

# An Updated Review on: Medicated Chewing Gum- A Novel Drug Delivery System

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**Abstract:** Chewing gums are mobile drug delivery systems. Unlike chewable tablets medicated gums are not supposed to be swallowed and maybe removed from the site of application without resort to invasive means and medicated chewing gum MCG is solid, single dose preparation. It is a potentially useful means of administering drugs either locally or systemically via, the oral cavity. The medicated chewing gum has through the years gained increasing acceptance as a drug delivery system. Several ingredients are now incorporated in medicated chewing gum, e.g. Fluoride for prophylaxis of dental caries, chlorhexidine as local disinfectant, nicotine for smoking cessation, aspirin as an analgesic, and caffeine as a stay alert preparation. In addition, a large number of chewing gum intended for prevention of caries, xerostomia alleviation, and vitamin, mineral supplementation are currently available. The objective of this systematic study is to appraise existing evidence concerning a possible therapeutic effect of sugar-free chewing gum for patients.

**Keywords:** Chewing gum, Dental carries, Mobile drug delivery, Patient convenience

## 1. Introduction

It is well known fact that the right drug delivery system is critical to the success of a pharmaceutical product. 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. One of the reasons that the oral route achieved such popularity may be in part attributed to its ease of administration. Medicated chewing gum (MCG) is the gum base incorporating drug(s). Chewing gum is a pleasure that almost everyone enjoys. Chewing gums are mobile drug delivery systems. Chewing gum usually consists of a gum core, which may or may not be coated. The water content of chewing gum is very low and requires no preservatives. Medicated chewing gums are defined by the European Pharmacopoeia and the guidelines for pharmaceutical dosage forms issued in 1991 by the Committee for Medicinal Products for Human Use (CPMP) as 'solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not to be swallowed, providing a slow steady release of the medicine contained. Generally, chewing gum is a combination of a water-insoluble phase, known as gum base and some other ingredients. These include powdered sugar whose amount and grain size determine the brittleness of the resulting gum, corn syrup and/or glucose which serve as humectants and coat the sugar particles to stabilize their suspension and keep the gum flexible, various softeners, food colorings, preservatives, flavorings etc.

It can be used either for local (mucosal) treatment of mouth disease or for systemic (transmucosal) delivery by direct intraoral absorption through the buccal mucosa. In 1848, the first commercial chewing gum, 'state of Maine pure spruce gum', was introduced into the US market and the first patent was filed as dentifrice in 1869. The first MCG product 'Aspergum' containing acetylsalicylic acid for headache was launched in 1928. The success story of nicotine chewing gum in the 1980s has led to more general acceptance of chewing gum as a drug delivery system<sup>8</sup>. Regarding local

actions, it is possible to achieve beneficial effects with medicated chewing gum that might be superior to those achieved with lozenges. Medicated chewing gum is a valid alternative to standard, chewable or orally disintegrating tablet. The chewing gum drug delivery possesses other advantages such as more patient compliance as compared to buccal and sublingual drug delivery systems. Recently, the chewing gum bases are widely used in controlled drug delivery systems. CGDDs provide various new competitive advantages over conventional drug delivery systems. These include fewer side effects due to avoidance of high plasma peak concentrations and the promotion of the controlled release of the drug, fast onset of action because the active substances pass by the jugular veins directly to the systemic circulation. Also, Chewing gum has been used for centuries to clean the mouth and for freshening the breath. Medicated chewing gums are more effective in the removal of the extrinsic tooth stain. These days, MCG meets the same superior quality of standards as tablets as per current good manufacturing practices (GMP) guidelines, and it can be easily formulated to obtain different release rates of active pharmaceuticals.

