

REVIEW ARTICLE

A Holistic Concept on Medicated Chewing Gum

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ABSTRACT

Chewing gum has been used for centuries to clean the mouth or refresh the breath. Chewing gum was patented for first time on filed in 1869 and the first medicated chewing gum was commercially made available 1928. In 1991 The European Pharmacopoeia defines medicated chewing gum as “solid, single-dose preparations with a base consisting mainly of gum that are intended to be chewed but not swallowed”. Medicated chewing gum is a masticatory gum base containing active ingredient which offers various advantages over conventional tablets. Medicated chewing gums are not supposed to be swallowed and may be removed from the site of application without resorting to invasive means. The release of drug in medicated gums requires the active and continuous masticatory activities for activation and continuation of drug release. Medicated chewing gums are used for both local and systemic action and not only for special population groups with swallowing difficulties such as children and the elderly people, but also for the general population, including the young generation. It was concluded that Chewing gum is an excellent drug delivery system for self-medication as it is convenient and can be administered discretely without water or any other liquid. Basics of the gum formulation, quality control tests, regulatory and safety issues have been addressed to ensure desired therapeutic effects.

Key words: Medicated Chewing Gum, Dental caries and Oral Drug Delivery System.

INTRODUCTION

Pharmacological Active Agents or Drugs are formulated into variety of dosage forms like Tablets, Capsules, Injectable, Inhalers, and Ointments etc. considering physiochemical properties, Pharmacokinetic and Pharmacodynamics parameters and Biopharmaceutical aspects of Drugs. The Medicated Chewing Gum (CG) has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients^[1]. MCG has become the most convenient drug delivery system in present age which is appropriate for a wide range of active substances^[2].

Majority of therapeutic agents are absorbed in the oral mucosa. The drugs which show significant buccal absorption, dosage forms such as Chewing Gum permits more rapid therapeutic action compared to other oral dosage forms^[3]. Chewing gum has been very well received by the parents for use in children. Children particularly may consider chewing gum as a more preferred method of drug administration compared with oral liquids and tablets. MCG is used in the local treatment of diseases of oral cavity as well as treatment of

systemic disorders. Chewing gum has been used for over centuries to clean the mouth and freshen the breath^[4]. In 1991, Chewing Gum was approved as a term for pharmaceutical dosage form by the commission of European Council.^[5]



Figure 1: Medicated Chewing gum

HISTORY^[6]

Chewing gum has an old and long history, in 50 AD, the Greeks uses mastiche, and a resin from the bark of mastic tree to clean their teeth. (The English word "masticate" is derived from the root word mastiche.) One thousand years ago, the ancient Mayan Indians of Yucatan chewed tree resin (chicle) from the Sapodilla tree. In 1848 Spruce gum was manufactured which became the first chewing gum product to be manufactured

commercially named as "STATE OF MAINE PURE SPRUCE GUM." Many years later due to many drawbacks its use was replaced by paraffin, which is still being chewed in many areas. The first patent for chewing gum was filed on December 28, 1869 by Dr. William F. Sample, a dentist from Mount Vernon, Ohio was U.S. number 98,304. The product composition was liquorice and rubber dissolved in alcohol and naphtha was intended to be used as a dentifrice initially.

In 1891, William Wrigley Jr., arrived in Chicago with \$32 in cash with a desire to market his special variety of soap. Eventually, he switched from soap to baking powder sales and offered chewing gum premiums to merchants who became his customers. By 1892, when the chewing gum premiums had become more popular than the baking powder, Wrigley launched his first chewing gum, LOTTA and VASSAR. Then after one year, he developed JUICY FRUIT, and then after, WRIGLEY's SPEARMINT gum.

