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A REVIEW ON MEDICATED CHEWING GUM

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ABSTRACT

Oral drug delivery system is most common route of administration which is highly accepted by the patients. The reasons behind such popularity is due to its ease of administration. The main objective of' the study is to provide an existing evidence concerning a possible therapeutic effect of sugar free chewing gum for patients. MCG has more potential uses in pharmaceuticals, over the counter medicines and nutraceuticals. Medicated chewing gum (MCGs) is effective locally as well as systemically in dental caries, smoking cessation, pain, obesity, xerostomia, acidity, allergy, nausea, motion sickness, diabetes, anxiety, dyspepsia, osteoporosis, cough, common cold etc. MCGs are not only used by some special population groups who are having swallowing difficulties such as children and the elderly, but also popular among the young generation. Hence it was proven to be an excellent drug delivery system for self-medication. This review article gives detailed information regarding history, advantages, disadvantages, formulation, manufacturing process, limitation of manufacturing process, factors affecting release of active substance, quality control tests for chewing gum, importance, stability studies, future trends and patent filled on MCGs.

KEYWORDS

Medicated chewing gum, Dental caries, Medicament, Xerostomia, Neutraceuticals and Dyspepsia.

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INTRODUCTON

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. MCG is considered as vehicle or a drug delivery system to administer active principles that can improve health and nutrition[1]. MCG represents a new system with potential uses in pharmaceuticals, over the other counter medicines and nutraceuticals. Chewing gum is being used

from centuries to clean the mouth and freshen the breath. A MCG containing Acetyl Salicylic Acid was commercially introduced in 1928[2]. Chewing gum was approved in 1991 as a term for pharmaceutical dosage form by the commission of European Council. Approximately 80 to 100 million, 55% of it being sugar free gum. Seventy nine percent of the chewing gums sold in Switzerland are sugar-free, 70% of the consumers are teenagers, and girls chew more gum than boys. Chewing gum was initially sweetened with sugar, which contributed to dental caries. Today, however, more than 50% of chewing gum sold in Europe is sweetened with sugar substitutes (polyols). Clinical evidence shows that sugar substituted chewing gum does not lead to dental caries, because the polyols do not lead to a clinically relevant production of metabolic acids in dental plaque. The objective of this systematic literature review is to appraise existing evidence concerning a possible therapeutic/anti-carcinogenic effect of sugar-free chewing gum for patients. MCG represents the newest system with potential uses in pharmaceuticals, over the counter medicines and nutraceuticals[3,4].

History of Medicated Chewing Gum

One thousand years ago, the May an Indians chewed tree resin from the sapodilla tree in order to clean their teeth and freshen the breath[5,6]. The first patent was filed in 1869 and was issued to Mr. W. F. Semple in Ohio under U.S. Patent No. 98,304, for the production of chewing gum.

The first medical chewing gum, Aspergum R, was launched in1928[7,8]. This chewing gum contains the analgesic substance acetylsalicylic acid known from Aspirin R tablets. Until 1978 Chewing gum did not gain acceptance as a reliable drug delivery system, when nicotine chewing gum became available. Dimenhydrinate is another medical chewing gum which is commercially available and is used for motion sickness.

Chewing gum has an old and long history, in 50 AD; the Greeks sweetened their breath and cleansed their teeth by using mastiche, a resin from the bark of mastic tree. (The English word "masticate" is derived from the root word mastiche) At the beginning of its history this product was not so much accepted by the public. Spruce gum became the first chewing gum product which was manufactured in 1848 commercially Called as "STATE OF MAINEPURE SPRUCE GUM. "However, its use was eventually replaced by paraffin, which is still being chewed in some areas.

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. The product which contains liquorice and rubber dissolved in alcohol and naphtha, was initially intended to be used as a dentifrice. At the time of 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 sorbital as a sugar substitute. HARVEY's was the first brand for which marketing is 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 gums.

ADVANTAGES[9,2,1]

Convenient – promoting higher compliance
Discreet- less stigmatization
Administration without water can be taken anywhere
Excellent for acute medication
More advantage for those patients who feel difficult in swallowing the tablets
Pleasant taste
Candidacies and caries
Highly acceptable by children
The active compounds absorbed at oral level avoid the hepatic circulation and the associated metabolism.

Effect on dry mouth (xerostomia)

Dry mouth is one of the side effect of many types of medicament (e.g. antidepressants) and it is also the part of the symptomatology of several diseases

(e.g. sjogren's syndrome-an autoimmune disorder characterized by lymphocytic infiltration of the salivary and lacrimal glands)[10]. Chewing gum stimulates salivary secretion thereby decreasing dryness in the mouth.

DEMERITS OF MCGS

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[11].