**Table 1:** Marketed MCG Products

Sr no	Marketed MCG	Active ingredient	Indication
1	Aspergum	Aspirin	Pain relief
2	Orbit white	Calcium as tricalcium phosphate	Dental hygiene
3	Happydent white	Sodium chloride	Prevention of dental caries
4	Travel gum	Dimenhydrinate	Motion sickness
5	Nicorette	Nicotine	Smoking cessation
6	Hexit	Chlorhexidine	Antibacterial
7	Stay alert	Caffeine	CNS stimulant

### 1.1 Advantages

- 1) Convenient – promoting higher compliance
- 2) Discreet- less stigmatization
- 3) Administration without water can be taken anywhere
- 4) Excellent for acute medication

- 5) Advantageous for patients with difficulty in swallowing tablets
- 6) Pleasant taste.
- 7) Counteracts dry mouth: Through stimulation of the salivary secretion thereby Preventing.
- 8) Candidacies and caries.
- 9) Highly acceptable by children
- 10) The active compounds absorbed at oral level avoid the hepatic circulation and the associated metabolism.
- 11) The product is rapidly released from the gum after a short period mastication; some absorption takes place by directly through the oral mucosa depending on the active ingredient. Importantly not being swallowed the gum does not reach the stomach. Moreover, the stomach does not suffer from direct contact with high concentrations of active principle, thus reducing the risk of intolerance of the gastric mucosa.
- 12) Consequently, a lower dosage of substance may be therapeutically sufficient, possibly resulting in a fewer side effects, and promote fast absorption. Active substances released from chewing gum are dissolved in saliva when swallowed and are, therefore, readily accessible for absorption in the gastrointestinal tract.

### 1.2 Disadvantages

- 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 and diarrhoea.
- 3) Additives in gum like flavouring agent, Cinnamon can cause ulcers in oral cavity and liquorice cause hypertension.
- 4) Chlorhexidine or mucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue.
- 5) Prolong chewing on gum may result in pain in facial muscles.

### 1.3 Problems Occurred During Manufacturing of Chewing Gums

- Generally the chewing gum will jam the grinding machine, sticking to blades, screens and other surfaces if the moisture level is not controlled.
- Another problem associated with the above methods is that the gum base is heated to a fluid mass to facilitate mixing of other ingredients. Such elevated temperatures can cause degradation of heat sensitive compounds, including active agents and flavors.
- In manufacturing of chewing gum, sometimes organic solvents are used to dissolve the active agents. It is difficult to eliminate these organic solvents from the final product and may present certain health risks if even trace amounts remain in the final dosage forms.
- Water can also be utilized in gum preparations, but it is difficult to eliminate at low temperature. Heating the gum mass to eliminate water is not advisable because the gum will then become stickier, which makes handling difficult and. Interferes with large-scale production.

## 2. Composition of Medicated Chewing Gum

**1) Gum Base:** Gum base is an inert and insoluble nonnutritive product used as a support for the edible and soluble of the chewing gum (sugar, glucose, poly oils and flavors) Other raw materials are generally grouped in the following classes:

**2) Elastomers:** Including natural and synthetic rubbers. The gum base composition may contain conventional elastomer solvents to aid in softening the elastomer base component. Such elastomer solvents may comprise terpinene resins such as polymers of alpha-pinene or beta-pinene, methyl, glycerol or pentaerythritol esters of resins or modified resins and gums, such as hydrogenated, dimerized or polymerized resins or mixtures. The elastomer solvents may be employed in amounts from 5.0% to 75.0%, by weight of the gum base, and preferably from 45.0% to 70.0%, by weight of the gum base. Synthetic elastomers such as butadiene, styrene copolymers, polyisobutylene, isobutylene isoprene copolymers, polyethylene mixtures, and non-toxic vinyl polymer, such as polyvinyl alcohol are widely used bases. The molecular weight of the vinyl polymer may range from 3,000 to 94,000. The amount of gum base employed varies greatly depending upon various factors such as the type of base used, the consistency of the gum desired and the other components used in the composition to make the final chewing gum product. In general, the gum base will be present in amount from 5% to 94%, by weight of the final chewing gum composition. Preferably, the gum base is used in amounts from 15% to 45% and more preferably in amounts from 15% to 35% by weight of the final chewing gum composition.

