



## Medicated Chewing Gums – A Modern Era

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### ABSTRACT

Absorption of drugs through the oral cavity was noted as early as 1847 by Sobrero, the discoverer of nitroglycerin, and systemic studies of oral cavity absorption were first reported by Walton and Lacey in 1935. As a site for drug delivery, the oral cavity offers many advantages over other routes of drug administration. The mucosal lining of the oral cavity are readily accessible. Chewing gums are mobile drug delivery systems. 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 gums intended for prevention of caries, xerostomia alleviation, and vitamin/ mineral supplementation are currently available. Today improved technology and extended now have made it possible to develop and manufacture medicated chewing gum with predefined properties.

**Keywords:** mobile drug delivery system, gum bases, taste, elastomers

### INTRODUCTION

Medicated chewing gum is a solid, single-dose preparation that has to be chewed and not swallowed; chewing gums contain one or more active ingredients that are released by chewing. A medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose, after which the remaining mass is discarded.

During the chewing process the drug contained in the gum product is released from the mass into saliva & could be absorbed through the oral mucosa or swallowed reaching stomach for gastro-intestinal absorption.<sup>1</sup>

Chewing gum can be used as a convenient modified release drug delivery system.

Medicated chewing gums are currently available for pain relief, smoking cessation, travel illness, and freshening of breath. The first commercial chewing gum "State of Maine pure spruce gum" was marketed in 1948 in the U.S.A. The first patent was filed in 1869. The gum was intended as dentifrices but it has never been marketed.<sup>2</sup>

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 (a) local treatment (b) systemic effect after absorption through the buccal and sublingual mucosal and from the gastrointestinal tract. Chewing gum can be retained in the oral cavity for a long period and, if the drug is readily absorbed across oral mucosa, chewing gum can provide a

fast onset time for a systemic effect and the potential for avoidance of gastrointestinal and hepatic first-pass metabolism of susceptible drugs.

Physicochemical properties of the drug like aqueous solubility, 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.

Pharmacological Active Agents or Drugs are formulated into variety of dosage forms like Tablets, Capsules, Injectables, Inhalers, Ointments etc considering Physicochemical properties, Pharmacokinetic, Pharmacodynamic parameters and Biopharmaceutical aspects of Drugs. In addition to its confectionary role, Chewing Gum (CG) also has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients.

Many therapeutic agents are absorbed in the oral cavity. For the drugs having significant buccal absorption, dosage forms such as Lozenges, Chewable tablets and Chewing Gum permits more rapid therapeutic action compared to per-oral dosage forms<sup>3</sup>.

Chewing Gum was approved as a term for pharmaceutical dosage form by the commission of European Council.

Today improved technology and extended know how have made it possible to develop and manufacture medicated chewing gum with pre-defined properties.



**Advantages of MCGs<sup>3</sup>**

- Dose not requires water to swallow. Hence can be taken anywhere.
- Advantageous for patients having difficulty in swallowing.
- Excellent for acute medication.
- Counteracts dry mouth, prevents candidiasis and caries.
- Highly acceptable by children.
- Avoids First Pass Metabolism and thus increases the bioavailability of drugs.
- Fast onset due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation.
- Gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients.
- Aspirin, Dimenhydrinate and Caffeine shows faster absorption through MCG than tablets.
- Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased.

**Disadvantages of MCGs<sup>4,5,6,7</sup>**

- 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.
- Sorbitol present in MCG formulation may cause flatulence, diarrhoea.
- Additives in gum like flavouring agent, Cinnamon can cause ulcers in oral cavity and liquorice cause hypertension.
- Chlorhexidine oromucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue.
- Chewing gum have been shown to adhere to different degrees to enamel dentures and fillers.
- Prolong chewing on gum may result in pain in facial muscles and earache in children.

**Saliva – Chewing Gum<sup>8</sup>**

Chewing gum stimulates one of the most powerful defense mechanisms in the body – saliva. Saliva is vital to good oral health.