The "Happy Tooth", a registered trademark which proves product to be tooth-friendly. Labeling such as "safe for teeth" or "tooth-friendly" under the license of the "Tooth friendly Sweets International Association" are included in the chewing gum, and this labeling proved informative for the alert consumer.^[7]

ADVANTAGES OF MCG ^[1, 5]

1. Does not require water to swallow so can be easily taken anywhere.
2. Compatible for patients having difficulty in swallowing.
3. Excellent for acute medication.
4. Counteracts dry mouth, prevents candidiasis and caries.
5. Highly acceptable by children.
6. Bypasses first pass metabolism and thus increases the bioavailability of drugs.
7. Fast onset of action due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation.
8. Gum does not reach the stomach which leads to the minimal effect of formulation in the gastrointestinal tract.
9. Stomach does not suffer from direct contact with high concentrations of active medicaments thus reducing the risk of intolerance of gastric mucosa.
10. Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly.

11. Duration of action is increased.
12. Aspirin, Dimenhydrinate and Caffeine shows faster absorption through MCG than tablets.
13. Stimulates flow of saliva in the mouth.
14. Neutralizes plaque acids that form in the mouth after eating fermentable carbohydrates.
15. Helps whiten teeth by reducing and preventing stains.

DISADVANTAGES OF MCG ^[4- 11]

1. Risk of over dosage with MCG compared with chewable tablets or lozenges that can be consumed in a considerable number and within much shorter period of time.
2. Sorbitol present in MCG formulation may cause side effects like diarrhea.
3. Additives in gum like flavoring agent and the products obtained from natural sources like Cinnamon can cause Ulcers in oral cavity and liquorice cause Hypertension.
4. Chlorhexidine oromucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue.
5. Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers.
6. Prolong chewing on gum may result in pain in facial muscles and earache in children.

ANATOMY AND PHYSIOLOGY OF ORAL MUCOSA ^[12, 13]

The oral mucosa can be subdivided into two general regions, the outer vestibule and oral cavity. Microscopically the oral mucosa consists of three main layers:

- A. Oral epithelium
- B. Lamina propria
- C. Sub mucosa

A. Oral epithelium:

The epithelium of mouth consists of stratified, squamous epithelium, which may be either keratinized or non-keratinized. Keratinized epithelium is dehydrated, mechanically tough and chemically resistant. It is found in oral cavity such as mucosa of gingival and hard palate. Nonkeratinized epithelium is relatively flexible and is found in areas such as the soft Palate, the floor of mouth, the lips and the cheeks. The epithelium of the oral cavity is supported by the basement membrane. The membrane separates the epithelium from the underlying connective tissue layer. This process is represented in four morphological layers:

- Basal layer;
- Prickle cell layer;
- Intermediate layer;
- Superficial layer

B. Lamina propria:

The lamina propria contains a sheet of connective tissue containing collagen elastic fiber and cellular components in hydrated ground substance. It also consists of blood capillaries and nerve fibers which serves the mucosa. The blood vessels in the lamina propria are mainly engaged in the delivery of drug moieties in systemic circulation.

C. Submucosa:

A submucosa may or may not be present deep to the dense layer of the lamina propria, depending on the region of the oral cavity. The submucosa usually contains loose connective tissue and also adipose connective tissue or salivary glands and also overlying bone or muscle within the oral cavity. Saliva is a hypotonic, watery secretion containing variable amount of mucus, enzyme, antibodies and inorganic ions. The surface of mucus membrane is constantly washed by a stream of about 0.5 to 2L of saliva daily produce in the salivary gland the chief secretion is supplied by three pairs of glands i.e. the parotid, the sub maxillary and the sublingual glands.