**3) Plasticizers:** waxes, vegetable oils, glycerides. Plasticizers or softeners such as lanolin, palmitic acid, oleic acid, stearic acid, sodium stearate, potassium stearate, glyceryl triacetate, glyceryl lecithin, glycerylmonostearate, propylene glycol monostearate, acetylated monoglyceride, glycerine, natural and synthetic waxes, hydrogenated vegetable oils, polyurethane waxes, paraffin waxes, microcrystalline waxes, fatty waxes, sorbitolmonostearate, propylene glycol, may be incorporated into the gum base to obtain a variety of desirable textures and consistency properties.

**4) Adjuvants:** calcium carbonate, talc, or other charging agents are used. Mineral adjuvant such as calcium carbonate, magnesium carbonate, aluminum hydroxide, aluminum silicate, talc, tricalcium phosphate, dicalcium phosphate serve as fillers and textural agents.

**5) Antioxidants:** An anti-oxidant such as butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate and mixtures thereof, may be included as antioxidants.

**6) Compression adjuncts:** Suitable compression adjuvant such as silicon dioxide, magnesium stearate, calcium stearate and talc can be used in medicated chewing gum for ease of compression. The alkaline earth metal phosphates and alkali metal phosphates prevent caking and balling of "High" i.e. 2 to 8% moisture- containing chewing gum compositions during grinding. Additionally, it has been

discovered that maltodextrin enhances the grinding of "high" moisture-containing chewing gum compositions by absorbing moisture to allow lubrication in the gum as it separates into granules. If oil lubricants are used, it is preferred to be 0.4% to 1% by weight of the tableted chewing gum composition. The amount of glidant present in the tableted chewing gum composition is from 0.5% to 5% by weight of the tableted chewing gum composition. Those glidants useful are selected from the group consisting of alkali metal salts, talc, starch, polyhydric alcohols and mixtures. Antiadherents function to prevent tablet granulations from sticking to the faces of the punches and the die walls, but most importantly, prevent adherence of chewing gum granules from adhering to one another, a phenomenon known as blocking. Anti-adherents may be added to the chewing gum composition while the composition is in the hoppers, or subsequent to grinding and are selected from the group consisting of silicates, silicon dioxide, talc and mixtures thereof present in amount of 0.2% to 1% by weight of the tableted chewing gum composition and preferably about 0.3 to about 0.6% by weight. Generally anti-adherent is a finely divided low bulk density powder, which is preferably water insoluble. The preferred anti-adherents are fumed silica and talc. The term-fumed silica is meant to include pyrogenic silicas, micron sized silicas and hydrated silicas.

### 7) Sweeteners

In that mainly 5 sub parts are as following

- a) **Water-soluble sweetening agents:** xylose, ribulose, glucose, mannose, galactose, fructose, sucrose, maltose, invert sugar partially hydrolyzed starch, dihydrochalcones, monellin, steviosides, glycyrrhizin, and sugar alcohols such as sorbitol, mannitol, hydrogenated starch hydrolysates.
- 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 phenylglycerine and L-aspartyl- L 2,5-dihydrophenylglycine, L-aspartyl 2,5- dihydro-L phenylalanine – L aspartyl – L (1-cyclohexen) alanine.
- d) **Water-soluble sweeteners:** derived from naturally occurring water solublesweeteners, chlorinated derivatives of ordinary sugar (sucrose, known as Sucralose)
- e) **Protein based sweeteners:** such as thaumaococcusdanielli (Thaumatococcus 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.

**8) Coloring Agents:** The coloring agents include pigments, which may be incorporated in amounts up to about 6% by weight of the gum composition, titanium dioxide may be incorporated in amounts up to about 2%. The colorants may also include natural food colors and dyes suitable for food drug and cosmetic applications.

**9) Flavoring Agents:** Flavoring agents suitable for use are essential oils and synthetic flavors such as citrus oils, fruit essences, peppermint oil, spearmint oil, clove oil wintergreen oil, and anise oil.

