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MEDICATED CHEWING GUM - A 21st CENTURY DRUG DELIVERY SYSTEM

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ABSTRACT

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In recent years scientific and technological advancements have been made in the research and development of oral drug delivery system. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration. Over the years, patient convenience and patient compliance-oriented research in the field of drug delivery has resulted in bringing out potential innovative drug delivery options. Out of which, medicated chewing gum (MCG) offers a highly convenient patient-compliant way of dosing medications, not only for special population groups with swallowing difficulties such as children and the elderly, but also for the general population, including the young generation. Today, medicated chewing gum meets the same high quality standards as tablets.

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 ¹. Medicated chewing gum (MCG) is the gum base incorporating drug(s) ².

Chewing gum is a pleasure that almost everyone enjoys ³. Chewing gums are mobile drug delivery systems ⁴. 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 ⁵. 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 ⁶. The first MCG product 'Aspergum' containing acetylsalicylic acid for headache was launched in 1928 ⁷. The success story of nicotine

chewing gum in the 1980s has led to more general acceptance of chewing gum as a drug delivery system⁸. Regarding local actions, it is possible to achieve beneficial effects with medicated chewing gum that might be superior to those achieved with lozenges⁹. Medicated chewing gum is a valid alternative to standard, chewable or orally disintegrating tablet¹⁰. 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 circulation¹¹. Also, Chewing gum has been used for centuries to clean the mouth and for freshening the breath¹². Medicated chewing gums are more effective in the removal of the extrinsic tooth stain³. These days, MCG meets the same superior quality of standards as tablets as per current good manufacturing practices (cGMP) guidelines, and it can be easily formulated to obtain different release rates of active pharmaceuticals¹⁴.

TABLE 1: MARKETED MCG PRODUCTS

Marketed MCG	Active ingredient	Indication
Aspergum ¹⁵	Aspirin	Pain relief
Orbit white	Calcium as tricalcium phosphate	Dental hygiene
Happydent white	Sodium chloride	Prevention of dental caries
Travvel gum	Dimenhydrinate	Motion sickness
Nicorette ¹⁶	Nicotine	Smoking cessation
Hexit ¹⁷	Chlorhexidine	Antibacterial
Stay alert ¹⁸	Caffeine	CNS stimulant

Advantages of Chewing gum over Conventional Drug Delivery System:

1. Fast/rapid onset of action.
2. High bioavailability.
3. Pleasant taste.
4. Easy for administration without water promotes higher patient compliance¹⁹.

5. Ready for use.
6. High acceptances by children and for patients who find swallowing tablets difficult are obvious.
7. Fewer side effects.
8. Systemic effect²⁰.
9. Local effect²¹.
10. Effect on dry mouth (xerostomia)²²⁻²³.
11. Product distinctiveness from a marketing perspective.
12. Gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients.
13. Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa.
14. Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly duration of action is increased.
15. Less first-pass metabolism and improved bioavailability²⁴.
16. Improved focus and concentration.
17. Stress relief.
18. Increase the rate of saliva secretion. Stimulated saliva has a buffering capacity and may therefore help reduce acidity of gastric fluid²⁵.

Disadvantages of MCG:

1. Sorbitol present in MCG formulation may cause flatulence, diarrhoea.
2. Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers²⁶.
3. Influence of rate and pattern of chewing on drug release.
4. Variability in absorption site owe to salivary dilution and involuntary swallowing²⁷.