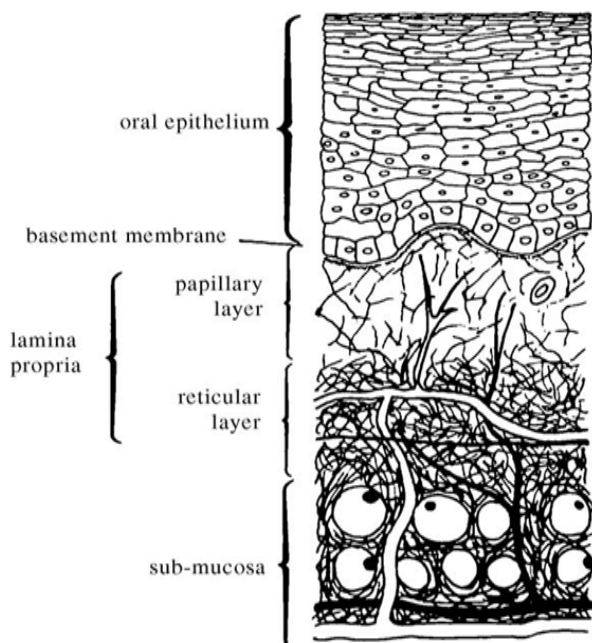


Figure 2: Generalized Structure of Oral Mucosa

COMPOSITION OF MEDICATED CHEWING GUM ^[5, 14]

Chewing gum is a mixture of natural or synthetic gums and resins, sweetened with sweetening agents like sugar, corn syrup & artificial sweeteners. It may also contain coloring agents and flavors. The basic raw material for all CG is

natural gum chicle, which is obtained from the sapodilla tree. Chicle is quite expensive and difficult to procure therefore is usually replaced by other natural gum or synthetic materials like polyvinyl acetate and similar polymers can be used as gum base.

Typically Medicated Chewing Gum consists of two parts:

- A. Water insoluble chewable gum base portion
- B. Water-soluble bulk portion

A. Water insoluble gum base portion:

- Elastomers:** Elastomer provides elasticity and controls gummy texture. E.g. Polyvinyl pyrrolidone, Polyvinyl chloride, polyvinyl alcohol, polyvinyl acetate.
- Plasticizers:** These are used to regulate cohesiveness of product. E.g. Castor oil, Glycerol, Di-butyl phthalate and Polyethylene glycol.
- Fillers or Texturizers:** Provide texture, improve chewability, and provide reasonable size of the gum lump with low dose drug. E.g. Magnesium and Calcium Carbonate, Ground Limestone, Magnesium and Aluminum Silicate, Clay, Alumina, Talc, Titanium Oxide & Mono/ di/ tricalcium Phosphate.

B. Water soluble portions:

- Softeners and Emulsifiers:** These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. e.g.; Glycerin, Lecithin, Mono/ di/tri- Glycerides, Fatty acids like Stearic acid, Palmitic acid, Oleic acid and Linoleic acid.
- Colorants and Whiteners:** May include FD&C type dyes and lakes, fruit and vegetable extracts, Titanium Dioxide.
- Sweeteners:** These are divided into two types, Aqueous and Bulk.
 - Aqueous Sweeteners: These include Sorbitol, hydrogenated Starch and Corn Syrups.
 - Bulk Sweeteners: Sugar and Sugarless components.

Sugar Components: Saccharides like Sucrose, Dextrose, Maltose, Dextrin, Fructose, Galactose, and Corn Syrup.

Sugarless Components: sugar alcohols such as Sorbitol, Mannitol and Xylitol.

- Bulking agents:** These include Polydextrose, Oligofructose, Inulin, Fructo Oligosaccharides.

- e. **Flavoring Agents:** These include essential oils, such as Citrus oil, fruit essences, Peppermint oil, Mint oil, Clove oil & Oil of Wintergreen.
- f. **Active Component:** In medicated chewing gum active pharmacological agent may be present in core or coat or in both. It is used in the concentration of 0.5-30% of final gum weight. Smaller, unionized, lipophilic and enzymatically stable active agent is likely to be absorbed more readily.

IDEAL REQUIREMENTS FOR DRUG PROFILE^[15]

1. The drug should not have any type of disagreeable taste or odour which can affect patient Compliance.
2. The particle size of the drug should be kept below approximately 100 μ m to avoid unpleasant gritty feeling during chewing.