### 3. Methods of Preparation

Different methods can be Employed for the manufacturing of Chewing Gum; however, these

Can be broadly classified into three main classes namely:

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

#### 1) Conventional/ traditional Method (Melting).

The first step of a typical process for manufacturing chewing gum is to melt and soften the gum base at about 60°C and place it in a kettle mixer, in which blades soften the base, then other ingredients such as sugar, glycerin, sweeteners, taste-masking agent are added to the softened base, lately the flavoring agent is added in the mixing procedure at 40°C, then cooling and rolling steps would be done, and the rolled chewing gum would then be cut into pieces of desired shapes and sizes. To make a coated gum tablet, a coating agent should be sprayed to form a uniform surface. Second type of this method is somehow different: The primary step of preparation is to set up a mixer (the mixer could be sigma blade or other types of mixers), if a sugar-containing gum is needed, the first step is to add corn syrup to the mixer, and then finely powdered sugar is added gradually. Sugar, used in this step, could be powdered sucrose, dextrose, fructose, corn syrup solids or combination of them.

After adding these sweeteners, plasticizers are added to modify the texture and regulate the cohesiveness. Glycerin is the most preferably plasticizer used. such as fillers, colorants, and flavorings. But it is recommended that flavorants being added to the matrix at the end of procedures when gum base is totally and completely homogenized because most flavorants are relatively volatile.

The proportions of components in the matrix are variable between sources and depend to desired characteristics. But powdered sugar has approximately the most proportion. The mechanical forces of mixer, that is, compressive and shear and heat can ease the softening process. When no heat is applied, a higher power is demanded. The mixing process continues until a homogenous mass is formed. The mixing process should last about 8 min. Another way of mixing ingredients is to add sugar gradually till the end of adding other components. After matrix preparation and completely mixing it, the commercially prepared particles of gum base are added to the chamber all at once. But it is believed that these particles should have been heated and mixed before adding all other ingredients to the mass of gum base. In this stage, mixing will continue for 10-20 min. The difference between this almost new method from the conventional (fusion) method in mixing techniques is wherein the sweetener matrix is first formed then gum base particles as pellets are added, but in conventional (fusion) method, the sweeteners and other ingredients are added to the molten gum base. This new processing method has advantages over



the previous way of processing, that is, the probability of producing sugar lumps is less than before.

### Limitations

- Elevated temperature used in melting restricts the use of this method for thermo labile drugs.
- Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult.
- Lack of precise form, shape or weight of dosage form.
- Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.
- 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

suitable sweeteners, corn syrups, starches, flavoring agents, and colorants, and then refrigerate and cool it by a freezer. One other method to provide a chewing gum with desired taste, color, and flavor is to mix gum base with favorable and apparatus or by contacting with a coolant like carbon dioxide to a temperature below  $-15^{\circ}\text{C}$  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. The minute particles may be coated by edible substances or premixed with powdery materials. For tabletization, compressing punches may be needed but an anti-adherent agent should be applied to avoid sticking to surfaces of punches.

### 3) Direct Compression Method

A new technology to make a chewing gum tablet is direct compression and tableting at high-speed standard machine, but as explained in a patent, this way of forming chewing gum tablets provides a quickly dissociable chewing gum, but after a few seconds of chewing, particles adhere together to form a uniform and homogenous mass. In this method; we need a granulating agent, most preferably that is sorbitol which can also act as a sweetener. A lubricant such as magnesium stearate, talc, stearic acid, hydrogenated vegetable oils, and sodium stearyl fumarate is added to formulation before tableting. First step of this method is dry mixing of gum base, granulating agent and at least one processing material then adding active ingredient, sweeteners, and other needed ingredients to the formulation in free flowing form of materials then directly compressing the chewing gum into tablets. In the first step, the temperature should not raise higher than the melting point of the gum base. After obtaining a uniform and slick mass, the temperature would lower to add other ingredients. The

compressed tablet is capable of releasing the active ingredient into the mouth cavity, after 2-10 chews dissociation reaches to maximum. We can formulate many sensitive active substances in model of compressed chewing gum that is advantage over previous methods, other significant benefits are:

- 1) Fast release.
- 2) Fast absorption, and
- 3) High content uniformity. Bi-layered compressed chewing gum tablets are now found in new pharmaceutical products.