Sorbitol present in MCG formulation may cause flatulence, diarrhea[12].

Additives like flavoring agent, Cinnamon which are present in the gum can cause Ulcers in oral cavity and Liquorice cause Hypertension.

Chlorhexidine oro mucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue[13].

Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers[14].

Prolonged chewing of gum may result in pain in facial muscles and ear ache in children[15]

Mechanism of Drug Transport[16-18]

During the chewing process, most of the medications contained within the drug product are released into the saliva and are either absorbed through buccal mucosa or swallowed or absorbed through GIT.

Fickian diffusion is the major pathway of drug transport across buccal mucosa. Passive diffusion does not occurs in accordance with the pH partition theory. Some carrier mediated transport also observed. Equation for drug flux is:

$J = DKp/\Delta Ce$

Where, J = drug flux

D = diffusivity

Kp = partition coefficient

ΔCe = concentration gradient

h = diffusional path length

The flux may be increased by decreasing the diffusional resistance of the membrane by making it more fluid, increasing the solubility of the drug in the saliva which is adjacent to the epithelium or enhancing the lipophilicity through pro-drug modification. Because of the barrier properties of the tight buccal mucosa, the rate limiting step is the movement of the drug molecules across the epithelium.

The two major pathways of permeation that occurs across the buccal mucosa are transcellular and paracellular. Permeability coefficient typically ranges from 1x10-5 to 2x10-10 cm/s. The drug transport pathway across oral mucosa is studied by using:

Microscopic techniques using fluorescent dyes

Autoradiography and

Confocal laser scanning microscopic procedures

FACTORS AFFECTING MUCOSAL DRUG DELIVER[19-21]

Membrane factor

Difference in permeability and thickness not only affect the rate and but also the extent of drug reaching the systemic circulation. Keratinisation and composition also affect systemic mucosal deliver. Other factors like absorptive membrane thickness, blood supply, blood or lymph drainage, renewal rate of cell, and enzyme content will also govern the rate and extent of drug absorption.

Environmental factor

Saliva

Saliva is composed of 99% water and the pH ranges between 6.5 to 7.5 depending upon the flow rate and location. And increase in the salivary flow rate leads to the secretion of watery saliva. Stimulated saliva secretion affects the film thickness and aids in the easy migration of the test compounds. Salivary pH is one of the important parameter that is to be considered for the passive diffusion of the unionized drug.

Salivary glands

Drug delivery system shall be placed either over a duct or adjacent to the salivary duct because it may result in excessive washout of drug or rapid dissolution of the system which makes it difficult to achieve high local drug concentration.

Chewing time and chewing rate

Time should be around 20 to 30 min because the chewing rate may also affects the drug release. The average chewing rate is about 60 chews/min.

Aqueous solubility of the drug

Release rate of the water soluble drug (solubility > 1:10) about7 5% or more during 5mins of chewing and 90% or more during 15mins of chewing at a rate of 60 chews per min. Drug with the aqueous solubility between 1:10 and 1:300 demonstrate upto 60%release during ten minutes of chewing and between 60% and 90%when the gum is chewed for 15mins. The release of the drug which is only slightly water soluble can only be expected to be small i.e. less than 5% even if the gum is chewed for 30mins.

% of drug

The release rate of fluoride from a chewing gum (1g) containing 0.1 mg and 1mg NaF (aqueous solubility 1:25) has been compared. The percentage of the drug retained in the gum for two formulations are similar. Indeed the percentage released for 0.1 mg and 1mg fluoride are very similar after 8mins. At 75% and 80%respectively.

Contact Time

Contact time of MCG in oral cavity is responsible for local or systemic effect. Chewing time of 30 minutes was considered close to ordinary use in the clinical trails.

Physicochemical properties of active ingredient

Properties of the active ingredient plays a very important role in the drug release from MCG. The ingredients which are soluble in saliva will be immediately released within few minutes whereas lipid soluble drugs are released first into the gum base and then released slowly.

Inter individual variability

Both the frequency of chewing and intensity of chewing affect the drug release from MCG as it 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 ingredient[22].

Formulation factor

Both the composition and amount of gum base affect the release rate of active ingredient. If lipophilic fraction of gum is increased, the rate of release is decreased[22].

Composition of Medicated Chewing Gum[23]

Chewing gum consists of the following ingredients like natural or synthetic gums and resins, sweetened with sugar, corn syrup, artificial sweeteners and may also contain coloring agents and flavor. Natural gum Chicle is the basic raw material for all chewing gums, obtained from the sapodilla tree. Other natural gum or synthetic materials like polyvinyl acetate and similar polymers can be used as gum base because chicle is very expensive and difficult to procure. Typically Chewing Gum comprises two parts viz.