Saliva has three main protective (anti-caries) functions:

1. Dilutes and washes away food debris;
2. The bicarbonate neutralizes and buffers plaque acids; and

3. The calcium and phosphate ions contribute to remineralization of early dental caries lesions. Saliva also contains antibacterial agents.

Saliva alone is a powerful protector of the oral cavity. And, chewing gum is an efficient and pleasant way to increase saliva without drugs. Increasing saliva in the mouth is accomplished by the stimulation of flavors and the gustatory action of chewing.

Together these forces stimulate the salivary glands to increase their flow rate by about 10 times the resting state during the first few minutes of chewing and keep it significantly elevated for as long as one chews.

**Chewing Gums – Taste and Texture<sup>8</sup>**

To succeed in the market, the chewing gum formulation must have a pleasant taste and texture. Most active substances have an unpleasant, bitter or metallic taste. Since the active substance will be released in the oral cavity and remain there for a longer period of time than in the case with ordinary delivery forms (usual chewing time is 10 to 20 minutes), unique expertise in taste definition, taste masking and taste modification are essential for the success of a medical chewing gum product. Moreover, there are no official standards for unpleasant taste, making it necessary to establish information on taste properties for all new active substances. In most cases, it is desirable that the taste fades out when the active substance has been fully released.

The release profile of the flavours and sweeteners, therefore, is usually designed to follow the release profile of the active substance. One of the major challenges for the product developer is that any small adjustment in the amount of active substances, flavours and sweeteners often changes the gum base texture, requiring adjustments to tailor-make the gum base to the active substance. During the development process, therefore, it is necessary to test several parameters related to taste and texture continuously.

**Mechanism of Drug Transport<sup>9</sup>**

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

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:

$$J = \frac{DKp}{\Delta C_e}$$

Where, J = drug flux, D = diffusivity, Kp = partition coefficient,  $\Delta C_e$  = concentration gradient, h = diffusional path length



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

Two pathways of permeation across the buccal mucosa are transcellular and paracellular. Permeability coefficient typically ranges from  $1 \times 10^{-5}$  to  $2 \times 10^{-10}$  cm/s. The pathway of drug transport across oral mucosa may be studied using:

- Microscopic techniques using fluorescent dyes
- Autoradiography and
- Confocal laser scanning microscopic procedures.

### Composition of MCGs<sup>10</sup>

#### 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:

#### 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.

#### 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, glyceryl monostearate, propylene glycol monostearate, acetylated monoglyceride, glycerine, natural and synthetic waxes, hydrogenated vegetable oils, polyurethane waxes, paraffin waxes, microcrystalline waxes, fatty waxes, sorbital monostearate, propylene glycol, may be incorporated into the gum base to obtain a variety of desirable textures and consistency properties.

#### 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 serves as fillers and textural agents.

#### Antioxidants

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

#### Compression Adjuvants

Suitable compression adjuvants 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 antiadherents are fumed silica and talc. The term-fumed silica is meant to include pyrogenic silicas, micron sized silicas and hydrated silicas.



## Sweeteners

### 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 hydrosates.

### Water-Soluble Artificial Sweeteners

Soluble saccharin salts, i.e. sodium or calcium saccharin salts, cyclamate salts.

### Dipeptide based Sweeteners

Laspartic acid derived sweeteners such as Aspartame, Alitame, methyl esters of L-aspartyl-L phenylglycerine and Laspartyl-L 2,5-dihydrophenylglycine, L-aspartyl 2,5-dihydro-L phenylalanine – L aspartyl – L(1-cyclohexen) alanine.

### Water-Soluble Sweeteners

Derived from naturally occurring water soluble sweeteners, chlorinated derivatives of ordinary sugar (sucrose, known as Sucralose)

### Protein based Sweeteners

Such as thaumaococcus danielli (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.

### 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.

### 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.

### 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. MCG consists of masticatory gum core that may be coated. The core is composed of an aqueous insoluble gum base which can be mixed with

Sweeteners and Flavours. The coating can be applied as a film of polymers, waxes, sweeteners, flavours and colours or a thick layer of sugar or sugar alcohol shown in Table 1.