### 3.1 Apparatus

Mainly two apparatus used

#### Apparatus I: Chewing Gum Apparatus, Compendial - European Pharmacopoeia

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

#### Apparatus II: Alternative Chewing Gum Apparatus, Noncompendial – Wennergren

The chewing procedure consists of reciprocations of the lower surface in combination with a shearing (twisting) movement of the upper surface that provides mastication of the chewing gum and at the same time adequate agitation of the test medium. The upper jaw has a flat surface that is parallel to the central part of the lower surface. The small brim of the lower surface is angled upwards (45 degrees) so that the lower surface functions as a small bowl with a flat bottom. This bowl prevents the chewing gum from sliding during mastication.

### 3.2 Factors Affecting Release of Active Ingredient

#### 1) Contact Time

The local or systemic effect is dependent on time of contact of Medicated Chewing Gum in oral cavity. In clinical trial chewing time of 30 minutes was considered close to ordinary use. The average chewing rate is about 60 chews every minute.

#### 2) Physicochemical properties of active ingredient

Physicochemical properties of active ingredient plays very important role in release of drug from Medicated Chewing Gum. 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.

### 3) Inter individual variability

The chewing frequency and chewing intensity which affect the drug release from Medicated Chewing Gum 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.

### 4) Formulation factor

Composition and amount of gum base affect rate of release of active ingredient. If lipophilic fraction of gum is increased, the release rate is decreased.<sup>19</sup> The influence of gum base mass on drug release has been investigated using salicylamide as model drug. When salicylamide was incorporated into a chewing gum, which contained a relatively large percentage of gum bases, the release after 30 min. of chewing was significantly lower (25.6%) compared to a gum in which less gum base was present (52%).

## 4. Evaluation Tests

### Content uniformity

Ten MCGs are selected randomly then their contents are measured, if each single content is between 85% and 115% of average content, it will comply with the test, but if one single preparation is out of this range the preparation will not comply with the test.

### Mass uniformity

Twenty MCGs are selected randomly and weighed, not more than two single mass should vary the average mass.

### Dissolution test

Mastication devices are designed to simulate human chewing behavior. To mimic a drug release in these devices or machines, the following test is specified.

This test determines the dissolution rate of active ingredients in MCG, a part of MCG is placed in the chamber of an apparatus which contains:

- Chewing chamber.
- A vertical piston and
- Horizontal pistons with sealed rings. MCG is chewed by horizontal pistons and is fixed by vertical piston.

During each chewing cycle, apparatus speed and pistons' movements should be controlled not to interfere with each other's work. Actually, horizontal and vertical pistons are, respectively, instead of teeth and tongue. One of the first chewing machines constructed by Christrup and Moller consists of two pistons, a reservoir, a thermostat and a regulator of the rate of chewing chamber. The chewing machine was developed again. The dissolution medium is swirled by ribs. The machine provides the rotation speed of 20 rpm and cycle frequency of 30 cycles per minute. In another apparatus designed by Wennergren (Kvistet *et al.*) they considered the effect of occlusal surfaces, rotary and shearing movements and the medium temperature on drug release. In the first apparatus adopted by EP, a defined volume of dissolution medium is shed into mastication chamber, the acidity of medium reaches to pH 6.0 by

phosphate buffer and the temperature should be  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ , the piston speed is 60 rpm. The usual number of chews per minute of a normal person is 60 strokes/min, then a part of MCG or the whole gum is placed into the chamber and the apparatus is set and the procedure is started. The machine is stopped at determined time, the remaining part of the gum is then removed and a sample of dissolution medium is prepared, the content of active agent(s) is determined by a suitable method, after each sampling, dissolution medium could have been replaced by a new and fresh medium so that the dilution factor should be calculated. The content of active agent(s) in the gum residue could be determined too. This test is carried out on three MCGs for three times.