Water Insoluble Gum Base Includes Elastomers, Plasticizers, Resins, Fats, Oils, and Inorganic Fillers.

Elastomers

Elastomer provides elasticity and controls gummy texture. Natural elastomer which is a natural rubber like Latex or Natural gum such as Jelutong, Lechi Caspi, Puerile, Chicle.

Plasticizers

Which are used to regulate cohesiveness of product and are divided into Natural and Synthetic Natural Plasticizers - Natural resin esters like Glycerol esters or partially hydrogenated resin, Polymerized glycerolesters, Glycerol esters of partially dimerized resin and Pentaerythritol esters of resin. Synthetic Plasticizers - Terpene resins derived from α-pinene and/or d-limonene.

Fillers or Texturizers

Provide texture, improve chewability and provide reasonable size of the gum lump with low dose drug. Commonly used fillers are Magnesium and Calcium Carbonate, Ground Limestone, Magnesium and Aluminium Silicate, Clay, Alumina, Talc, Titanium Oxide and Mono/ Di/ Ttri Calcium Phosphate.

Water Soluble Portions Contain Bulk Sweeteners, High intensity Sweeteners, Flavouring agents, Softners, Emulsifiers, Colours and Antioxidants, 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.

Colourants and Whiteners

It may include FD and C type dyes and lakes, fruit and vegetable extracts, Titanium Dioxide.

Sweeteners

These are of two types, Aqueous and Bulk. Aqueous Sweeteners 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 Sweeteners include Sugar and Sugarless components. Sugar components include Saccharides like Sucrose, Dextrose, Maltose, Dextrin, Fructose and Galactose. Sugarless components include sugar alcohols such as Sorbitol, Manitol, Xylitol, Hydrogenated Starch Hydrolysate. Those artificial sweetners of High intensity can also be included to provide longer lasting sweetness and flavour perception e.g. Sucralose, Aspartame, salt of Acesulfame, Alitame, Saccharin, Glycyrrhizin, Dihydrochalcones.

Bulking Agents

Bulking agents are used when the low calorie gum is desired. Examples of low calorie bulking agents include Polydextrose, Oligofructose, Inulin, Guargum hydrolysate, Indigestible Dextrin.

Flavouring Agents

A variety of flavouring agents are used to improve flavour in chewing gum includes essential oils, such as Citrus oil, fruitessences, Peppermint oil, Spearmint oil, Mint oil, Clove oil and Oil of Wintergreen. Artificial flavouring agents can also be used.

Active Component

The active pharmacological agent may be present either in core or coat or in both of the MCGs. The proportion may vary from 0.5-30% of final gum weight. An active agent which is small, unionized, lipophilic and enzymatically stable is found to be absorbed more readily. Only those Ingredients which are soluble in saliva will be completely released within 10-15 minutes of chewing whereas lipid soluble ingredient will dissolve in the gum base and thereafter be slowly and completely absorbed. The coating can be applied as a film of polymers, waxes, sweeteners, flavours and colours or a thick layer of sugar or sugaralcohol[24].

MANUFACTURING PROCESSES

Manufacturing of MGCs can be broadly divided into three main classes namely:

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

Conventional/Traditional method (Melting)[25,26]

The gum base components 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. Later the gum is sent through a series of rollers that forms into a thin, wide ribbon. Sugar coating is added during the process 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. At the end of this method 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

Accurate dosing is not possible, if the gum is highly viscous.

Lack of shape and weight of dosage form

In grinding and compression it is difficult to formulate chewing gum as tablets due to high moisture content.

Cooling, grinding, and tabletting method

One other method to provide a chewing gum with desired taste, color, and flavor is to mix gum base with favorable and suitable sweeteners, corn syrups, starches, flavoring agents, and colorants, and then refrigerate and cool it by a freezer apparatus or by contacting with a coolant like carbon dioxide to a temperature below −15°C which is therefore crushed and pulverized with a cutter or grinding apparatus to obtain minute particles then these finely ground particles are heated to a temperature which makes them adhere to each other and form a slick and uniform bulk with consistent texture and

low specific gravity. If the fragments are such that they do not self-adhere, low pressure would be applied manually or mechanically before they are warmed to the normal room temperature to thereby promote self-adhesion.

The cooling and grinding steps can be combined by cooling the grinding apparatus. After the grinding step, we can let the coolant (if used) evaporate and disappear from our desired composition. For tabletization, compressing punches may be needed but an anti-adherent agent should be applied to avoid sticking to surfaces of punches[27].

Limitation

High-tech, expensive equipments are required;

Careful monitoring of humidity during manufacturing process becomes a challenge.

