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Medicated Chewing Gum: A Recent Trend of Drug Delivery System

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ABSTRACT

From the past few decades scientific and technological advancement have been made in the pharmaceutical research and development of oral drug delivery system. Medicated chewing gum (MCG) has drawn attention to the researcher as potential drug delivery system. MCGs are the non-dissolving intraoral dosage form intended for local treatment of diseases of the oral cavity as well as systemic delivery after absorption through buccal mucosa in which the continuation of drug release depends up on masticatory activities. A special *in-vitro* apparatus was designed and constructed for release testing of MCGs which is official in European Pharmacopoeia. It is an excellent and convenient drug delivery system for self-medication and can be administered discreetly without water. Consequently at present chewing gum is a convenient drug delivery system, which is appropriate for a wide range of active substances. It is very likely that MCGs will be a common drug delivery system and could be a commercial success in imminent future. Purpose of this review article is to discuss the advantage and drawback, methods of preparation, evaluation, and release of drugs, factors affecting release, safety aspects and development with respect to the medicated chewing gums.

Keywords: Medicated chewing gums (MCGs), Oral drug delivery system, *In-vitro* apparatus, Systemic delivery.

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INTRODUCTION

Medicated Chewing gums are the 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 the buccal mucosa[1]. MCGs represent the newest system with potential uses in pharmaceuticals. 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. Due to new social and behavioural 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 in a convenient way. Medicated chewing gums 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, vitamin / mineral supplement and treatment of are currently available. In the present days improved technology and extended mean, how have made it possible to develop and manufacture medicated-chewing gum with pre-defined propertie[2]. Consequently, today chewing gum is a convenient drug delivery system, which is appropriate for a wide range of active substances. Medicated chewing gum offers advantages in comparison to conventional oral mucosal and oral dosage forms both for local treatment and systemic effect after absorption through the buccal and sublingual mucosal and from the gastrointestinal tract[3]. As a drug delivery system, chewing gum enables rapid drug absorption through the oral mucosa to achieve fast onset of action and bioavailability. It also has superior organoleptic properties compared with other dosage forms; it has a more attractive appeal and offers the patient active control over the treatment. This drug delivery system offers two absorption pathways. Drug absorbed directly via the buccal membrane avoids metabolism in the gastrointestinal tract and thus the chance of first pass effect of the liver. As a result drug formulation as medicated chewing gum may require reduced dose compared to other oral drug delivery systems[4]. Moreover, it also benefits from the advantages inherent to chewing gum, such as oral care, stress relief, improved focus and concentration, and weight management. Also added to the therapeutic benefits of the drug is the positive synergistic effect brought on by the chewing action, which we believe boosts patient compliance. In general, medicated chewing gum has a good stability, the medicine can be taken easily and directly without the prerequisite of water, and if required, prompt discontinuation of medication is possible. Physiochemical properties of the

drug like aqueous stability, pKa value, distribution between gum/ saliva, product properties like, composition, mass, manufacturing process and the process of chewing i.e. chewing time, chewing rate, affects the release of drugs from the medicated chewing gum. Varying the formulation and manufacturing process, chewing gum as a drug delivery system can be formulated for an extended period of time and also represents the novel system with potential uses in pharmaceuticals, over the counter medicines and neutraceuticals[5]. Preferably for pharmaceutical companies, medicated chewing gum is an accepted dosage form in current Pharmacopoeias and the ingredients are compliant with different monographs.

Advantages of Medicated Chewing Gums[6, 7, 8]

1. Dose not requires water to swallow; hence it can be taken anywhere.
2. Advantageous for patients having difficulty in swallowing.
3. Counteracts dry mouth through stimulation of the salivary secretion prevents candidiasis and caries.
4. More convenient and highly acceptable by children due to it resembles to confectionary (non-medicated) chewing gums.
5. Onset of action is faster due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation.
6. The active compounds absorbed at oral level avoid the hepatic circulation and the associated metabolism.
7. The release rate of drug can be carefully controlled through the formulation of the chewing gum allowing extended exposure in the oral cavity.
8. Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa.
9. Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased.
10. Highly soluble and quick action drugs like Aspirin, nicotine, Ondansetron, Dimenhydrinate, Caffeine etc. shows faster absorption through MCGs than tablets.
11. Gum does not reach the stomach. Hence GIT suffers less from the effects of excipients.

