test medium. The upper jaw has a flat surface that is parallel to the central part of the lower surface. The small brim of the lower surface is angled upwards (45 degrees) so that the lower surface functions as a small bowl with a flat bottom. This bowl prevents the chewing gum from sliding during mastication.

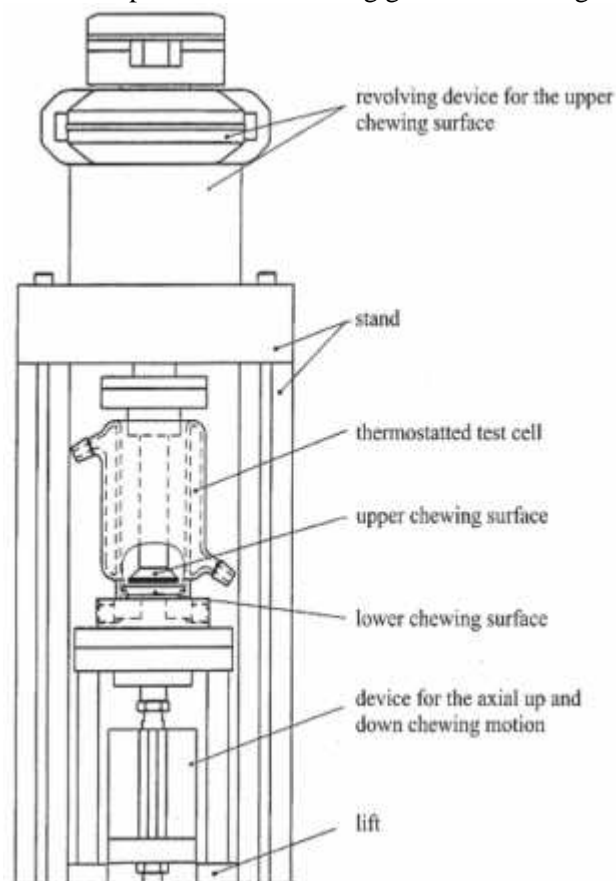


Figure 3: Schematic representation of unofficial single module chewing apparatus

In Vivo ‘Chew-Out’ Studies:²⁷

The in vivo release of active ingredient from chewing gum during mastication can be studied by recruiting a panel of sufficient numbers of tasters and scheduled chew-out studies. For the duration of the chewing process the drug contained within the MCG is released in the saliva and then it is either absorbed through oral mucosa or, if swallowed, it is absorbed through the gastrointestinal tract.

Release of drug in saliva:

Panel of volunteers is asked to chew the drug delivery device for a certain period of time and to assess the remaining quantity of active substance in the residual gum. In this way, the gums are really chewed and the formulation is subjected not only to the mechanical stresses of an artificial machine but also it undergoes all the phenomena involved in this process (increase of salivary secretion, saliva pH variation, swallowing and absorption by the oral mucosa, etc.) which can strongly influence the performance of the dosage form as well as the amount and rate of drug release. Optimized formulation with good consistency can be selected for there lease of drug in the saliva. Minimum four human volunteers can be selected (two male and two female). Volunteers are instructed to rinse their mouth with distilled water and allowed to chewing the medicated chewing gum for 15 minutes, so that its maximum release has to be taken. Sample of saliva are taken after 2, 4, 6, 8, 10, 12, 14 and 15 minutes. The saliva samples are made diluted in required solvent and absorbance is measured using suitable analytical method.

Dissolution test of residual MGCs: ^{28,29}

In this experiment, gums are tested by a panel of volunteers to verify the drug release process from the drug delivery system. Each person chews one sample of the tableted gum for different time periods (1, 5, 10 and 15 minutes). The residual gums are cut into small pieces, frozen and then ground till obtaining a fine powder. The residual drug content is determined by using suitable analytical method. The amount of drug released during mastication is calculated by subtracting the amount of residual active ingredient present in the gum from the total content, where as pharmacokinetics can be determined from withdrawn blood samples at specific time intervals. The prerequisites of human volunteers, person-to-person variability in the chewing pattern, chewing frequencies, composition of individual salivary fluid and flow rate of saliva are a few limitations of chew-out studies.

Urinary excretion profile of MGCs:

This method can be applicable only to those drugs which are excreted via urine. In that minimum four healthy human volunteer are selected for the study of formulations. Volunteers are strictly instructed that they should not take any medicine in the last 48 hours. They are fasted overnight, and emptied their bladder in the volumetric flask. Sample collection starts from blank of zero hour urine. Then sample collection is done on 15 minutes, 1, 2, 3, 4, 6, 7, 8, 10, 11, 12 and 24 hour intervals after administration of medicated chewing gum. The volunteers are asked to drink water at regular intervals of 30 minutes. and urine samples are analyzed by suitable analytical methods.

