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Medicated Chewing Gum: A Boon to Oral Dosage forms

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ABSTRACT

Medicated chewing gum (MCG) is a drug delivery system that consists of an active ingredient incorporated into a chewing gum and released by the mechanical action of chewing. The first Medicated chewing gum product.' Aspergum', which contained acetyl salicylic acid for headaches, was launched in 1928. Medicated chewing gum is a good vehicle for administering active ingredients in pharmaceuticals and nutraceuticals. It offers a highly convenient, patient-compliant way of dosing medications, particularly for people with swallowing difficulties such as children and the elderly. It is also an ideal dosage form for drugs that help cure or relieve oral diseases, including toothache, periodontal disease, bacterial and fungal infections, and aphthous and dental stomatitis. Medicated chewing gum containing chlorhexidine is used to treat inflammatory conditions such as gingivitis. Using the medicated chewing gum formulation, the revitalization of old products and the reformulation of new patented products will differentiate them from upcoming generics competition. Thus, the potential of Medicated chewing gum for direct systemic delivery with higher patient compliance, its fast onset of action and the opportunity for product-line extension make it a likely drug delivery system.

Keywords- Medicated chewing gum (MCG), periodontal disease, gingivitis, patient compliance

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INTRODUCTION

A novel drug delivery system creates additional patient benefits that will add new competitive advantages for a drug and thus increase revenue. Oral route is the most preferred route amongst the patient and clinicians due to various advantages it offers and most important is its ease of administration[1].The Intra oral route is one of the more preferred routes of the drug administration as it is convenient and, with certain drugs, may provide a more rapid onset of action. MCGs are oral solid, single dose preparations with a base consisting mainly of gum that is intended to be chewed but not swallowed. 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 buccal mucosa [2]. Chewing Gum (CG) also has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients[3]. Today CG is convenient drug delivery system which is appropriate for a wide range of active substances [4]. Medicated Chewing Gum (MCG) is 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 and nutrition that can improve health, and creates additional patient benefits that will add new competitive advantages for a drug and thus increase revenue. Moreover there is need of reformulation of existing drug into New Drug Delivery Systems (NDDS) to extend or protect product patents thereby delaying, reducing or avoiding generic erosion at patent expiry. To provide additional patient benefit, meet competitive challenges and to conserves revenues, the research on NDDS is gaining importance now a days. MCG is one of them. Owing to new social and behavioral trends in the past modern age, such as the growing consumer health awareness and increasing attention to safety products, chewing gum has been known for a new image and Potential. Chewing gum today is gaining consideration as a vehicle or a delivery system to Administer active principles that can improve health and nutrition. MCG represents the newest system with potential uses in pharmaceuticals, over the counter medicines and nutraceutical[5]. The drugs intended to act in oral cavity often have low water/saliva solubility and chewing gum constitute a valuable delivery system for such drugs.

Advantages of Medicated Chewing Gums: [3, 6]

1. Dose not requires water to swallow. Hence can be take anywhere.
2. Advantageous for patients having difficulty in swallowing.
3. Excellent for acute medication

4. Counteracts dry mouth, prevents candidacies and caries.

5. Highly acceptable by children

6. Avoids First Pass Metabolism and thus increases the bioavailability of drugs.

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 mucosa

10. Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased.

11. Aspirin, Dimenhydrinate and Caffeine shows faster absorption through MCG than tablets.

Demerits of MCGS [7,8,9,10,11]

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 time.

2. Sorbitol present in MCG formulation may cause flatulence, diarrhoea .

3. Additives in gum like flavoring agent, Cinnamon can cause Ulcers in oral cavity and Liquorice cause Hypertension.

4. Chlorhexidine oromucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue .

5. Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers

6. Prolonged chewing of gum may result in pain in facial muscles and ear ache in children.

COMPOSITION OF MCGS[12]

Chewing gum is a mixture of natural or synthetic gums and resins, sweetened with sugar, corn syrup, artificial sweetners and may also contain coloring agents and flavor. The basic raw material for all CG 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 polyvinyl acetate and similar polymers can be used as gum base.

Typically Chewing Gum comprises two parts

1. Water insoluble chewable gum base portion.

2. Water-soluble bulk portion.

1. Water insoluble gum base generally comprises elastomers, resins, fats and oils, and inorganic fillers:

Elastomers:

Elastomer provides elasticity and controls gummy texture. Natural elastomer: Natural rubbers like Latex or Natural gums such as Jelutong, Lechi Caspi, Perillo, Chicle.

Plastisizers:

These are used to regulate cohesiveness of product. These are again divided into Natural and Synthetic.Natural Plastisizers include Natural rosin esters like Glycerol Esters or Partially hydrogenatedRosin, 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.

Fillers or Texturizers:

Provide texture, improve chewability, 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.

2. Water soluble portions contains bulk sweetners, high intensity sweetners, flavouring agents, Softners, emulsifiers,

Colours & 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

May include FD & C type dyes and lakes, fruit and vegetable extracts, Titanium Dioxide.

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, Corn Syrup.

Sugarless Components

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.

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.

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.