**Table 1:** Optimal Properties of Drug

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

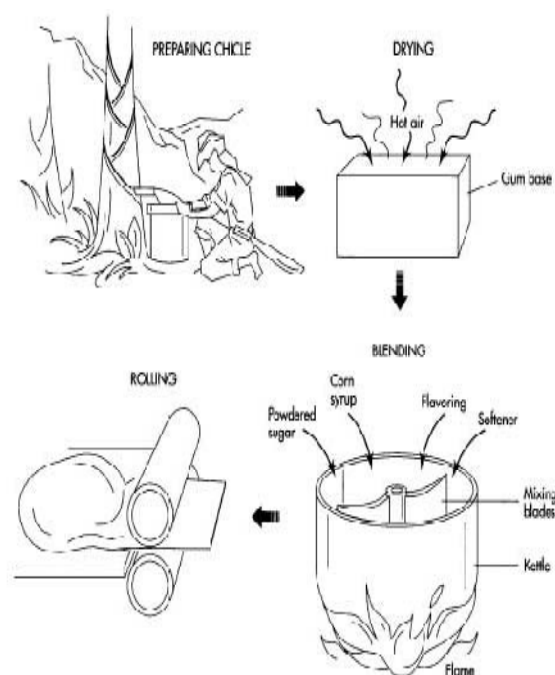
## Methods of Manufacturing of Chewing Gums

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

### 1. Conventional/ Traditional Method (Fusion)<sup>11</sup>

Components of gum base are softened or melted and placed in a kettle mixer to which sweeteners, syrups, active ingredients and other excipients are added at a definite time. The gum is then sent through a series of rollers that forms into a thin, wide ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavor. In 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.



**Figure 1:** Conventional/Traditional (Melting) Manufacture of a Medicated Chewing Gum



## Limitations

1. Elevated temperature used in melting restricts the use of this method for thermo liable 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<sup>12</sup>

This method has been developed with an attempt to lower the moisture content and alleviates the problems mentioned in conventional method. In Cooling and Grinding method 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 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 sublimates 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 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.

### *Use of 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.

### *Use of Grinding Agents*

To prevent the gum from sticking to the grinding apparatus, 2-8% by weight of grinding aid such as alkaline metal phosphate, an alkaline earth metal phosphate or maltodextrin can be incorporated.

However practical use of these substances is limited because these substances are highly alkaline and hence would be incompatible with acidic ionisable therapeutic agents.

They also tend to remain in the composition and chewing gum tablet and thus may be problematic from therapeutic and safety point of view.

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.

### **Tableting**

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 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.

### Limitation

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

### 3. Direct compression<sup>13</sup>

Recently, free flowing directly compressible co-processed gum materials such as Pharmagum developed by SPI Pharma and Health in gum developed by CAFOSA, have become available in the market. Chemically, it is a mixture of polyols (sorbitol/xylitol/mannitol) and of sugar with gum, plasticizers and anticaking agents. These gums are manufactured under cGMP conditions and comply with food chemical specifications and are 'generally regarded as safe' (GRAS), regulated by FDA title 21 C.F.R Section 172.615. Chewing gum made by this gum material can be directly compressed on a pharmaceutical in-house tablet compression machine, which enables rapid and low cost development of MCG. As it does not require high temperature, thermosensitive APIs can also be processed.

This method is also ideal for water-sensitive APIs. Formulations made with Pharmagum M and Health in gum is similar to the tablet in appearance. Gum formed using a compressible formulation is many times harder and crumbles, and when pressure is applied it gives faster release of drugs than conventional methods owing to lower bonding of drug with gum material.

### Some Important Formulation Aspects<sup>14</sup>

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

### Factors Affecting Release of Active Ingredient<sup>15</sup>

1. **Contact Time:** The local or systemic effect is dependent on time of contact of MCG in oral cavity. In clinical trial chewing time of 30 minutes was considered close to ordinary use.
2. **Physicochemical properties of active ingredient:** Physicochemical properties of active ingredient plays very important role in release of drug from MCG. The saliva soluble ingredients will be immediately

released within few minutes whereas lipid soluble drugs are released first into the gum base and then released slowly.