Table 1: Optimal Properties of Drug.^[4]

Patient Related Factors	Physicochemical Properties of Drug
<ul style="list-style-type: none"> • Nontoxic 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 	<ul style="list-style-type: none"> • High salivary solubility • PH independent solubility • Tasteless

MANUFACTURING PROCEDURES

Chewing gum can be manufactured by following methods:

- A. Conventional/Traditional Method
- B. Cooling, Grinding and Tableting Method
- C. Direct compression

A. Conventional/Traditional Method:^[16]

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 period of time. The gum is then sent through a series of rollers that forms into a thin and wide ribbon. During this process, a 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 and in sequential manner the gum is cooled for about 48 hours. This allows the gum to set properly. Lastly, the gum is cut into the desired size and cooled at a carefully controlled temperature and humidity.

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 and punches of the machine and would be difficult to compress.

B. Cooling, Grinding and Tableting Method:^[17]

This method has been developed with an attempt to lower the moisture content and alleviate the problems mentioned in conventional method.

a. Cooling and Grinding:

The CG composition (base) is cooled to a temperature at which the composition is sufficiently brittle and would remain brittle during the subsequent grinding step without adhesion to the machine. The cooling temperature is determined in part by the composition of the CG and is easily determined empirically by observing the properties of the cooled formulation composition. The temperatures of the refrigerated mixture are around -15°C or lower. Coolants like liquid nitrogen, hydrocarbon can be used but solid carbon dioxide is preferred as it can give temperatures as low as -78.5°C , it sublimates readily on warming the mixture and is not absorbed by the components of chewing gum as well as does not interact with the processing apparatus and does not leave behind any residue which can cause undesirable or potentially hazardous effect. 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 like 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. The chewing gum composition can be pre cooled prior to cooling to the refrigeration temperature in order to get more efficient cooling.

In a mill grinder, a mixture of chewing gum composition, solid CO₂ and precipitated silica is ground in a first step of grinding. Additional solid carbon dioxide and silica are added to the ground composition, and is further grounded in a second grinding step. The two step grinding process advantageously keeps the chewing gum composition at a very low temperature. The presence of solid carbon dioxide serves to enhance the efficiency of the grinding process. The above process can be made multiple by adding or incorporating additional carbon dioxide and/or precipitated silica at each step.

Certain additives can be added to the chewing gum composition which promotes cooling and grinding process as well as achieves the desired properties of chewing gum. It includes 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 the grinding process. This prevents 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 malt dextrin can be added in the formulation. But the practical use of these substances is limited because these substances are highly alkaline and hence would be incompatible with acidic ionisable therapeutic agents.

b. Tableting:

Once the coolant has been removed from the powder it is then mixed with other ingredients such as binders, lubricants, coating agents and sweeteners etc., which should be compatible with the components of the chewing gum base in a suitable blender such as sigma blade mixer or a high shear mixer. Alternatively a Fluidized Bed Processor (FBP) can be used. The use of FBP is advantageous as it partially rebuilds the powder into granules and the coating agent coats the powder, particles or granules thereby minimizing undesirable particle agglomeration. Granules obtained can be mixed with antiadherents like talc. Then the mixture can be blended in a V type blender then it is screened and staged for compression which 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.

C. Direct compression:

Recently, free flowing directly compressible co-processed gum materials such as PHARMAGUM developed by SPI Pharma^[18] and Health in gum developed by CAFOSA^[19], 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; this machine makes the process quite rapid and produces chewing gum of low-cost. As it does not require high temperature, thermo sensitive 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.