Active Component

In medicated chewing gum active pharmacological agent may be present in core or coat or in both. The proportion of which may vary from 0.5-30% of final gum weight. A small, unionized, lipophilic and enzymatically stable active agent is likely to be absorbed more readily. A saliva soluble ingredient 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.

MANUFACTURING PROCESSES [13,14, 15]

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

- Conventional/ traditional Method (Melting).
- Freezing, grinding and tabletting Method.
- Direct Compression Method

1. **Conventional/ traditional Method**

Components of gum base are softened or melted and placed in a kettle mixer to which

Sweetners, syrups, active ingredients and other excipients are added at a definite time. The gum is then sent through a series of rollers that form 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.

Cooling, Grinding and Tabletting Method

This method has been developed with an attempt to lower the moisture content and to avoid 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 temperatures of the refrigerated mixture is around -15^{o}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 -78.5oC, 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. Alternatively, the steps of cooling the chewing gum composition can be combined into a single step. As an example, cooling the grinding apparatus itself which can be done by contacting the grinding apparatus with a coolant or by placing the grinding apparatus in a cooling jacket of liquid nitrogen or other cold liquid. For more efficient cooling, the chewing gum composition can be pre cooled prior

to cooling to the refrigeration temperature. Sometimes a mixture of chewing gum composition, solid carbon dioxide and precipitated silica is ground in a mill grinder in a first grinding step. Additional solid carbon dioxide and silica are added to the ground composition, and the composition is further ground in a second grinding step. This two step grinding process advantageously keep the chewing gum composition at a very low temperature. The presence of solid carbon dioxide also serves to enhance the efficiency of the grinding process. The same process can be made multiple by adding incorporating additional carbon dioxide and/or precipitated silica at each step. After the composition is ground to a powder, the coolant can be removed by allowing the coolant to evaporate. Alternatively it has been found that such a powdered mass when warmed to room temperature from the refrigerated state, they become cross linked or self adhere together to form an integrated body which incorporates minute air bubbles in the texture between the particles. This provides a chewing gum product that is light and gives a soft chewing impression when chewed.

Tabletting

Once the coolant has been removed from the powder, the powder can be mixed with other Ingredients such as binders, lubricants, coating agents, 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.

Direct Compression Chewing Gum

Pharmagum is a compatible gum system that has been developed by SPI pharma. Pharmagum is a mixture of polyols and of sugar with gum base. It is a free flowing powder, which is directly compressible. This gum is manufactured under cGMP conditions and complies with food chemicals. Direct compression chewing gum can be directly compressed on a traditional tabletting machine, thus enabling rapid and low cost development of a gum delivery system.

Factors Affecting Release Of Active Ingredient [16]

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.

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.

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 ingredient.

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.

***In Vitro* Release Study[17]**

In vitro release study of chewing gums was carried out using an *in vitro* chewing release

apparatus consisting of two modules (AB FIA, Lund, Sweden) (Figure. 1). Each module consists of a thermo statted glass cell in which two vertically oriented pistons holding an upper and a lower chewing plate are mounted. The cells were filled with 40 ml of artificial saliva .The composition of artificial saliva is given in (table 1).