Limitations of Medicated Chewing Gums[9, 10]

1. Risk of over dosage with MCGs compared with chewable tablets or lozenges that can be consumed in a considerable number and within much shorter period of time.
2. Additives in gum like flavoring agent, Cinnamon can cause Ulcers in oral cavity and Licorice cause Hypertension.

3. Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers.
4. Prolong chewing on gum may result in pain in facial muscles and earache in children.
5. Sorbitol present in MCG formulation may cause flatulence, diarrhea.

Theory of Drug Transport[11, 12]

Due to 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 as depicted in Figure 1.

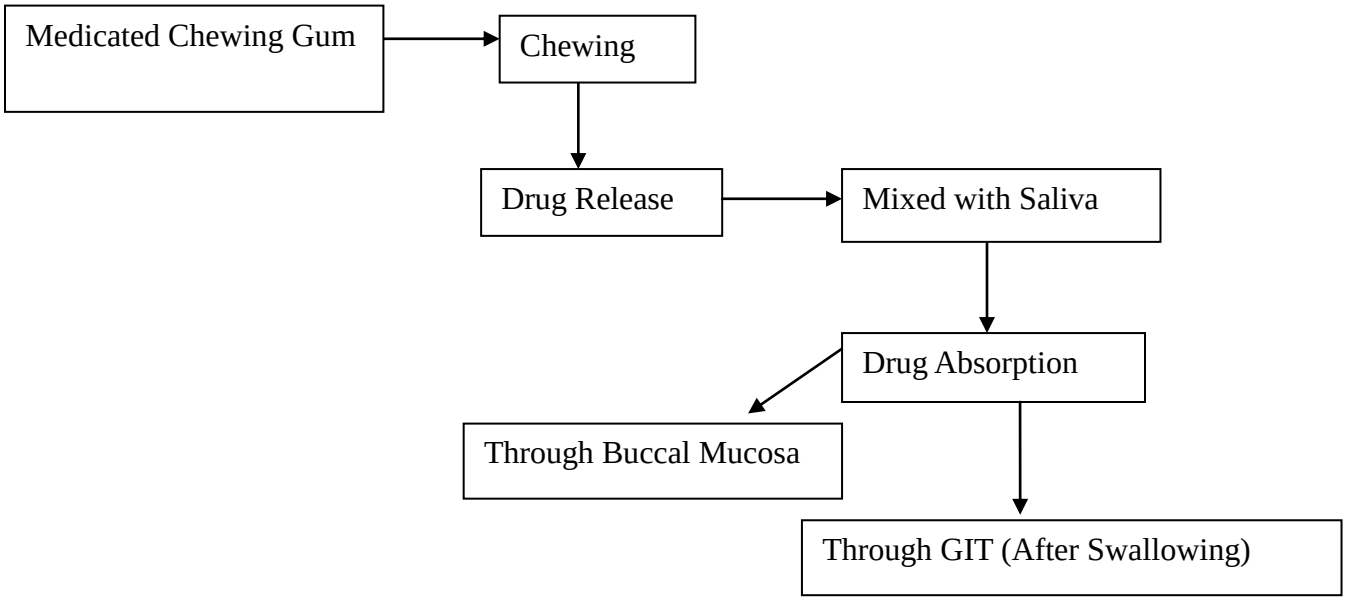

Figure 1: Schematic sequence of Mechanism of drug release from MCG

Major pathways of drug transport across buccal mucosa follow simple fickian diffusion. Passive diffusion occurs in accordance without 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 and Δ Ce= Conc. Gradient

Recent Innovations

Table 1: List of patents in relation with advancement of Medicated Chewing Gums (MCGs)

Patent No.	Year	Applicant	Background of the invention
US20130022652 A1	2013	Fertin Pharma A/S	The present invention provides stable medicament-containing chewing gum compositions comprising an inclusion complex comprising cyclodextrin and one or more active compound(s)[13].
WO2000013662A2	2008	Jsr Llc, Fuisz Technologies Ltd.	The present invention relates to medication delivery systems, and more specifically to nicotine delivery systems, and particularly to a nicotine