FACTORS AFFECTING RELEASE FROM CHEWING GUM^[20]

- **Contact Time:** The local or systemic effect is dependent on contact time of MCG in oral mucosa. In the clinical trial studies chewing time of 30 minutes was considered close to ordinary use.
- **Physicochemical properties of drug:** It plays a very important role in release of drug from MCG. Ingredients soluble in saliva will be immediately released within few minutes whereas lipid soluble drugs are released first into the gum base and then released slowly.
- **Inter individual variability:** The chewing frequency and chewing intensity which affect the drug release from MCG may vary from individuals. The *in-vitro* study prescribed in European Pharmacopoeia suggest 60 cycles per minute chewing rate for proper release of active ingredient.
- **Formulation factor:** Composition and amount of gum base affect rate of release of

active ingredient. The increased lipid fraction of gum leads to the delayed release rate of drug.

SOME IMPORTANT FORMULATION ASPECT [4, 21, 22]

- If the composition of softeners and emulsifiers is increased in gum base release rate becomes faster whereas hard gum may retard.

- Solubility of poorly water soluble agents is increased by Cyclodextrin complexation or solubilisation technique.
- A solid system of lipophilic active ingredients bound to the drug permits a sustained drug delivery system.
- Microencapsulation or agglomeration methods are adopted to modify and control the release of active ingredient.

Table 2: Some Examples of Patents

Patent No	Title	Inventor	Issue date	Ref .No
4647450	Chewing gum compositions containing magnesium trisilicate absorbents	David peters	March 3 1987	23
6696043	Teeth whitening composition in the form of a chewing gum	Orlowski, jan A.	February 24 2004	24
6869614	Chewing gum containing calcium	Barreca jack	March 22 2005	25
6958143	Chewing gum composition for effectively eliminating nicotine accumulated in a human body	Choi jinhawan	October 25 2005	26
US 2011/0038915	Chewing gum formulation for enhancing psycho spirituality	Eduardo josegonzalez	February 17 2011	27

Table 3: Some of the Commercially Available Chewing Gum and Trade Mark. [15]

S. No	Trade Mark ^(TM)	Active substance	Aim	Commercial availability
1	Aspergum	Aspirin	Pain Relief	North America
2	Nicorette	Nicotine	Smoking cessation	World wide
3	Nicotinelle	Nicotine	Smoking cessation	Western Europe, Australia, New Zealand
4	Travell	Dimenhydrinate	Travel illness	Italy, Switzerland
5	Superpep	Dimenhydrinate	Travel illness	Germany, Switzerland
6	Chooz	Calcium carbonate	Stomach acid neutralization	USA
7	Endekay Vit C	Vit C	General health	United Kingdom
8	Stamil Vit C	Vit C	General health	Australia
9	Brain	DHA and CCE	Enhanced brain activity	Japan
10	Stay alert	Caffeine	Alertness	USA
11	Café Coffee	Caffeine	Alertness	Japan
12	Buzz Gum	Guarana	Alertness	United Kingdom
13	Go Gum	Guarana	Alertness	Australia
14	Chroma slim	CR	Diet	USA

EVALUATION PARAMETERS OF MEDICATED CHEWING GUM [20]

1. Hardness

The hardness and texture of the Medicated Chewing Gum is determined by texture analyzer. It is determined in kg.

2. Thickness

The thickness of the Medicated Chewing Gum is determined by screw gauge and expressed in millimeter.

3. Friability

The friability of the Chewing Gum is measured by Roche friabilator. It is expressed in percentage (%). Ten Chewing Gum is weighed ($W_{initial}$) and transferred to the apparatus. The friabilator was operated at 25 rpm for 4 mins. The Chewing Gum is weighed again (W_{final}). The % friability was then calculated by:

$$F = (W_{initial} - W_{final} / W_{initial}) \times 100$$

4. Weight Variation

Twenty Chewing gums are weighed and the average weight is calculated. Then the Chewing gum is weighed individually. The percentage weight deviation of each Chewing gum from

average weight is calculated using the following formula

$$\% \text{ Deviation} = (\text{Avg weight} - \text{Individual weight} / \text{Avg weight}) \times 100$$

5. *In vitro* drug release from MCG:

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 3). 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. It prevents the chewing gum from sliding during mastication [28].