## 4.1 Evaluation of mechanical properties of chewing gums

### Tensile test

Simply that is a test in which the chewing gum specimens are subjected to a tension until such time as failure occurs. The load required for elongation before fracture is recorded by computer. The tensile testing machine is set for the determination of force-elongation properties. Engineering stress and strain are obtained as describe below:

Stress =  $\sigma = P/A_0$  (Load/Initial cross-sectional area).

Strain =  $e = \Delta l/l_0$  (Elongation/Initial gage length).

The first part of the curve obeys Hook's law where the ratio of stress to strain is constant, and a linear relationship can be observed. The shape, size, width, thickness, and gauge length are to be specified precisely because we wish to avoid having a break or nonuniformity within the area being gripped. Hence, the specimen should be suitably prepared for gripping into the jaws of the testing machine according to the standards. The major parameters obtained from the test and the explanations of the stress-strain curve are tensile strength, yield strength, and fracture strength as expressed by percent elongation and reduction in area, the highest stress the specimen sustains during the test and before failure is typically recorded as ultimate tensile stress. After yield strength, we enter the plastic region where the chewing gum will not revert to its first shape by removing the load.

## 4.2 Evaluation parameters of medicated chewing gum

**Product performance test:** Two different types of tests are performed to assess the drug product characteristics: product quality and performance tests. Currently USP contains individual monographs with product quality tests for Nicotine Polacrilex and Nicotine Polacrilex Gum. Ph. Eur. has adopted a general monograph on medicated chewing gums and a monograph describing the apparatus for dissolution testing of medicated chewing gums.

**Table 5** shows the product quality tests associated with the chewing gum preparations described in Ph. Eur. in general and specifically with nicotine polacrilex resins and gums in USP. In addition to the product quality tests, additional testing specific to the product may be performed to ensure the final quality of the finished product. This may include, for example, texture analysis, product feel and consistency, evaluation of flavors and sweeteners, tests for coatings,

impurities, water content, degradation products, residual solvents, etc.

**Table 5:** Product Quality Tests For Medicated Chewing Gums

Dosage Form	Nature	Patient Activation	Safety Test Requirement	Product Quality Tests
Medicated gums	Solid/semi-solid	Yes	Yes	Assay Identification, Uniformity of dosage units, content, and mass

### In vitro drug release from MCG:

Mainly 2 types:

1. Unofficial
2. Official

#### 1) Unofficial single-module chewing apparatus:

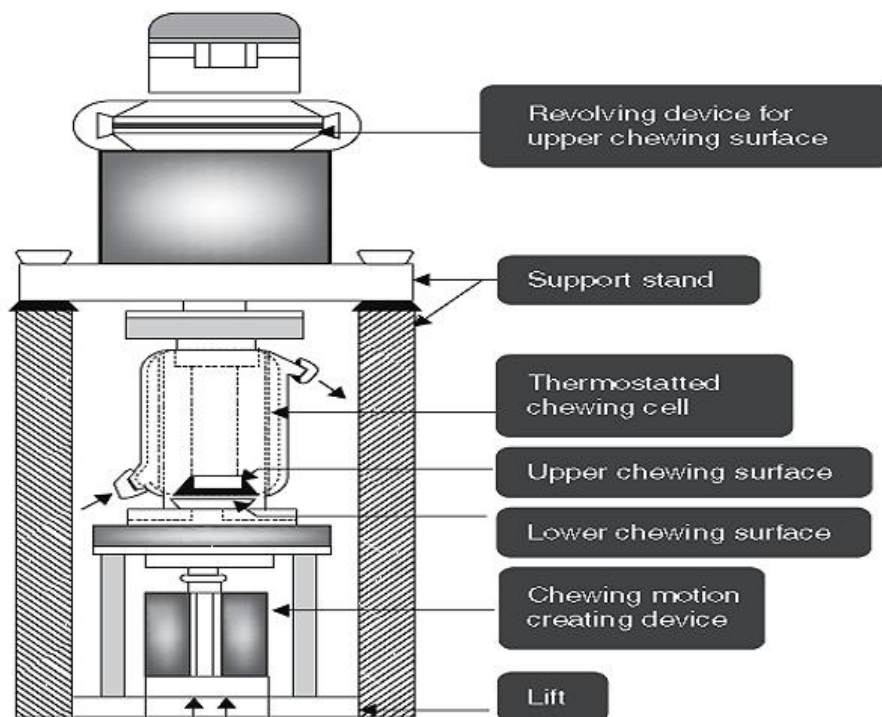
One of the unofficial apparatus for carrying out dissolution studies of MCG was designed by Wennergren. This apparatus consists of a two-piston and temperature-controlled reservoir for dissolution medium, as shown in a schematic representation in **Figure 1**. The upper jaw has a flat surface that is 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.