3. **Inter individual variability:** The chewing frequency and chewing intensity which affect the drug release from MCG may vary from person to person. In-vitro study prescribed by European Pharmacopoeia suggest 60 cycles per minute chewing rate for proper release of active ingredient.

### Evaluation of MCGs

#### Uniformity of Content

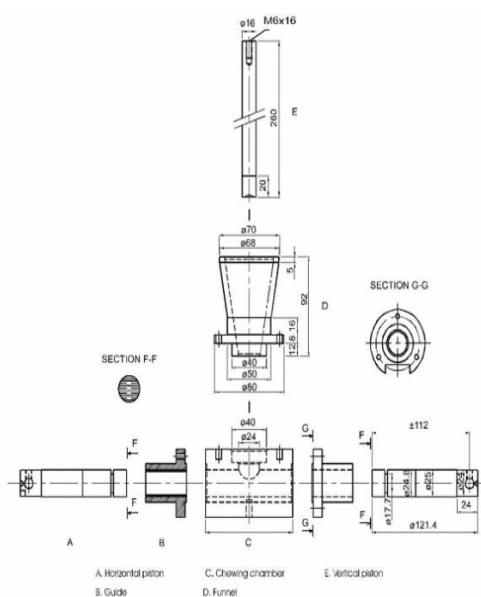
Unless otherwise prescribed or justified and authorised, MCGs with a content of active ingredient less than 2 mg or less than 2 per cent of the total mass comply with test A for uniformity of content of single-dose preparations. If the preparation contains more than one active substance, the requirement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

#### Uniformity of Mass

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

#### In-vitro Drug Release

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



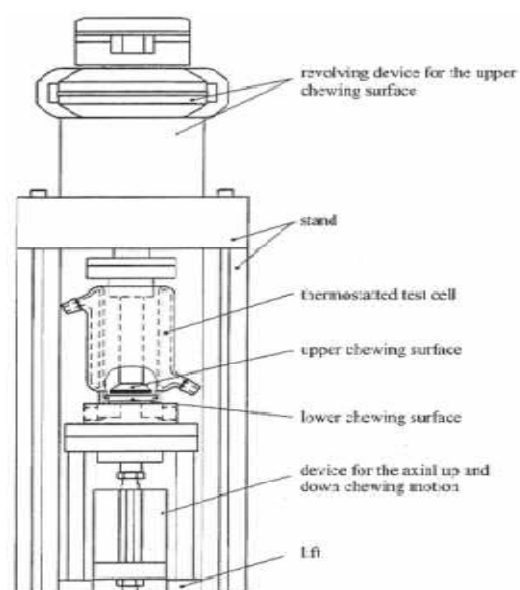
**Figure 2:** Construction of the Compendial chewing gum apparatus

### Apparatus I. Compendial Chewing Gum Apparatus

The chewing apparatus for MCG was adopted by Ph. Eur. in 2000. Figure 2 shows the construction of the apparatus. The chewing apparatus comprises a chewing chamber, two horizontal pistons, and a third vertical piston (tongue). The vertical piston operates alternatively with the two horizontal pistons and makes sure the gum stays in the right place between hews. If necessary, it is feasible to construct the machine so that at the end of the chew the horizontal pistons rotate around their own axes in opposite directions to each other to obtain maximum chewing.

### Apparatus II: Noncompendial Chewing Gum Apparatus

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



**Figure 3:** Schematic representation of unofficial single module chewing apparatus

### In Vivo 'Chew-Out' Studies<sup>16</sup>

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

swallowed, it is absorbed through the gastrointestinal tract.

### Release of Drug in Saliva

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

### Dissolution Test of Residual MCGs<sup>17,18</sup>

In this experiment, gums are tested by a panel of volunteers to verify the drug release process

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

### Urinary Excretion Profile of MCGs

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

30 minutes and urine samples are analyzed by suitable analytical methods.