Use of Directly Compressible Chewing Gum Excipients[28,29]

The manufacturing process can be made easier and faster if a chewing gum is prepared by directly compression. Gums which are formed by using compressible formulation are 10 times harder and crumble when pressure is applied resulting in faster release than conventional methods. Melting and freezing which are the limitations of conventional manufacturing methods 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) and or sugars with a chewing gum base. It is also available in the form of directly compressible powder, free flowing powder which can be compacted into a gum tablet using conventional tablet press thus enabling rapid and cost development also low for a gum delivery system. They are manufactured under the conditions of CGMP and complies with Food Chemicals Codex specifications as well as with FDA, so they can be considered as "Generally regarded as safe" (GRAS). S, M and C are three available forms of Pharmagum®. Amomg those 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 and Isomalt.

Health in Gum (HIG) is one of the innovative drug delivery system that offers 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 not only directly compressible and but also 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 more than that of the HIG 01. As HIG 03 contains higher percentage of gum base than HIG 01 and 02 and also contains isomalt, sorbitol and anti-caking agent.

Problems associated with manufacturing chewing gums

Capping, lamination, picking, and sticking are the most common processing problems[30].

In the first method, one of the problems is that the inordinate content of moisture in the matrix may cause a low viscosity which reduces the shear and compressive forces, indeed more gum base particles are more likely to dissociate and float[27].

Heating and melting can make controlling the accuracy and uniformity of the drug difficult[27].

It is hard to provide sanitary conditions to make MCGs[27].

In the second method, moisture content of chewing gum may cause the gum jam to the blades and punches of apparatus, screens, surfaces, and chamber's wall[30].

In the second method caking and balling of the gum prevent formation of gum fragments[27].

In the third method, ejection of final compressed mass from the mixer is difficult and may stuck up into the tubes and stick to punches[31].

Forming a low calorie chewing gum has resulted in a gum with hard chew, poor texture, and bad taste or off-taste[32].

Bad smell and undesired taste of ingredients applied in the compound[33].

Sugar spots or lumps may appear in the final texture and cause undesired feeling[34].

Some ingredients and active agents can irritate mucosa[33].

High temperature to facilitate the mixture of gum base, leads to spoil other ingredients[33].

Water elimination from final formulation requires advanced techniques to avoid the hardness ofgum[33].

EVALUATION OF MGCs

Uniformity of content[35]

Unless otherwise prescribed or justified and authorised, MGCs with a content of active ingredient less than 2 mg or less than 2 percent of the total mass complies with the test A in the 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 mass[35]

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

In-vitro drug release

Drug release from the MGCs has been reported as per the specification given in European Pharmacopoeia and is determined by applying a mechanical kneading procedure to a piece of gum which is placed in a small chewing chamber containing a known volume of buffer solution.

Apparatus I. Compendial chewing gum apparatus

For the MCGs the chewing apparatus was adopted by Ph. Eur. in 2000[36]. Figure No.1 shows the construction of the apparatus. Chewing apparatus consists of a chewing chamber, two horizontal pistons, and a third vertical piston (tongue). Vertical piston operates alternatively along 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.

Apparatus II Noncompendial chewing gum apparatus

One of the noncompendial apparatus commercially available was designed by Wennergren[37]. The schematic representation of the Wennergren chewing apparatus is shown in Figure No.2. The process involves both the 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. Sliding of gum during mastication is prevented by the bowl.

In Vivo 'Chew-Out' Studies[38]

In the *In-vivo* chew-out studies we can determine the release of active ingredient from chewing gum during mastication by recruiting a panel of sufficient numbers of tasters and scheduled chew-out studies. Throughout 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. The gums are really chewed and the formulation is subjected to the mechanical stresses of an artificial machine and it undergoes many phenomena which are involved in this process (increase of salivary secretion, saliva pH variation, swallowing and absorption by the oral mucosa, etc.) which can strongly influence not only the performance of the dosage form but also the amount and drug release rate. 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). Instructions for Volunteers include rinsing of their mouth with distilled water and allowed to chew 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[39,40]

It involves the testing of gums 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). Gums are cut into small pieces, frozen and then ground till obtaining a fine powder and 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, whereas pharmacokinetics can be determined from withdrawn blood samples at specific time intervals. Here, the prerequisites of the 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 is applicable only to those drugs which are excreted through urine. In this method it involves minimum four healthy human volunteer are 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. Sample collection is done at different time periods of 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 15 minutes and then expelled out. The saliva expelled by the volunteers is analyzed for drug content and back calculated for buccal absorption.