			chewing gum delivery system that provides for an improved nicotine release profile over existing systems[14].
US20120276187 A1	2012	Bagger-Sorensen & Co. A/S	The present invention relates to a tableted chewing gum sweet and more especially a tableted chewing gum sweet comprising at least two integral parts which has a novel effect in the mouth by giving an initial crunch followed by a normal chewing gum stage[15].
US6322806	2001	Wm. Wrigley Jr. Company	Over-coated chewing gum formulations including tableted center[16].
US6350480	2002	Wm. Wrigley Jr. Company	Chewing gum product including a hydrophilic gum base and method of producing[17].
US6455533	2002	UCB, S.A.	Pharmaceutical compositions for oral administration, comprising an active substance and a cyclodextrin[18].
US6531114	2003	Wm. Wrigley Jr. Company	Sildenafil citrate chewing gum formulations and methods of using the same[19].
US6905672	2005	The Procter & Gamble Company	Compositions and methods to inhibit tartar and microbes using denture adhesive compositions with colorants[20].

BASIC COMPONENTS OF MEDICATED CHEWING GUMS[21, 22, 23]

I. Active pharmaceutical ingredient (API)

The active pharmaceutical ingredients should be comply the following criteria

- The drug should not have any type of disagreeable taste, this can affect patient compliance.
- The particle size of the drug should be kept below approximately 100 µm avoid unpleasant gritty feeling during chewing.
- Physicochemical Properties of Drug such as high salivary solubility and pH independent solubility.
- Patient Related Factors such as nontoxic to oromucosa and salivary ducts, non-carcinogenic should not cause tooth decay and oromucosa staining should not affect salivary flow rate.

II. Gum base

It 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) other raw materials are generally grouped in the following classes:

1. Elastomers

Itprovides elasticity, gummy texture and cohesion to the chewing gum. Natural elastomer Natural rubbers like Latex or Natural gums such as Jelutong, LechiCaspi, Perillo, and Chicle. Synthetic elastomers like polyethylene acetate, polyisobutylene and butyl rubber are used.

2. Plasticizers

These are used to regulate cohesiveness of product. These are again divided into Natural and Synthetic Natural Plasticizers include Natural rosin esters like Glycerol Esters or Partially hydrogenated Rosin, Glycerol Esters of Polymerized Esters, Glycerol Esters of Partially dimerized Rosin & Pentaerythritol Esters of Resin. Synthetic Plasticizers include Terpene Resins derived from α- pinene and or d-limonene.

3. Resins

They serve two functions. One, as mastication substance and other as binding agent between elastomers and fillers, they contribute to the balance between the properties of elasticity and plasticity. Glycerol esters from pine resins are examples of natural resins. Synthetic resin polyvinyl acetate can be used. It reduces the tendency of the gum to adhere to the teeth (detackifier) and to be divided into pieces during chewing. It has only a slight taste, its stability is good and it is available in range of different molecular weights.

4. Emulsifiers and fats

These are used to soften the mixture and give the required chewing consistency and mouth feel. Emulsifiers promote the uptake of saliva into the chewing gum during mastication. Monoglycerides, diglycerides and partly hardened vegetable and animal fat are examples. Softeners include Glycerin, Lecithin, Tallow, Hydrogenated Tallow, Mono/ di/ tri-Glycerides, Fatty acids like Stearic acid, Palmitic acid, Oleic acid and Linoleic acid.

5. Fillers or Texturizers

They provide the right texture, improve chewability, and provide reasonable size of the gum lump with low dose drug for the gum base. Commonly used fillers are Magnesium and Calcium Carbonate, Ground Limestone, Magnesium and Aluminium Silicate, Clay, Alumina, Talc, Titanium Oxide & Mono/ di/ tri Calcium Phosphate. Antioxidants: They may be added to protect the gum base and flavors from oxidation. Ascorbic acid, tocopherol, butylhdroxytoluene have been used.

6. Sweeteners

a. Water-soluble sweetening agents: Xylose, ribulose, glucose, mannose, galactose, fructose, sucrose, maltose, and invert sugar partially hydrolyzed starch, dihyrochalcones, monellin, steviosides, glycyrrhizin, and sugar alcohols such as sorbitol, mannitol, and hydrogenated starch hydrolsates.

b. Water-soluble artificial sweeteners: Soluble saccharin salts, i.e. sodium or calcium saccharin salts, cyclamate salts.

c. Dipeptide based sweeteners: L-aspartic acid derived sweeteners such as Aspartame, Alitame, methyl esters of L-aspartyl-L phyenylglycerine and Laspartyl-L 2, 5-dihyrophenylglycine, L aspartyl 2, and 5- dihydro-L phenylalanine-L aspartyl-L (1-cyclohexen) alanine.

d. Protein based sweeteners: such as thaumaoccousdanielli (Thaumatin I and II) In general an effective amount of sweetener is utilized to provide the level of sweetness desired, and this amount will vary with the sweetener selected and are present in amounts from 0.0025% to 90% by weight of the gum composition.