Excipients in MCG formulation: The fundamental raw (untreated) material for chewing gum is natural gum chicle, obtained from the sapodilla tree, a member of the family Sapotaceae, which is botanically known as *Manilkara zapota* (L.) van Royen. This product is harvested in Mexico, Belize and Guatemala during the rainy season from July to February ²⁸. Chemically, chicle is made up of polyterpenes that are composed of thousands of C₅H₈ isoprene (2-methyl-1, 3-butadiene) subunits. As chicle is very costly and not easy to obtain, other natural gums or synthetic materials such as butadiene-styrene-like basic copolymer, isobutylene-isoprene copolymer (butyl rubber), polyvinyl acetate and identical polymers are used as a chewing gum base. When proper consistency of gum is desired, synthetic elastomers such as butadiene-styrene copolymers, polyisobutylene,

isobutyleneisoprene copolymers and polyethylene are very useful. The gum base may include polyvinyl alcohol and polyvinyl acetate of different molecular mass depending on the consistency of gum base desired, which reduces the tendency of the gum to adhere to the teeth (detackifier) and to be divided into pieces during chewing. The gum base determines the basic characteristics of the product, such as texture, softness, hardness, elasticity, crumbliness, stickiness and mouth feel. It also determines the release profile of active ingredients and flavors ²⁹. Texturizing or filling agents such as talc, magnesium and calcium carbonate, tricalcium phosphate are also included to provide texture and evenhanded size of the gum lump.

Various excipients used in MCG are given in **Table 2**. The major excipients used in MCG are described below.

TABLE 2: EXCIPIENTS USED IN MCG

Category	General range	Examples
Elastomers	15-45%	Natural (chicle, crown gum, nispero) and synthetic (butadiene-styrene copolymers, polyisobutylene, isobutyleneisoprene copolymers)
Elastomers solvents	45-70%	Natural rosin esters such as partially hydrogenated rosin, pentaerythritol esters of rosin or glycerol esters of partially hydrogenated wood or gum rosin and glycerol esters of partially dimerized rosin. Synthetic terpenes (D-limonene, α-pinene, β-pinene)
Bulking agents	q.s	Guar gum hydrolysates, indigestible dextrin, polydextrose, inulin, oligofructose and fructooligosaccharides
Softening agents	0.5-15%	Glycerin, lecithin and fatty acids such as stearic acid, palmitic acid, oleic acid and linoleic acid
Sweetening agents	Up to 50%	Sugars (sucrose, dextrose), sugar alcohols (mannitol, sorbitol), aspartame, neotame
Flavoring agents	0.01-1%	Natural and artificial volatile essential oils
Coloring agents	0.1%	Various FD & C-approved colors
Opacifiers	0.5-2%	Titanium dioxide, magnesium oxide
Texturizing or Filling agents	Upto 50%	Talc, magnesium and calcium carbonate, tricalcium phosphate, colloidal aluminium silicate (Bentonite) or magnesium aluminium silicate
Antioxidants	0.02% of gum base	Propyl gallate, butylated hydroxy anisole and butylated hydroxy toluene

Bulking agents: Bulking agents are used to produce required bulk of chewing gum when potent drug or low-dose drug is to be incorporated. A low-calorie gum is preferred as a bulking agent, especially for health-conscious and diabetic people. Examples of low-caloric bulking agents are guar gum hydrolysates, indigestible dextrin, polydextrose, inulin, oligofructose and fructooligosaccharides, which also provide a sweet taste.

Softening agents: Softening agents are included to provide enormous softness during chewing of the medicated gum for better mouth feel. Commonly used softeners are glycerin, lecithin and fatty acids such as stearic acid, palmitic acid, oleic acid and linoleic acid.

Sweetening agents: Sweetening agents are classified into two categories, aqueous and bulk ³⁰. *Aqueous sweeteners* are utilized to retain moisture within the

formulation for freshness, and include sorbitol, corn syrups and hydrogenated starch hydrolysates. These may also be used as a softening agent or binding agent in MCG. *Bulk sweeteners* are further classified into *nutritive* and *non-nutritive* sweeteners. The amount of bulk sweetener used in chewing gum composition is from 30 to 75%. Sugar and sugar alcohols are each considered nutritive sweeteners.