Buccal absorption test:

Human volunteer swirled fixed volume of drug solution of known concentration at different pH value of 1.2, 5, 6, 6.5, 7, 7.5, 7.8, 8.0, in the oral cavity for 15minutes and then expelled out. The expelled saliva is analyzed for drug content and back calculated for buccal absorption.

Texture analysis***Texture studies by instrument***

Instrumental texture analysis is mainly concerned with the evaluation of mechanical characteristics where a material is subjected to a controlled force from which a deformation curve of its response is generated. For evaluating texture properties of MCG a “compression” probe was used in this deformation method using the texture analyzer. Squashing solid and self-supporting samples enabled a number of textural properties to be evaluated, including hardness (peak force that results from a sample being compressed to a given distance, time, or % of deformation) and adhesiveness (stickiness-related to how a MCG adheres to the inside of the mouth surfaces during chewing). It is recommended to use a compression probe with a greater surface area than that of the sample being tested, so a compression platen probe of 50 mm ϕ was used. During evaluation, a constant force should be applied on the surface of self-supporting MCG and upon fracture it should be withdrawn. Through which, a deformation curve can recorded and interpreted.

Texture studies by human volunteer

For assessment of the product quality, volunteers have to just chew the product without swallowing for a particular time period. Then, they are allowed to give their experience that they felt appropriate for respective qualities of MCG product, i.e. product feel, product consistency, its taste, and total flavor lasting time during chewing the product

APPLICATION OF MGCs

MCGS are widely been used for its local effect in oral cavity and well as its systemic effects. The marketed formulation of MCGs are enlisted in table 3. Table 4 enlists the list of patent filed on MCGs.

Table 3: List of marketed MCGs

Therapeutic effect	Active pharmaceutical ingredient	Trade name
Local therapy		
Cariostatic- re-elevates plaque pH which lowers intensity and frequency of dental caries	Fluoride	Fluorette
Dental hygiene and for tooth whitening	Calcium as a tricalcium phosphate	Orbit white
		Happydent white
		Trident white
		Recaldent
Antibacterial agent – preventing tooth decay & to treat gingivitis, periodontitis, oral and pharyngeal infections	Chlorhexidine	VitaFlo CHX
		Advanced +
		HEXIT
Systemic therapy		
Pain relief- in treatment of minor pains, headache and muscular aches	Aspirin	Aspergum
Smoking cessation	Nicotine	Nicorette
		Nicotinelle
		NiQuitin CQ
Stomach & neutralization	Calcium carbonate	Chooz
General health	Vitamin C	Endykay
		Stamil
		Source
Enhanced brain activity	DHA & CCE	Brain
Alertness and lipolysis and have a thermo genic effect (increased energy expenditure) and reduce feeling of hunger	Caffeine	Stay alert
		Café coffee
	Guaran	Buzz gum
		Go gum
Diet	CR	Chroma slim
Reduces the symptoms associated with stress, anxiety and depression	Extracts of Ashwagandha, Passion Flower and Jujube Fruit and Calcium carbonate	Zoft stress gum
Symptomatic relief from post-menopausal syndrome	Extracts of Dong Quai Root, Black Cohosh Root, Damiana Leaf, Mexican Wild Yam Root	Zoft menopause gum
Appetite suppressant for weight loss	Extracts of Hoodia gordonni -- nature's calcium channel blocker	Slim n trim
		Chew away gum
Increases male sexual desire and performance	Extracts of Hawthorn Berry, Horny Goat Weed, Damiana Leaf, Muira Puama Root, Ginkgo Biloba Leaf, Ginseng Root, Catuaba Bark Extract, Saw Palmetto Berry	Zoft virility gum

Table 4: List of patent filled on MCGs

Inventor	Title	Patent no.	Issued on date
TESTA, Emilio	Process for making a medicated chewing gum with a pleasant taste Containing an inclusion complex	EP 0 909 166 B1	28.03.2001
BADETTI, Rolando	Composition for medicated chewing gums, process for manufacturing the Same and tablets so obtained	EP 1 162 946 B1	16.12.2009
BADETTI, Rolando	A process for the preparation of medicated chewing gums	EP 1 408 769 B1	13.01.2010
Kenneth A. Bartlett, Essex Fells, and William J. Schultz.	Chewing gum tablet	US 2262097	11.11. 1941