7. Flavoring Agents

A variety of flavoring agents are used to improve flavor in chewing gum includes essential oils, such as Citrus oil, fruit essences, Peppermint oil, Spearmint oil, Mint oil, Clove oil & Oil of Wintergreen. Artificial flavoring agents can also be used.

8. Anti-caking agent

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

9. Antioxidants

An anti- oxidant such as butylatedhydroxytoluene, butylatedhydroxyanisole, propyl gallate and mixtures thereof, may be included as antioxidants.

10. Grinding agents

To prevent the gum from sticking to the grinding apparatus 2-8% w/w of grinding aid such as alkaline metal phosphate, an alkaline earth metal phosphate or malto dextrin can be incorporated. However practical use of these substances is limited because these substances are highly alkaline and hence would be incompatible with acidic ionizable therapeutic agents. They also tend to remain in the composition and final chewing gum tablet and thus may be problematic for therapeutic and safety point of view.

Manufacturing Processes

Different methods can be employed for the manufacturing of MCGs; however, these can be broadly classified into three main classes namely:

1. Conventional/ Fusion Method
2. Cooling, grinding and tabletting Method
3. Direct Compression Method

1. Conventional/ Fusion method

Components of gum base are softened or melted and placed in a Planetary 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, flat 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 to2 days. 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 as depicted in Figure 2.[24].

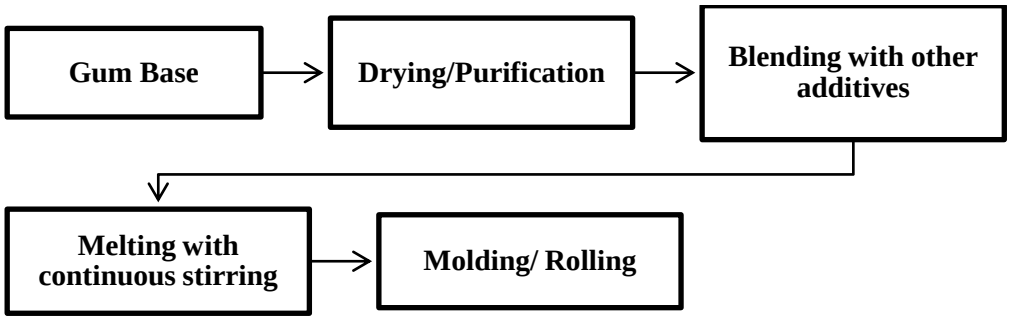

Figure 2: Schematic sequence of Conventional/Fusion method

Limitations

1. Elevated temperature used in melting restricts the use of this method for thermo labile drugs.
2. Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult.
3. Lack of precise form, shape or weight of dosage form.
4. Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.
5. Such a chewing gum composition is difficult to form into chewing gum tablets because of their moisture content (2-8%). If attempted to grind and tablet such a composition would jam the grinding machine, stick to blades, screens adhere to punches and would be difficult to compress.

2. Cooling, Grinding and Tableting Method

This method has been developed with an attempt to lower the moisture content and alleviate the problems mentioned in conventional method. The MCG 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 MCG and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperature of the refrigerated mixture is around -15°C or lower. Amongst the various coolants like liquid nitrogen, hydrocarbon slush use of solid carbon dioxide is preferred as it can give temperatures as low as -78.5°C, it

sublimes readily on warming the mixture, is not absorbed by the chewing gum composition, does not interact adversely with the processing apparatus and does not leave behind any residue which may be undesirable or potentially hazardous. The refrigerated composition is then crushed or ground to obtain minute fragments of finely ground pieces of the composition. 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 chilled 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 the first step. Additional solid carbon dioxide and silica are added to the ground composition, and the composition is further ground in the second step. This two-step grinding process advantageously keeps 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. Certain additives can be added to the chewing gum composition to facilitate cooling, grinding and to achieve desired properties of chewing gum. These include use of anti-caking agent and grinding agent[25]. Once the coolant has been removed from the powder, the powder can be mixed with other ingredients such as binders, lubricants, coating agents, and sweeteners etc, all of which are compatible with the components of the chewing gum base in a suitable blender such as sigma mill or a high shear mixer. Alternatively a Fluidized Bed Processer (FBP) can be used. The use of FBP 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 anti-adherents like talc. The mixture can be blended in an octagonal blender, screened & staged for compression as depicted in Figure 3 [26].