Texture analysis

Texture studies by instrument

This method is mainly related 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 ø 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

Here the product quality can be assessed, 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 having both local effect in oral cavity and well as its systemic effects. Hence, they are widely been used. The marketed formulation of MCGs are enlisted in Table No.1 and Table No.2 enlists the list of patent filed on MCGs:

REGULATORY ISSUES

The first monograph on medicated chewing gum was published in the European Pharmacopoeia in

1998. It describes the use of a solid tasteless masticatory gum base and coating, if necessary, to protect from humidity and light, is described. Medicated chewing gums being a single dose preparations, they has to comply with tests for uniformity of content and uniformity of mass. In addition, the microbial quality has to be ensured[35].

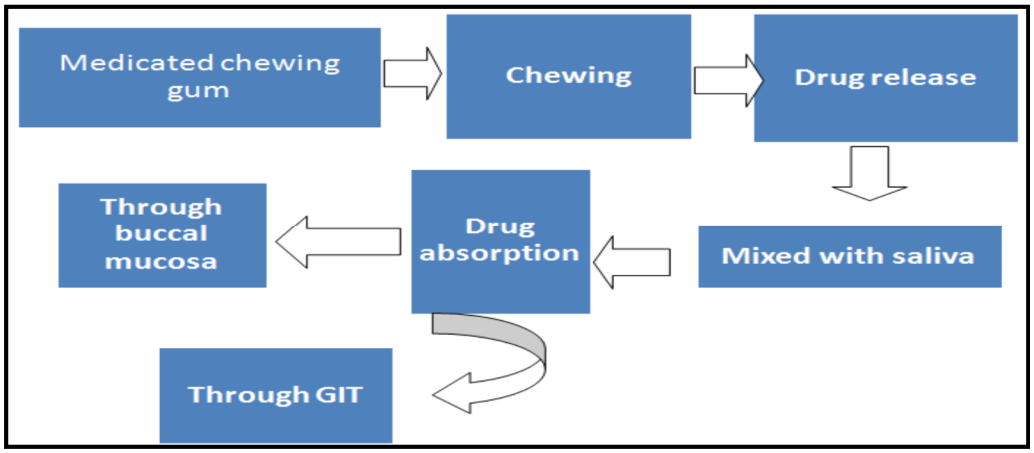
Release testing is prescribed to control the bioavailability of the drug(s). In the year 2000 the first monograph on a principle chewing apparatus and a procedure for the determination of drug release from medicated chewing gum was published in the European Pharmacopoeia.