Theodore C. Goggin	Amphetamine chewing gum	US 2536168	02.01.1951
Frederick G. Merckel. Laszlo Reiner.	Fluorine chewing gum process	US2627493	03.02.1953
Harold M. Sellers	Chewing gum containing gas And a medicament	US 3316154	25.04. 1967
John H. Litchfield and Victor G. Vely	Anticaries chewing gum	US 3651206	21.03 1972
	Dialdehyde-containing anti Caries chewing gum Compositions	US 3679792	25.07.1972
	Aldehyde-containing anticaries chewing gum composition	US 3749765	31.07 1973
Carsten Andersen and Morten Pedersen	Chewing gum composition with Accelerated, controlled release of active agents	US 5487902	30.01. 1996
Barbara Eisenstadt, Penny A. Cash and Abraham I. Bakal	Chewing gum containing cough Suppressing agent	US 5846557	08.12. 1998
Subraman R. Cherukuri, John M. Pinney, Jack E. Henningfield, Aradhana Sasan, Edward J. Cone, Saul Shiffman, Joe Gitchell, Carlos D. Malvestutto	Medicated chewing gum delivery System for nicotine	US 6,344,222 B1	05.02. 2002
Henry T. TYRPIN, Michael P. Russell, David L. Witkewitz, Sonya S. Johnson, Ronald L. Ream, Christine L. Corriveau	Caffeine coated chewing gum Product and process of making	US 6,444,241 B1	03.09. 2002
Pardeep NijhaWan	Medicated gumstick for treatment In anti-inflammatory conditions And prophylaxis against nsaid Gastropathy	US 2007/0003490 A1	04.01. 2007
Carsten Andersen	Tobacco alkaloid releasing chewinggum	WO 2006000232 A1	05.01. 2006
Terence Cosgrove, Beth Mary Foster, Erol Ahmed Hasan, Hongli Yang	Medicatedchewinggum	WO 2008104547 A1	04.09. 2008

Local effect

- To re-elevate plaque pH which lowers intensity and frequency of dental caries.
- For tooth whitening
- To inhibit plaque growth.
- To treat gingivitis, periodontitis, oral and pharyngeal infections.

Systemic effects

Drug may be absorbed from oral cavity and directly reach to systemic circulation or it may reach to GIT and absorbed therein. In both the cases, the drug can be used for various indications like pain, smoking cessation, obesity, Xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety, etc.

REGULATORY ISSUES

The first monograph on medicated chewing gum was published in the European Pharmacopoeia in 1998. Use of a solid tasteless masticatory gum base and coating, if necessary, to protect from humidity and light, is described. Being a single dose preparation, medicated chewing gum has to comply with tests for uniformity of content and uniformity of mass. In addition, the microbial quality has to be ensured²⁴.

Release testing is prescribed to control the bioavailability of the drug(s). In the year 2000 the first monograph on a principle chewing apparatus and a procedure for the determination of drug release from medicated chewing gum was published in the European Pharmacopoeia.

STABILITY

- The stability of chewing gum is comparable to that of most other solid delivery systems. Chewing gum contains little water (2–5%) and the water can be bound to other components in the formulation and is therefore not very reactive. The water activity (a_w) in chewing gum is normally below 0.6 and typically 0.4– 0.5. If the water content is very critical for the stability of a drug, the chewing gum can be manufactured without water (less than 0.2%). However, it will often make the product hygroscopic and affect the texture.
- The low water content also inhibits microbial growth in the chewing gum during storage.
- Antioxidants are normally added with the gum base. Furthermore, the product can be protected against oxidation by a sealed coat and by an appropriate packaging.
- For very temperature-labile components, e.g., enzymes, during mixing, the process temperature of 50–60 ° C may create a stability problem. However, it is possible to operate the process at a lower temperature to avoid this issue³⁰.

CHALLENGES IN FORMULATION OF MCGs

The potential of medicated chewing gums has not yet been fully explored. The manufacture of chewing gum requires different technology to that used in pharmaceutical production. Standard chewing gum manufacturing requires specific equipment and facilities involving hot-melt processes, which are usually rare in the pharmaceutical industry. Another reason why medicated chewing gum has not yet been fully explored is because of therapeutic uncertainty related to the drug delivery method namely, a patient's mechanical chewing action. The gum's therapeutic effect depends on chewing, and as each person has their own chewing force, frequency and time, the results can vary. Manufacturers must also take into account that chewing gum has new parameters to monitor such as desired taste, texture, mouth-feel, appearance, interaction between ingredients, flavoring etc. which influences the final product. It is necessary to meet these challenges for the success of this drug delivery system.