#### 2) Official MCG chewing apparatus

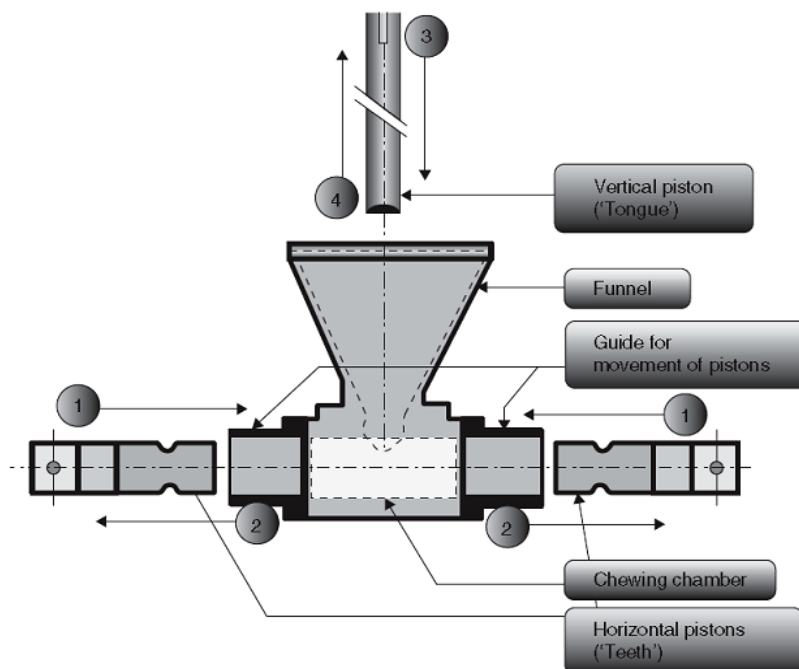
The official modified dissolution apparatus for assessing drug release from MCG, as per European Pharmacopoeia, is depicted in **Figure 2**. In this apparatus, in addition to the pair of horizontal pistons ('teeth'), the chewing chamber is supplied with a vertical piston ('tongue') working alternate 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  $37 \pm 0.5^\circ\text{C}$  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.



**Figure 1:** Schematic Representation of Unofficial Single Module Chewing Apparatus





**Figure 2:** Schematic Representation of Modified Dissolution Apparatus as Per European Pharmacopoeia, where Numbered Arrows Indicate Sequence Of Motion

**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.

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.