Throughout one cycle of chewing, 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 point. In the drug release test, a known quantity of chewing gum is placed in the 20 ml of dissolution medium, which is maintained 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 per minute. At a specified time intervals i.e. 3, 5 and 10 min, samples are collected and analyzed to evaluate percentage drug release.

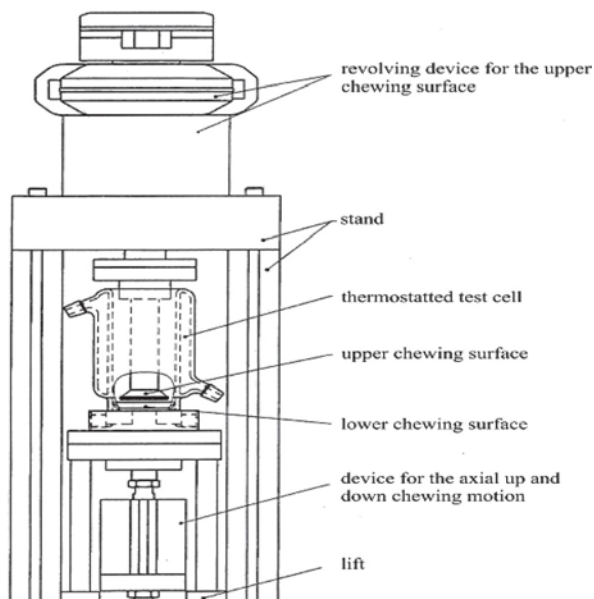


Figure 3: Schematic Representation of Unofficial Single Module Chewing Apparatus

Official MCG chewing apparatus: [29]

The official modified dissolution apparatus for assessing drug release from MCG, as per European Pharmacopoeia, is depicted in **Figure 4**. In this apparatus, the pair of horizontal pistons ('teeth') and the chewing chamber is supplied with a vertical piston ('tongue') working alternate to the horizontal pistons which indicates that the gum is always positioned in the correct place during the mastication process. As per the need, 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 $37 \pm 0.5^{\circ}\text{C}$ with varied chew rate. Other settings which can be adjusted include the volume of the medium, 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.

1. *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 the chew-out studies. During 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 cavity or, if swallowed, absorbed through the gastrointestinal tract.

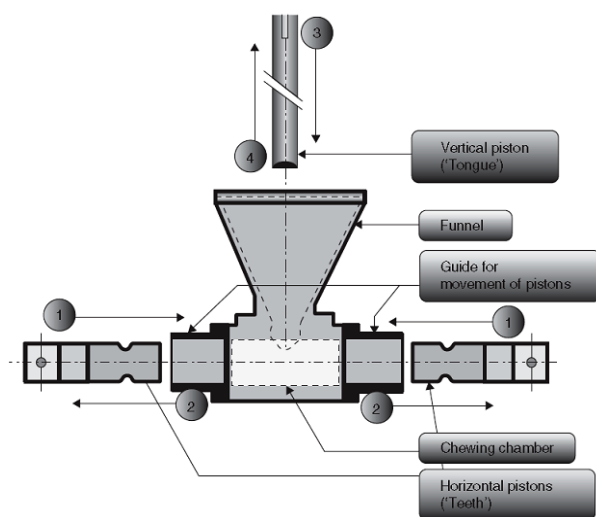


Figure 4: Schematic Representation of Modified Dissolution Apparatus as Per European Pharmacopoeia

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. 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, pH variation in saliva, swallowing and absorption in the oral mucosa, etc.) these factors strongly influence the efficacy of the dosage form and the amount and rate of drug release in the systemic circulation. The Optimized formulation having 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 about 15 minutes and its maximum release has to be taken. Sample of saliva are taken at an interval of 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 [30].

b. Dissolution test of residual medicated chewing gum:

In this experiment, formulations are tested by a panel of volunteers to verify the drug release process from the drug delivery system. One

sample of the tableted gum is given to each person for different time periods (1, 5, 10, 15 min) ^[31]. The residual gums obtained are cut into small pieces, frozen and grounded 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 and the pharmacokinetics can be calculated from the withdrawn blood samples at specific intervals of time. The basics of 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 through urine. Four healthy human volunteer are selected for the study of formulations. The Volunteers are instructed that they should not take any medicine in the last 48 hour. They are fasted overnight, and emptied their bladder. Samples are collected which starts from blank of zero hour urine. Then sample collection is done after the specific time period of 15 min, 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 24 hour intervals after chewing 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. Drug content and buccal absorption are assayed from the expelled saliva.