Limitation: It requires equipment other than conventional tableting equipment and requires careful monitoring of humidity during the tableting process.

3. Direct compression Method

The manufacturing process can be accelerated if a directly compressible chewing gum excipient is available. The limitations of melting & freezing can be overcome by the use of these. SPI pharma has developed a compatible gum system known as Pharmagum. Pharmagum is a mixture of polyols and of sugar with gum base. Pharmagum S consists primarily of gum base and sorbitol. Pharmagum M contains gum base, Mannitol and Isomalt. These are free flowing powders, which

are directly compressible. 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)[27].

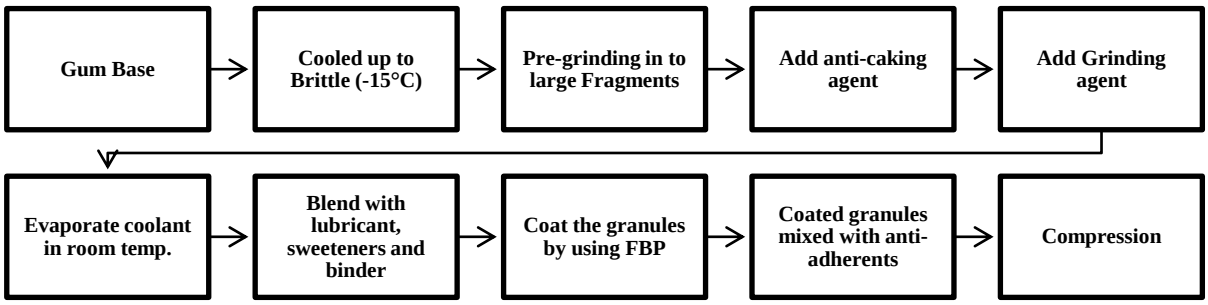

Figure 3: Schematic sequence of Cooling, Grinding and Tableting Method

Formulation Aspects

- Cyclodextrin complexation or Solubilization technique increases aqueous solubility of drugs that are poorly water soluble.
- Increased amount of softeners and emulsifiers in gum base fasten release whereas hard gum may retard.
- A solid system of lipophilic active ingredients bound to the cation exchange resin permits a sustained drug delivery system.
- Microencapsulation or agglomerations are the methods to modify and control the release of active ingredient.

Evaluation Tests

The following evaluation tests are specified in European Pharmacopoeia:

1. **Uniformity of Content:** Unless otherwise prescribed or justified and authorized medicated chewing gum with content of 2 mg or less than 2 percent of the total mass of gum comply with test[28].
2. **Uniformity of mass:** Uncoated medicated chewing gum and unless otherwise justified and authorized coated medicated chewing gum comply with the test for uniformity of mass of single- dose preparations.
3. ***In vitro* drug release from MCGs:**

a. Single-module chewing apparatus: One of the unofficial apparatus for carrying out dissolution studies of MCG was designed by Wennergren. This apparatus consists of a two-piston and

temperature-controlled reservoir for dissolution medium, as shown in a schematic representation in