### 3) Chewing gum packaging

The advantages of chewing gum packaging are clear to the world since it extends shelf-life of the product by preventing aroma and flavor to disappear. It also provides moisture retention and gum stability. There are too many packaging methods with a wide range of options. In almost all of packaging types, we need a wrapping machine that receives and wraps the sticks of gums; in some cases, the wrapper machine seals the end of the package. In the following, a

formed blister pack may be used then a foil will be heat-sealed at the back or a traditional packaging may be applied by lining the pellets up in a row and wrapping then sealing the both ends. The manufacturing and packing steps should be performed at about 20-25°C and relative humidity of 57%. Packaging has a substantial portion in the whole process both in terms of cost and time.

Undoubtedly, packaging influences attraction of product among consumers, thus a well-favored and stylish design can attract more consumers to buy the specific product. Therefore, besides protecting the content, avoiding impurity, expediting transport and improving storage, packaging can influence consumers' willingness to buy the product and capture his attention during purchase competition.

## 5. Applications

### Dental Caries

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

### Systemic Therapy

Chewing gum as a drug delivery system is beneficial to a number of indications, some of which are discussed below:

- a) Pain-Treatment of minor pains, headache, muscular aches can be successfully accomplished.
- b) Smoking Cessation-Chewing gum formulation containing nicotine, lobeline and silver acetate has been clinically tested as aids to smoking cessation. Nicotine is a natural alkaloid occurring in the leaves of tobacco plant. It is a therapeutic agent intended to help smokers break the psychological habit of smoking by reducing the nicotine withdrawal symptoms normally experienced when smoking is stopped. Thus the patient can control the drug intake to match his needs. Increasing the Ph of the medium in which it is dissolved can enhance nicotine absorption.
- c) Obesity-Active substances like chromium, guaran and caffeine are proved to be efficient in treating obesity. Chromium is claimed to reduce craving for food due to an improved blood-glucose balance. Caffeine and guarantee stimulate lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger.
- d) Other indications- xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety etc are all indications for which chewing gum as drug delivery system could be beneficial.

### Safety aspect

Generally, today it is perfectly safe to chew chewing gum. Previously, hard chewing gum has caused broken teeth. Extensive chewing for a long period of time may cause painful jaws muscle, and extensive use of sugar alcohol containing chewing gum may cause 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, colour etc. may cause allergic reactions. Overdosing by use of chewing gum is unlikely because a large amount of gum has to be chewed in a short period of time to achieve this. Swallowing pieces of medicated chewing gum will only cause minor release of the drug because the drug can only be released from the gum base by active chewing. As a general rule, medicated chewing gum (like other medicines) should be kept out of reach of children, if required; drug delivery may be promptly terminated by removal of the gum.

## 6. Future Trends

Future of chewing gum will reveal all of the scientists' efforts for the development of chewing gum as a modern drug delivery system and progress of chewing gum production technology. In the future, other attempts will be seen to formulate more drugs using chewing gum as a drug delivery system. Treatment of fungal diseases, prevention of caries and other dental health issues, smoking cessation, etc., are common health work of MCGs. But remineralization of teeth, cold relief, energy enhancing, anti-nausea and so many new advantages of this novel drug delivery system are going to play an important role through future studies. MCGs are admissible alternatives of chewable or standard tablets and oral disintegrated dosage forms.

Actually, it takes time for chewing gum to get acceptance by people as a drug delivery system, but we hope that MCG finds its real place in industry and market and between patients soon, through its numerous advantages.

Long lasting flavored, filled gums, timed-release, and other new MCGs formulated for diseases that previous delivery systems have been used for, are trendy products to be seen in the future as a new kind of chewing gum which is made biodegradable and can be dissolve in around 1 month. We predict a brighter future for MCG as a novel drug delivery system than previous oral systems.

### Chewable Birth Control Will Be Available Soon:

Women will have another birth control option next year - chewable pills. Next spring, Warner Chilcott Inc. will start marketing its spearmint-flavored Ovcon 35, a chewable birth control drug approved by the Food and Drug Administration.

## 7. Conclusion

Chewing gum offer several advantages over chewable tablet, lozenges and other related formulations. Chewing gum is an excellent drug delivery system for self-medication, as it is convenient and can be administered discreetly without water. 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 revenue.



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