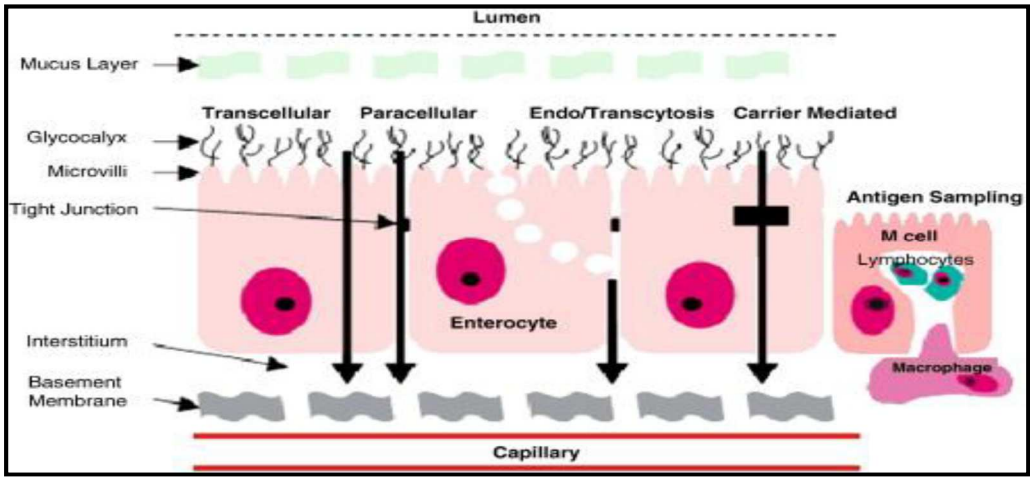
Table No.1: List of marketed MCGs

S.No	Therapeutic effect	Active pharmaceutical ingredient	Trade name
		Local therapy	
1	Cariostatic- re-elevates plaque pH which lowers intensity and frequency of dental caries	Fluoride	Fluorette
2	Dental hygiene and for tooth whitening	Calcium as a tricalcium phosphate	Orbit white, Happydent white, Trident white Recaldent
3	Antibacterial agent – preventing tooth decay and to treat gingivitis, periodontitis, oral and pharyngeal infections	Chlorhexidine	Vitaflo CHX, Advanced +, HEXIT
		Systemic therapy	
4	Pain relief- in treatment of minor pains, headache and muscular aches	Aspirin	Aspergum
5	Smoking cessation	Nicotine	Nicorette, Nicotinelle, NiQuitin CQ
6	Stomach and neutralization	Calcium carbonate	Chooz
7	General health	Vitamin C	Endykay, Stamil, Source
8	Enhanced brain activity	DHA and CCE	Brain,
9	Diet	CR	Chroma slim
10	Reduces the symptoms associated with stress, anxiety and depression	Extracts of Ashwagandha, Passion Flower and Jujube Fruit and Calcium carbonate	Zoft stress gum
11	Symptomatic relief from postmenopausal Syndrome	Extracts of Dong Quai Root, Black Cohosh Root, Damiana Leaf, Mexican Wild Yam Root	Zoft menopause gum
12	Appetite suppressant for weight loss	Extracts of Hoodia gordonni -- nature's calcium channel blocker	Slim n trim
13	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 No.2: List of patent filled on MCGs

S.No	Inventor	Title	Patent no	Issued on date
1	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
2	BADETTI, Rolando	Composition for medicated chewing gums, process for manufacturing the Same and tablets so obtained	EP 1 162 946 B1	16.12.2009
3	BADETTI, Rolando	A process for the preparation of medicated chewing gums	EP 1 408 769 B1	13.01.2010
4	Kenneth A. Bartlett, Essex Fells, and William J. Schultz.	Chewing gum tablet	US 2262097	11.11. 1941
5	Theodore C. Goggin	Amphetamine chewing gum	US 2536168	02.01.1951
6	Frederick G. Merckel. Laszlo Reiner.	Fluorine chewing gum process	US2627493	03.02.1953
7	Harold M. Sellers	Chewing gum containing gas And a medicament	US 3316154	25.04. 1967
8	Carsten Andersen and Morten Pedersen	Chewing gum composition with Accelerated, controlled release of active agents	US 5487902	30.01. 1996
9	Barbara Eisenstadt, Penny A.Cash and Abraham I. Bakal	Chewing gum containing cough Suppressing Agent	US 5846557	08.12. 1998
10	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
11	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
12	Pardeep Nijha Wan	Medicated gumstick for treatment In anti-inflammatory conditions And prophylaxis against nsaid Gastropathy	US 2007/0003490 A1	04.01. 2007
13	Carsten Andersen	Tobacco alkaloid releasing chewinggum	WO 2006000232 A1	05.01. 2006
14	Terence Cosgrove, Beth Mary Foster, Erol Ahmed Hasan, Hongli Yang	Medicated chewinggum	WO 2008104547 A1	04.09. 2008