SAFETY ASPECTS³¹

Generally, today it is perfectly safe to chew chewing gum. Previously, hard chewing gum has caused broken teeth. Extensive chewing for a long period of time may cause painful jaws muscle, and extensive use of sugar alcohol containing chewing gum may cause diarrhoea. Long term frequent chewing of gum has been reported to cause increased release of mercury vapors from dental amalgam fillings. However MCGs does not normally require extensive chewing, or consumption to great extent. Flavors, colour etc. may cause allergic reactions. Overdosing by use of chewing gum is unlikely because a large amount of gum has to be chewed in a short period of time to achieve this. Swallowing pieces of medicated chewing gum will only cause minor release of the drug because the drug can only be released from the gum base by active chewing. As a general rule, medicated chewing gum (like other medicines) should be kept out of reach of children, if required; drug delivery may be promptly terminated by removal of the gum.

FUTURE TRENDS

MCGs is the potential drug delivery system to treat the disease by its local and systemic action of drug. It can be utilised for its systemic drug delivery where the rapid onset of action is needed like motion sickness, pain, nausea, allergy, infection and hypertension provided that the drug is easily absorbed through oral mucosa. For local action of drug in oral cavity it has various applications like the treatment of toothache, periodontal disease, bacterial and fungal infections, aphthous and dental stomatitis, which require a long period of drug release to the oral cavity.

As chewing gum is needed to be retained in mouth for long time, persistent feel of flavour and taste masking becomes the biggest challenge for formulation. The expediency and high acceptability of chewing gum along with better flavouring, sweetening and taste masking will lead to improved compliance. New gum base formulations that are compressible, digestible and potential biodegradable will extend applications for chewing

gum, but the influence of these bases on drug release must be well investigated. Drug entrapment and release is still being developed on a product-by-product basis. By using optimal release systems and an appropriate combination of flavours, more drugs will be successfully formulated in chewing gum in the future.

The problem with consumption of chewing gum is it sticks to the surface where it is thrown after chewing. Moreover Chewing gum of the future will most likely be composed such that it can be removed from indoor and outdoor surfaces by conventional cleaning method and technology. It will disappear by means of nature's own remedies like water, light and bacteria.

Various class of medicaments can be investigated for incorporated in chewing gum. Drug used for dental care like treatment for sensitive teeth and for tobacco stain prevention, throat diseases, nausea, allergy and pain are being investigated. Food and pharmaceuticals industries has the opportunity to deliver nutraceuticals through this formulation. Chewing gum containing probiotics or soluble fiber have been launched. Highly successful nicotine chewing gum is the evidence of systemic buccal drug delivery giving faster onset of action and overcoming first pass metabolism.

A few decades ago, the only treatment for some disease was surgical procedure but now more and more disease can be treated with Novel Drug Delivery Systems (NDDS). Moreover, there is need of reformulation of existing drugs into NDDS to extend or protect product patents thereby delaying, reducing or avoiding generic erosion at patent expiry. To provide additional patient benefit, meet competitive challenge and to conserve revenue, the research on NDDS is gaining importance now days. Generally NDDS takes time to become popular and acceptable among the patient, chewing gum could be highly convenient and advantageous drug delivery system

CONCLUSION

MCGs is most convenient, self medicated, easily administered without water and highly patient compliant. Its capability to allow local and systemic delivery of drug makes it preferable over other delivery system. Thus in upcoming years it is sure that the medicated chewing gum would be most popular drug delivery system.