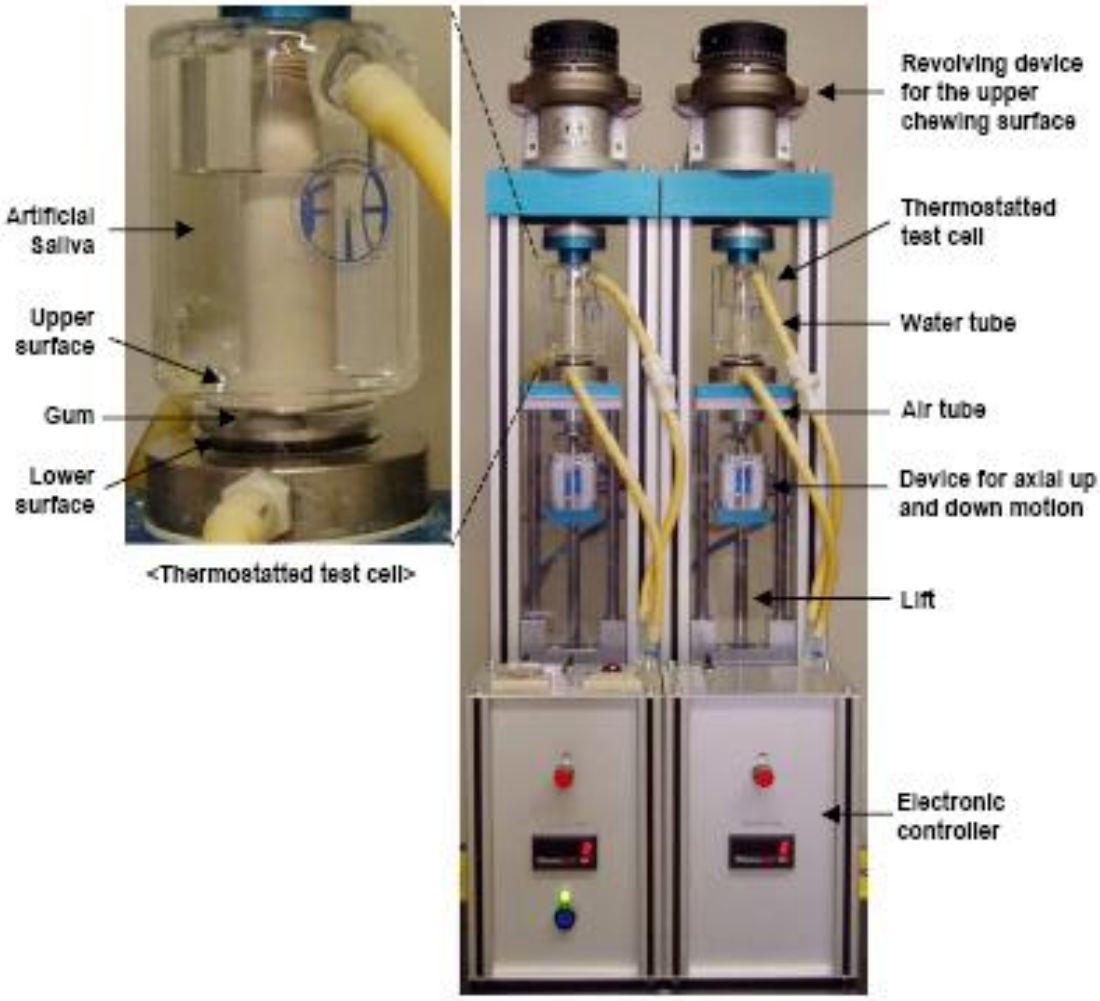

Figure 1: Photographs of chewing apparatus and thermo stated test cell.

Table 1: Composition of artificial saliva

Components (mmol L-1)	Quantity
KH2PO4	2.50
Na2HPO4	2.40
KHCO3	15.00
NaCl	10.00
MgCl2	1.50
CaCl2	1.50
Citric Acid	0.15

pH adjusted to 6.7 with NaOH or HCl

The chewing gum was loaded onto the lower chewing surface. The chewing procedure consisted of up and down strokes of the lower surface in combination with a twisting movement of the

upper surface; this action provides mastication of the chewing gum and agitation of the test medium. The temperature of the test medium was controlled at 37 ^{0}C and the chew frequency was 50F2 strokes per min. At predetermined time intervals, 400 Al of supernatant were removed. The dissolution medium was replaced with fresh artificial saliva after each sampling. The released amount of drug was determined by RP-HPLC.

***In Vivo* 'Chew-Out' Studies[18,19]**

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.

A. 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 and the amount and rate of drug release. Optimized formulation with good consistency can be selected for the release of drug in 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, 15 min. The saliva samples are made diluted in required solvent and absorbance is analyzed by suitable analytical method.

B. Dissolution test of residual medicated

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, 15 min).64 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, whereas 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.

C. Urinary excretion profile of medicated

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 hour. 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 the 15 min, 1, 2,3, 4, 6, 7, 8, 10, 11, 12, 24 hour intervals after administration of medicated chewing gum. The volunteers are asked to drink water at regular intervals of 30 min. and urine samples are analyzed by suitable analytical methods.

D. 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, in the oral cavity for 15 min and then expelled out. The expelled saliva is analyzed for drug content and back calculated for buccal absorption.

COMMERCIALLY AVAILABLE CHEWING GUMS IN WORLD MARKET.[20]

Some of the commercially available chewing gums are mentioned in table 2

Table 2: Medicated chewing gum available Worldwide

Trade Mark	Active substance	Aim	Commercially available
Aspergum	Aspirin	Pain relief	North America
Nicorette	Nicotine	Smoking cessation	Worldwide
Nicotinelle	Nicotine	Smoking cessation	Australia, New Zealand
Trawell	Dimenhydrinate	Travel illness	Italy, Switzerland
Superpep	Dimenhydrinate	Travel illness	Germany, Switzerland
Chooz	Calcium carbonate	acid neutralization	USA
Endekay	Vitamin C	General health	Middle East, United Kingdom
Stamil	Vitamin C	General health	Australia
Brain	DHA & CCE	Enhanced brain activity	Japan
Stay Alert	Caffeine	Alertness	USA
Cafe Coffee	Caffeine	Alertness	Japan
Buzz	Gum Guarana	Alertness	United Kingdom
Go Gum	Guarana	Alertness	Australia
Chroma	Slim CR	Diet	USA
Fluorette	Fluoride	Cariostatic	USA
Travvel	Dimenhydrinate	motion sickness	USA, Australia

FUTURE TRENDS

Chewing gum not only offers clinical benefits but also is an attractive, discrete and efficient drug delivery system. 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. 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. The potential of MCG for buccal delivery, fast onset of action and the opportunity for product line extension makes it an attractive delivery form. Reformulation of an existing product is required for patent protection, additional patient benefits and conservation of revenues.

CONCLUSION

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. Medicated Chewing gums can produce both local effects as well as systemic effects in the oral cavity. They can be used for the purpose of taste masking of certain drugs too.Thus medicated chewing gum will be a boon to the patients in future.

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