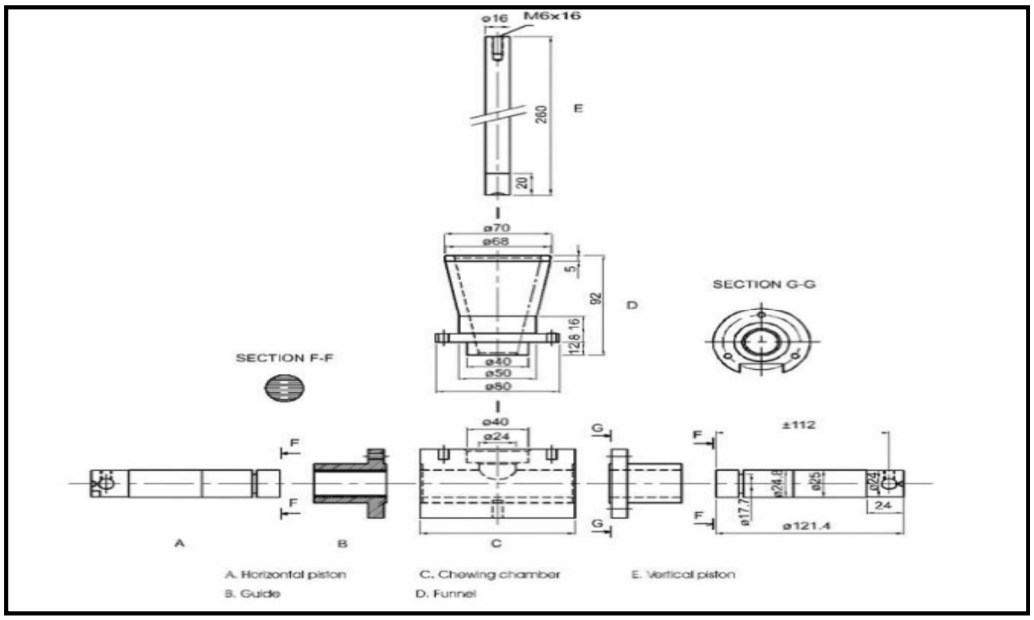


Figure No.1: Construction of the Compendial chewing gum apparatus

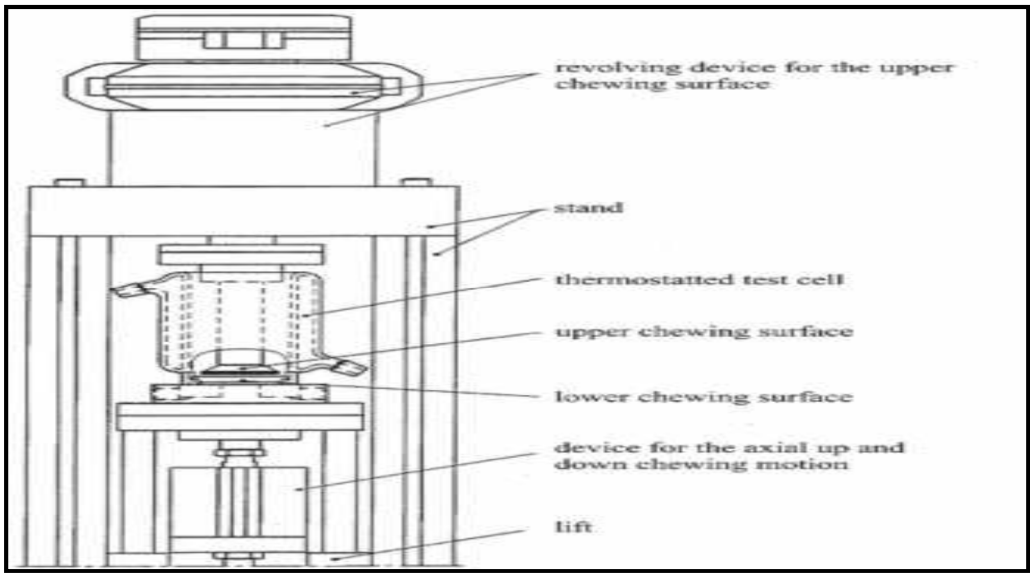


Figure No.2: Schematic representation of unofficial single module chewing apparatus

CONCLUSION

MCG is having many advantages as it is most convenient, self-medicated, easily administered without water and highly patient compliant. Mainly because of its capability to allow drug both locally and systemically, it is preferable over other delivery system. Thus in upcoming years it is sure that the medicated chewing gum would be most popular drug delivery system.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBILIOGRAPHY

1. Lee W W. Chewing gum as a delivery vehicle for pharmaceutical and nutraceutical substances, *Pharm Tech Online,* 2, 2001, 1-11.
2. Conway B. Chewing gum as a drug delivery system, *The Drug Delivery Companies Report Autumn/Winter,* 2003, 33-35.
3. Patel P V, Desai T R, Dedakiya A S, Bandhiya H M. Medicated chewing gum: A review, *IJUPLS,* 1(1), 2011, 111-128.
4. Biswal P K and Kumar A. An Updated Review on Medicated Chewing Gum, *IJAPBC,* 2(2), 2013, 351-359.
5. Jacobsen J, Christrup L L, Jensen N H. Medicated chewing gum, *Am J Drug Deliv,* 2(2), 2004, 75-88.
6. Cloys L, Christen A, Christen J. The development and history of chewing gum, *Bulletin of the History of Dentistry,* 40(2), 1992, 57-65.
7. Owens L. Gumtech to Produce Aspergum and Chooz for Schering- Plough Health Care Products, *Business Wire,* 1998.
8. Khanekar P, Mhatre S, Momin M. Medicated Chewing Gum: A Potential Drug Delivery System, *IJPFR,* 2(4), 2012, 64-75.
9. Morjaria Y, Irwin W J, Barnett P X, Chan R S and Conway B R. "*In Vitro* Release of Nicotine from Chewing Gum Formulations", *Dissolution Technologies,* 11(2), 2004, 12-15.
10. Sjogren K *et al*. Medicated chewing gum and process for Preparing thereof. U.S. Patent 5, *Caries Res, in press Testa E S,* 2 February 1999, 2002, 866, 179.