APPLICATIONS ^[32, 33]

1. Dental caries:

- Chewing gum formulations prevents and cures mainly oral disease.
- It controls the release rate of active medicament providing a prolonged local effect.
- It also re-elevates plaque pH which in turn treats dental caries.
- Gums containing fluoride have been useful in preventing dental caries in children and in adults with xerostomia.

- Chlorhexidine chewing gum is used for the treatment of gingivitis, periodontitis, oral and pharyngeal infections.
- Chewing gum is also 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.

2. Systemic therapy:

- **Pain:** Medicated Chewing gum is used in treatment of minor pains, headache and muscular aches.
- **Smoking cessation:** Medicated 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 efficient in treating obesity. Chromium is basically claimed to reduce craving for food due to an improved blood-glucose balance. Caffeine and guairan stimulate lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger.
- **Other indications:** The common symptoms like Xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety, etc. can be effectively treat by chewing gum as drug delivery system.

SAFETY ASPECTS OF USING MEDICATED CHEWING GUM ^[34]

Generally, today it is perfectly safe to chew a gum. Many years ago, hard chewing gums have caused broken teeth. Chewing for a long period of time may cause painful jaw muscles, and extensive use of sugar-alcohol-containing chewing gum may cause diarrhea. Long-term frequent chewing of gums has been reported to cause increased release of mercury vapor from dental fillings. However, medicated chewing gum does not normally require extensive chewing or Consumption to a great extent. Sometimes Flavors, colors, etc. may cause allergic and undesirable reactions. Basically chewing gum does not cause overdosing because a large amount of gum has to be chewed in a short period of time. Swallowed 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. Medicated chewing gum (like other medicines) should be kept out of reach of children. In addition, if required, drug delivery may be promptly terminated by removal of the gum.

FUTURE TRENDS ^[35, 16]

Chewing gum not only offers clinical benefits but also is an attractive, discrete and efficient drug delivery system. Previously, the only treatment for some disease was surgical procedure but now more and more disease can be treated with Novel Drug Delivery Systems. It takes time for a new drug delivery system to establish itself in the market and gain acceptance by patients and chewing gum is believed to manifest its position as a convenient and advantageous drug delivery system as it meets the high quality standards of pharmaceutical industry and can be formulated to obtain different release profiles of active substances.

The potential of MCG for buccal delivery, rapid onset of action and the chances for product line extension makes it an attractive delivery system. Reformulation of an existing product is required for patent protection, additional patient benefits and conservation of revenues.

CONCLUSION

A chewing gum formulation must have a pleasant taste and texture. The active substances not have an unpleasant, bitter, or metallic taste because the active substance will be released in the oral cavity and remain there for a longer period of time (usual chewing time is 10 to 20 minutes). 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, huge interest in this mode of drug delivery system for a wide variety of other indications exists and continuously grows. Clinical trials studies have confirmed the advantages to be gained by exploiting the effects of chewing gum and the convenience of the delivery and the possibilities of buccal absorption and local effect in mucosa. After one trial study it was found that chewing gum is possibly a safer drug delivery system for active substances that are susceptible to abuse. Chewing gum as a drug delivery system is to be expanded into additional therapeutic areas and the most important thing is that the delivery form is acceptable to all users. Clinical trials and market research have proven this to be the case. In the

future, new formulations will enter the market and chewing gum will become a much more common drug delivery system.

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