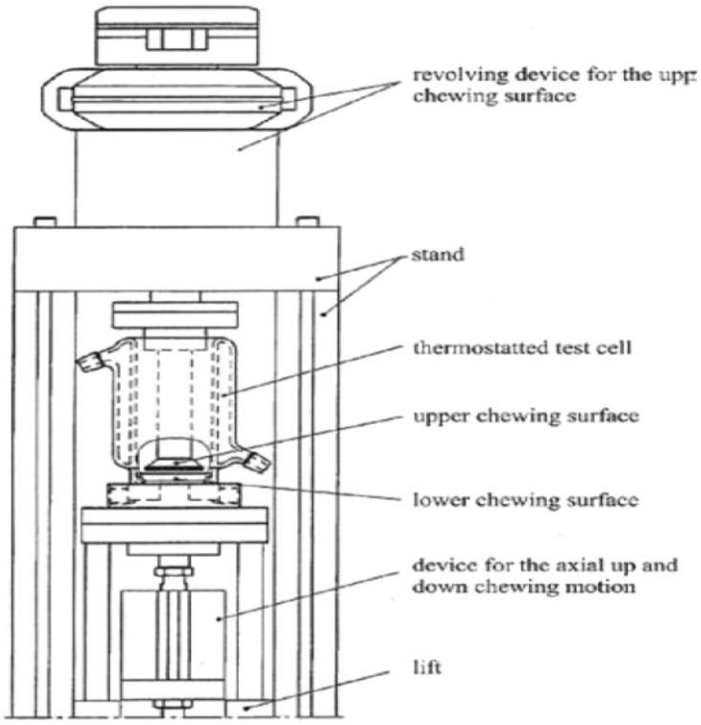

Figure 4: Schematic diagram of single-module chewing apparatus

Figure 4. 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. Throughout one cycle of chewing, one piston on each side shift towards each other. When they get together, they press the MCG between them and then make a twisting association before returning to the preliminary point. To carry out a drug release test, a known quantity of chewing gum is placed in the 20 ml volume of dissolution medium, which is equilibrated to a temperature of 37°C. The pressing and twisting forces are transmitted to the gum through the pistons at a chewing rate of 60 strokes a minute. At specified time intervals, that is, 3, 5 and 10 min, samples are collected and analyzed to evaluate percentage drug release[29].

b. MCG chewing apparatus: The official modified dissolution apparatus for assessing drug release from MCG, as per European Pharmacopoeia, is depicted in Figure 5. In this apparatus, in addition to the pair of horizontal pistons (‘teeth’), the chewing chamber is supplied with a vertical piston (‘tongue’) working alternate to the horizontal pistons, which ensures that the gum is always positioned in the correct place during the mastication process. If required, it is possible to construct the machine so that at the end of the chew the horizontal pistons rotate in opposite directions around their own axis to each other to attain maximum mastication. The temperature of the

chamber can be maintained at 37±0.5°C and the chew rate can be varied. Other adjustable settings include the volume of the medium, the distance between the jaws and the twisting movement. The European Pharmacopoeia recommends 20 ml of unspecified buffer (with a pH close to 6) in a chewing chamber of 40 ml and a chew rate of 60 strokes a minute. This most recent device seems promising, competent and uncomplicated to operate. Several studies have been carried out using the European Pharmacopoeia apparatus and the results indicate the methodology is rugged and reproducible[30].

4. *In vivo* 'chew-out' studies

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.

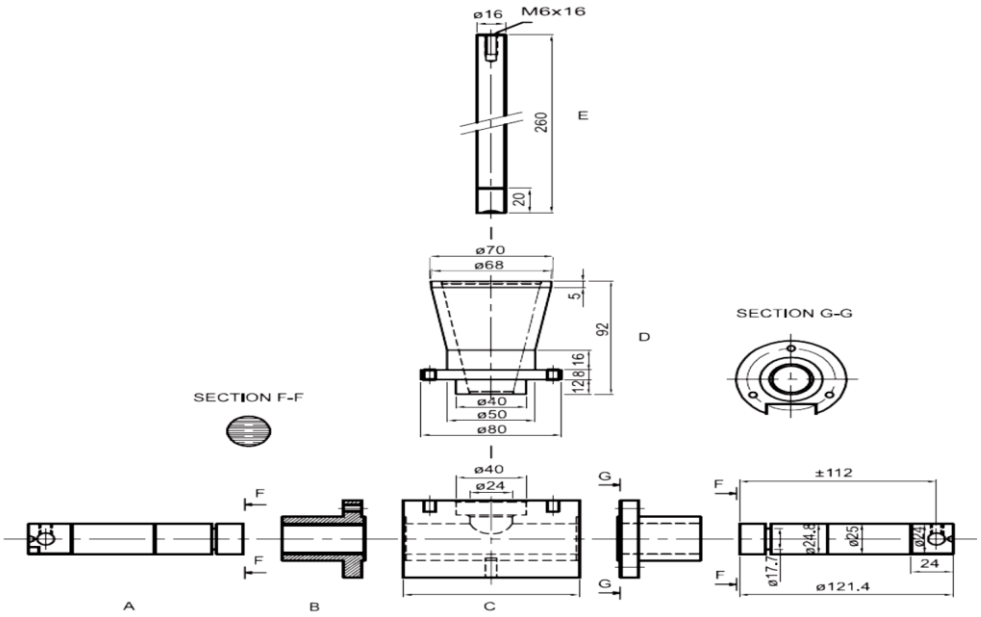

Figure 5: Schematic representation of modified dissolution apparatus as per European Pharmacopoeia, containing chewing chamber and pistons