11. Jacobsen J, Christrup L L, Jensen N H. Medicated Chewing Gum, *Am J Drug Deliv,* 2(2), 2004, 75-88.
12. Goldberg L D, Ditchek N T. Chewing gum diarrhea, *Am J Dig Dis,* 23(6), 1978, 568.
13. Addy M, Roberts W R. Comparison of the bisbiguanide antiseptics alexidine and chlorhexidine. II. Clinical and *in vitro* staining properties, *J Clin Periodontol,* 8(3), 1981, 220-230.
14. Munksgaard E C, Nolte J, Kristensen K. Adherence of chewing gum to dental restorative materials, *Am J Dent,* 8(3), 1995, 137-139.
15. Weil A T. Coca leaf as a therapeutic agent, *Am J Drug Alcohol Abuse,* 5(1), 1978, 75-86.
16. Rathbone M J *et al*. In: Rathbone, M J. (Ed.) Oral Mucosal Drug Delivery, *Marcel Dekker, Inc., New York, NY, USA,* 1996, 121-156.
17. Squier C A, Wertz P W. In: Rathbone M J. (Ed.) Oral Mucosal Drug Delivery, *Marcel Dekker, Inc., New York, NY, USA,* 1996, 1-26.
18. Abhilash Mund, Byomakesh Panda, Shakti Prasad Mund. Medicated Chewing Gum: A Recent Trend of Drug Delivery System, *Am. J. Pharm Tech Res,* 5(1), 2015, 181-199.
19. Rhodus N L, Schuh M J. Effects of pilocarpine on salivary flow in patients with Sjögren's syndrome, *Oral Surg. Oral Med. Oral Pathol,* 72(5), 1991, 545-549.
20. Rider P H, Walker L A, Wyandt C M, Jones A B. Development and evaluation of a novel dissolution apparatus for medicated Chewing gum products, *Pharm. Res,* 9(2), 1992, 255-259.
21. Rindum J, Holmstrup P, Pedersen M, Rassing M R, Stoltze K. Miconazole chewing gum for treatment of chronic oral candidosis, *Scand. J. Dent. Res,* 101(6), 1993, 386-390.
22. European Pharmacopoeia. Strasbourg: European Directorate for the Quality of Medicines, *Chewing Gums: Medicated,* 5th Edition, 2004, 260, 601.
23. Zyck D J, Greenberg M J, Barkla D G, Marske S W, Schnell P G, Mazzone P. Method of making coated chewing gum products containing various antacids, US Patent 6, 2003, 635-645.
24. Kahtani D. Chewing gum: trick or treat, *SDJ,* 11(1), 1999, 27-34.
25. Naik H, Gupta S *et al*. Medicated Chewing Gums-Updated Review, *International Journal of Pharmaceutical Research and Development,* 2(11), 2010, 66-76.
26. Parmar V W and Thosar M. A Comprehensive Review On: Medicated Chewing Gum, *Int J Res Pharma Biomedical Sci,* 3(2), 2012, 894-907.
27. Athanikar N K, Gubler S A. Process for Manufacturing a Pharmaceutical Chewing Gum, US Patent 6, 2001, 322, 828.
28. Gadhavi A G *et al*. Medicated Chewing Gum-A 21st Century Drug Delivery System, *International Journal of Pharmaceutical Science and Research,* 2(8), 2011, 1961-1974.
29. http://www.spipharma.com/ProductsFolder/120ParmaGum/120Pharmagum.
30. Cherukuri S R, Bikkina K. Tabletted Chewing Gum Composition and Method of Preparation, US Patent No. 4753805, 1988.
31. Chaudhary S A, Shahiwala A F. Directly compressible medicated chewing gum formulation for quick relief from common cold, *Int J Pharm Investig,* 2(3), 2012, 123-133.
32. Cherukuri S R, Hriscisce F, Wei Y C. Reduced Calorie Chewing Gums and Method, US Patent No.4, 1988, 765, 991.
33. Bindi G C, Vipul P P, Tushar R D. Medicated Chewing Gum: A Review, Pharmatotur-Art-1047, 2011, 1-5.
34. Kubota R M, Thomas S M, Chapdelaine A H, Courtright S B. Method of Making Chewing Gum, US Patent No.4, 1989, 806, 364.

35. European pharmacopoeia. Strasbourg: Directotate for the quality of medicine and health care of the council of Europe, *Medicines, Chewing gum,* 6th Edition, 2009, 278.
36. European Directorate for the Quality of Medicines, Council of Europe, European Pharmacopoeia. Suppl. General Chapter 2.9.25: Chewing Gum, Medicated Release from, Strasbourg, *France; European Directorate for the Quality of Medicines, Council of Europe,* 3rd Edition, 2000, 104.
37. 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,* 189(1), 1999, 57-65.
38. Maggi L *et al*. Preparation and Evaluation of Release Characteristics of 3Tab Gum, a Novel Chewing Device, *European Journal of Pharmaceutical Sciences,* 24(5), 2005, 487-493.
39. Savaliya P *et al*. Chewing Gum: A Modern Era of Drug Delivery, *Int Res J Pharm,* 2(10), 2011, 7-12.
40. Madan N *et al*. Chewing Gums for Optimal Health, *Chronicles of Young Scientists,* 2(1), 2011, 7-10.

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