### **Buccal Absorption Test**

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

### **Texture Analysis**

#### **Texture Studies by Instrument**

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

#### **Texture Studies by Human Volunteer**

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

#### **Stability:** <sup>19</sup>

The stability of chewing gum is comparable to that of most other solid delivery systems. Chewing gum normally contains little water (2.5%). If the water content is very critical for the stability of drug, the chewing gum can be manufactured without water (less 0.2%). This will however, often make the product hygroscopic and will affect the texture. The low water content also inhibits microbial growth in the chewing gum during storage. Furthermore, the product can be protected against oxidation by a sealed coat and by an appropriate packing. For every temperature-labile component, e.g. enzymes, the process temperature of 50-60 °C during mixing may create a stability problem. It is however possible to operate the process at a lower temperature to avoid this issue.

### **Applications**<sup>20-24</sup>

#### **Dental caries**

- Prevention and cure 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 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.

#### **Systemic Therapy**

- **Pain-** chewing gum can be used in treatment of minor pains, headache and muscular aches.
- **Smoking cessation-** Chewing gum formulation containing nicotine and lobeline have been clinically tested as aids to smoking cessation.
- **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 guaran stimulate lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger and crumble when pressure is applied resulting in faster release than conventional methods. Use of Pharmagum S, M and C enables formulators to utilize a gum delivery system quickly & more cost effectively than by traditional methods.
- **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.

#### **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.

**Table 2:** Medicinal Chewing Gum Sold Worldwide

Trade Mark	Active Substance	Aim	Commercially Available
Aspergum	Aspirin	Pain relief	North America
Nicorette	Nicotine	Smoking cessation	Worldwide
Nicotinelle	Nicotine	Smoking cessation	Western Europe, Australia, New Zealand
Trawell	Dimenhydrinate	Travel illness	Italy, Switzerland
Superpep	Dimenhydrinate	Travel Illness	Germany, Switzerland
Chooz	Calcium Carbonate	Stomach acid neutralization	USA
Endekay Vitamin C	Vitamin C	General health	Middle East, United Kingdom
Stamil Vitamin C	Vitamin C	General health	Australia
Source Vitamin C	Vitamin C	General health	Australia
Brain	DHA & CCE	Enhanced brain activity	Japan
Stay Alert	Caffeine	Alertness	USA
Café Coffee	Caffeine	Alertness	Japan
Buzz Gum	Guarana	Alertness	United Kingdom
Go Gum	Guarana	Alertness	Australia
Chroma Slim	CR	Diet	USA
Fluorette	Fluoride	Cariostatic	USA
Vitaflo CHX, Advanced Plus, Hexit	Chlorhexidine	Preventing Tooth decay	USA
Travvel	Dimenhydrinate	Motion sickness	USA, Australia
V6	Xylitol	Prevention of formation of dental caries	United Kingdom

## CONCLUSION

A chewing gum formulation must have a pleasant taste and texture. Most active substances have an unpleasant, bitter, or metallic taste. Since the active substance will be released in the oral cavity and remain there for a longer period of time than is the case with ordinary delivery forms (usual chewing time is 10 to 20 minutes), unique expertise in taste definition, taste masking, and taste modification are essential to the success of a medical chewing gum product. Though chewing gum as a drug delivery system has currently gained wide acceptance only within smoking cessation and oral healthcare, vast interest in this mode of drug delivery for a wide variety of other indications exists and continues to grow. Clinical trials have confirmed the advantages to be gained by exploiting the effects of chewing gum, the convenience of the delivery and the possibilities of buccal absorption and local effect. Furthermore, one trial has indicated that chewing gum is possibly a safer drug delivery system for

active substances that are susceptible to abuse. As chewing gum as a drug delivery system is to be expanded into additional therapeutic areas, it is important that the delivery form is acceptable to the end-users.

Clinical trials and market research have proven this to be the case. In the coming years, new formulations will enter the market and chewing gum will become a much more common drug delivery system.

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