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 chewing gum: 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, 15 min). 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 chewing gum: 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[31].

Factors Affecting Release of Active Ingredient[32, 33, 34]

Several factors have been shown to affect release of drugs from chewing gum. The major determinants include the chewing time, chewing rate, aqueous solubility of the drugs, and composition of the chewing gum.

1. Contact Time and rate: The local or systemic effect is dependent on time of contact of MCG in oral cavity; a survey was made to determine the length of chewing time. The mean chewing time per piece of gum was 30 to 35 min. the rate at which a subject chews gum also affects the amount of drug released. The average chewing rate is about 60 chews every minute.

2. 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.

3. Solubility of the Drug: 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. Release of water soluble drug (aqueous solubility greater than 1:10) is, in general, about 75% or more during 5 min. of chewing and 90% or more during 15 min. of chewing at rate of 60 chews per minute. Drugs with aqueous solubility between 1:10 and 1:300 demonstrate up to 60% release during 10 minutes of chewing and between 50 to 90% when the gum is chewed for 15 min. the release of the drug, which is only slightly water-soluble, can only be expected to be small (less than 5%) even if the gum is chewed for 30 min.

4. Formulation factors: the influence of gum base mass on drug release is depends upon changing the hydrophilic/lipophilic balance of the chewing gum formulation. The simplest way of achieving this is to increase or decrease the amount of gum base. An increase in the gum base will make the formulation more lipophilic and thus reduce the release rate of a given active substance. In principle, it is possible to manufacture products with a very low gum base content, but in practice a portion of chewing gum containing less than 20% gum base will have inferior chewing properties and may not be considered a viable formulation. Instead of changing the gum base content, it is far more effective to change the release properties by adding solubilizers to the formulation. This method enables release from the chewing gum of even highly insoluble substances, e.g. Nystatine.

APPLICATIONS OF MEDICATED CHEWING GUMS

1. Local action in oral cavity

Prevention and treatment of oral disease are targets for chewing gum formulations. It can control the release rate of active substances providing a prolonged local effect. It also re-elevates plaque pH which lowers intensity and frequency of dental caries. Fluoride containing gums have been useful in preventing dental caries in children and in adults with xerostomia. Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oral and pharyngeal infections. It can also be used for inhibition of plaque growth. Chlorhexidine chewing gum offers numerous

flexibility in its formulation as it gives less staining of the teeth and is distributed evenly in the oral cavity. The bitter taste of chlorhexidine can be masked quite well in a chewing gum formulation[35].

2. Systemic therapy

a. Pain: Chewing gum can be used in the Successful treatment of minor pains, headaches, pains of cold, muscular aches, etc. Chewing gum as a drug delivery system could be beneficial in minor pain treatment, when buccal absorption results in fast onset of action and reduces the risk of gastrointestinal side effects. Absorption from the chewing gum formulation was shown to be faster than absorption from the tablet, and consequently, a chewing gum formulation may provide faster pain relief. A chewing gum formulation may also be useful in the treatment of acute, strong pain[36].

b. Smoking cessation: Chewing gum formulations containing nicotine, lobeline and silver acetate have been clinically tested as aids to smoking cessation. A comparison of success rates and adverse reactions showed that nicotine was superior to the other two substances. Several clinical studies have proven the efficacy of nicotine chewing gum as an aid to smoking cessation. Nicotine chewing gum can be regarded as a convenient formulation for breaking an "oral habit" like smoking as the "oral habit" of smoking is substituted by another oral activity, namely gum chewing[37].

c. Obesity: Several chewing gum formulations containing caffeine, guarana or chromium are available. Caffeine and guarana are central stimulating anorectic agents that have proved to increase the metabolic rate. Moreover, they stimulate lipolysis, have a thermogenic effect (increase energy expenditure) and reduce the feeling of hunger. Chromium is claimed to reduce the craving for food due to an improved blood glucose balance.

d. Current therapeutic applications: Apart from the above applications, in recent trends the chewing gum delivery system is broadly applied in the treatment of Xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety, etc. as shown in the Table-2. It is also available commercially with worldwide acceptance as mentioned in Table-3.