REFERENCES

1. Commission of the European Communities CPMP list of allowed terms for the pharmaceutical dosage form, route of administration, container, and closure and administration devices, III/3593/91, 1991.
2. Morjaria Y., Irwin W.J., Barnett P.X., Chan R.S., Conway B.R., In Vitro Release of Nicotine From Chewing Gum Formulations, *Dissolution Technologies.*, 2004,12-15.
3. Conway B., Chewing Gum as a Drug Delivery System, *The Drug Delivery Companies Report.*, 2003, 33-35.
4. Kamimori G.H., Karyekar C.S., Otterstetter R., Cox D.S., Balkin T.J., Belenky G.L., The rate of absorption and relative bioavailability of caffeine, *Int J Pharm.*, 2002, 234(1-2), 159-67.
5. Jacobsen J, Christrup L.L, Jensen N-H, Medicated Chewing Gum., *Am J Drug Deliv.*, 2004, 2 (2), 75-88.
6. Goldberg L.D., Ditchek N.T., Chewing gum diarrhea., *Am J Dig Dis.* 1978, 23(6), 568.
7. Addy M., Roberts W.R., Comparison of the bisbiguanide antiseptics alexidine and chlorhexidine. II. Clinical and in vitro staining properties., *J Clin Periodontol.*, 1981, 8(3), 220-30.
8. Munksgaard EC, Nolte J, Kristensen K., Adherence of chewing gum to dental restorative materials., *Am J Dent.*, 1995, 8(3), 137-9.
9. Weil A.T., Coca leaf as a therapeutic agent., *Am J Drug Alcohol Abuse.* , 1978, 5(1), 75-86.
10. Cherukuri, S.R., Friello, D.R., Jewell, M. And D'Amelia, R.P., Gum base, chewing gum containing same and method, 1982, U.S. Patent 4,352,822.
11. Christrup, L.L., Rasmussen, S.N., Rassing, M.R., Chewing gum as a drug delivery system., *Farmaci. Sci Ed.*, 1988, 16, 44-47.
12. Khatun and Sutradhar., Medicated chewing gum: An unconventional drug delivery system., *International Current Pharmaceutical Journal.*, 2012, 1(4), 86-91.
13. Chaudhary S.A and Shahiwala A.F., Medicated chewing gum- a potential drug delivery system, *Expert opin. Drug. Deliv.*, 2010, 7(7), 871-885.

14. Naik H., Gupta S., et al., Medicated Chewing Gums-Updated Review, International Journal of Pharmaceutical Research And Development, 2010,2(11),66-76.
15. Parmar V.W and Thosar M. ,A Comprehensive Review On: Medicated Chewing Gum., Int J Res Pharma Biomedical Sci., 2012, 3(2),894-907.
16. Pagare PK et al., Medicated Chewing Gum: A Novel Drug Delivery System., J Applied Pharma Sci ., 2012, 2(6), 40-54.
17. Gadhavi A.G. et al., Medicated Chewing Gum-A 21st Century Drug Delivery System, International Journal Of Pharmaceutical Science And Research, 2011,2(8), 1961-1974
18. <http://www.spipharma.com/ProductsFolder/120ParmaGum/120Pharmagum.html>
19. Jacobsen J., Christrup L.L., Jensen N.H., Medicated Chewing Gum: Pros and Cons., Am J Drug Deliv,2004, 2 (2),75-88.
20. Barabolak R.; Hoerman K.; Kroll N., Chewing gum profiles in the US population., Community Dent Oral Epidemiol, 1991, 19:125-6.
21. Jacobsen J., Bjerregaard S., Pedersen M.: Cyclodextrin inclusion complexes of antimycotics intended to act in the oral cavity--drug supersaturation, toxicity on TR146 cells and release from a delivery system. Eur J Pharm Biopharm,1991,48(3),217-24.
22. Gudas V.V., Reed M.A., Schnell P. G.,Tyrpin H.T., Russell M.P.,Witkewitz D.L.,Method of controlling release of caffeine in chewing gum,1998, US Patent 6,165,516
23. Yang Robert K., Encapsulation composition for use with chewing gum and edible products,1988,US Patent 4,740,376.
24. European pharmacopoeia. Strasbourg: Directotate for the quality of medicine and health care of the council of Europe. Medicines. Chewing gum 2009; 6th edition : 278.
25. European Directorate for the Quality of Medicines, Council of Europe, European Pharmacopoeia. Suppl. General Chapter 2.9.25: Chewing Gum, Medicated Release from. 3rd Ed. Strasbourg, France; European Directorate for the Quality of Medicines, Council of Europe; 2000:104.
26. Kvist, C., Andersson, S.B., Fors, S., Wennergren, B., Berglund, J., Apparatus for studying in vitro drug release from medicated chewing gums., Int J Pharm. 1999,189 (1), 57-65.
27. Maggi L et al. Preparation and Evaluation of Release Characteristics of 3Tab Gum, a Novel Chewing Device., European Journal Of Pharmaceutical Sciences, 2005,24,487-493.
28. Savaliya P et al., Chewing Gum: A Modern Era of Drug Delivery., Int Res J Pharm. ,2011, 2(10), 7-12.
29. Madan N et al. Chewing Gums for Optimal Health. ,Chronicles Of Young Scientists., 2011, 2(1), 7-10.
30. US Angel. Chewing gum and process for manufacture thereof.1994, EP 2078186.
31. Margrethe Rømer Rassing and Jette Jacobsen., Medicated Chewing Gum. Modified release drug delivery technology.2003 Marcel Dekker, 419-429.