Table 2: Therapeutic applications of Medicated Chewing gum[38]

Therapeutic use	Specific example
Oral antifungal	Econazole, Nystatine, Miconazole
Smoking cessation	Nicotine, Silver acetate
Pain relievers	Aspirin, Methadone
CNS stimulation, memory stimulant	Caffeine
Treatment of otitis media	Xylitol
Treatment of dental carries	Chlorhexidine
Treatment of vitamin deficiency	Vitamin- C
Treatment of motion sickness	Dimenhydrinate

Table 3: List of commercially available medicated chewing gums[39, 40]

Sr. No.	Trade mark	Active ingredient	Indication
1.	Aspergum	Aspirin	Pain relief
2.	Orbit white	Tricalcium phosphate	Dental hygiene
3.	Happydent white	Sodium chloride	Anti caries agent
4.	Travvel gum	Dimenhydrinate	Motion sickness
5.	Superpep	Dimenhydrinate	Motion sickness
6.	Nicorette	Nicotine	Smoking cessation
7.	Nicotinelle	Nicotine	Smoking cessation
8.	Hexit	Chlorhexidine	Antibacterial
9.	Stay alert	Caffeine	CNS stimulant
10.	Chooz	Calcium carbonate	Antacid
11.	Endekay	Vitamin C	Supplement
12.	Stay alert	Caffeine	CNS stimulant
13.	Go Gum	Guarana	Alertness
14.	Brain	DHA and CCE	Enhanced brain activity

Safety Aspects

Medicated chewing gums are preferably safe in present days. Formerly, hard chewing gum has caused health hazards. Extensive chewing for a long period of time may cause painful jaws muscle, and extensive use of sugar alcohol containing chewing gum may cause diarrhea. Long term frequent chewing of gum has been reported to cause increased release of mercury vapors from dental amalgam fillings. However, medicated chewing gum does not normally require extensive chewing, or consumption to great extent. Flavors, colors 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[41].

Stability of Medicated Chewing Gum

As per the Specifications of European Pharmacopoeia chewing gum normally contains little water (2-5%) and the water can be bound to the other components in the product and is therefore not very reactive. The water activity (Aw) in chewing gum normally below 0.6 and typically (0.4-0.5) if water content is very critical for stability of the drug, the chewing gum can be manufactured without water (less than 0.2). This will, however, often make the product hygroscopic and affect the texture. The low water content 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 appropriate packaging. For every temperature component, e.g. enzymes, the process temperature of50-60°C during mixing may create a stability problem. It is however, possible to operate the process at lower temperature to avoid this issue. So that stability of Chewing gum is comparable to most of other solid delivery systems[42].

Future Trends

Pharmaceutical companies will adopt this technology as a way to differentiate their product range in the current competitive landscape. New drug delivery systems are also gaining greater importance as a way to improve consumer's compliance and preferences. Health in Gum is a good way to achieve this. Today, chewing gum is still perceived as a confectionary pleasure by consumers, but its visibility as an attractive, high-valued drug delivery system is increasing. Major successes have been seen in the nicotine replacement therapy gum market, and several new products have also been developed in diverse categories such as analgesics, digestive, cough and cold medicines, and anti-allergics. Gum technology has evolved very much in the recent years. New gum medications in weight management, energy supply or oral care categories are also beginning to appear in market. Medicated chewing gum will progressively very trendy and leave its current niche category to become a solid drug delivery system in the coming years.

CONCLUSION

In the upcoming days, we may see drugs formulated into chewing gum in preference to other delivery systems to deliver drugs locally to the oral cavity as well as Systemic through GIT. The reason is simple that the chewing gum delivery system is convenient, easy to administer anywhere, anytime and its pleasant taste improves patient compliance. Chewing gum can be used without water, at any time. Consequently at present chewing gum is a convenient drug delivery system, which is appropriate for a wide range of active substances. It is very likely that MCGs will be a common drug delivery system and could be a commercial success in imminent future.

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