Sugars are mainly sucrose, dextrose, maltose, maltodextrin, fructose and galactose and are used at between 2 and 15%. Sugar alcohols are low-intensity natural sweeteners such as mannitol, sorbitol and xylitol. Sugar alcohols or polyols contain fewer calories (average of 2 kcal/g) than sugar (4 kcal/g) because they are not completely absorbed from the intestine. They also provide a cooling sensation in the mouth. The sweetness of sugar alcohols varies from 25 to 100% as sweet as table sugar (sucrose).

The high-intensity artificial sweeteners such as saccharin, aspartame, neotame, acesulfame potassium and sucralose are considered as non-nutritive sweeteners. These sweeteners are evaluated based on their safety, sensory qualities (e.g., clean sweet taste, no bitterness, odorless) and stability in various pH environments. These are compounds with sweetness that is many times that of sucrose, common table sugar. As a result, much less sweetener is required and energy contribution is often negligible. The amount of high-intensity sweetener used in chewing gum composition is between 0.001 and 5.0%, most preferably in amounts from 0.05 to 1.00% of the final weight of chewing gum composition. FDA approved high-intensity artificial sweeteners with sweetness as compared with table sugar (sucrose) and special indications are listed in **Table 3**.

TABLE 3: FDA- APPROVED HIGH-INTENSITY ARTIFICIAL SWEETENERS

Approved artificial sweeteners	Times sweeter than sucrose	Description
Saccharin	200 -- 700	Sweet bitter profile is concentration dependent; it is sweet at very low concentrations, but bitter at higher concentrations. Approximately 20% of the populations are 'saccharin sensitive', that is, they perceive saccharin to be bitter even at low concentrations. On repeated tasting, saccharin becomes less sweet and increasingly bitter
Aspartame	160 -- 220	Chemically aspartyl-phenylalanine methyl ester. No bitter aftertaste. Very stable in dry solid-state, but unstable in liquid-state and hydrolyzed into aspartylphenylalanine and diketopiperazine, with loss in sweetness. In liquid-state it shows greatest stability between pH 3.4 and 5.0 at refrigerated temperatures. In the body, it is metabolized to phenylalanine, so it is not recommended for phenylketonurics (PKU)
Neotame (a new version of aspartame)	7000 -- 13,000	Chemically dimethylbutyl-aspartyl-phenylalanine methyl ester, related to aspartame. Resistant to hydrolytic degradation; not metabolized into phenylalanine so no danger for individuals with PKU
Acesulfame K	200	Heat-stable synergistic sweetening enhancement with aspartame
Sucralose	600	Chemically trichlorogalactosucrose Presence of chlorine is thought to be the most dangerous component of sucralose; stable over a broad pH range, heat stable

Flavoring agents: Flavoring agents are added to improve the flavor in chewing gum, which can overcome the bitter taste of the drug. There are several natural and artificial flavors that can be generally described to possess similar taste-masking effects, of which some popular flavorants used in

pharmaceuticals are listed in **Table 4**. The amount of flavoring agent used in chewing gum composition is normally a matter of preference subject to the set range and such factors as the individual flavor, the type of bulking agent or carriers used, and the strength of flavor desired.

TABLE 4: FLAVORING AGENTS FOR SPECIFIC TASTE-MASKING

Taste of drug	Flavors used for taste-masking
Sweet	Fruit and berry, honey, vanilla, bubble gum
Bitter	Wild cherry, raspberry, coffee, chocolate, mint, grapefruit, passion fruit, peach, orange, lemon, lime, anise
Acidic sour	Lemon, lime, orange, cherry, grapefruit, liquorice
Alkaline	Mint, chocolate, cream, vanilla
Metallic	Burgundy, berries, grape, marshmallow, Guyana
Salty	Butterscotch, maple, apricot, peach, melon

Coloring agents: In the US, FD & C numbers (which generally indicate that the FDA has approved the artificial coal tar dye colorant for use in foods, drugs and cosmetics) are given to approved synthetic food dyes that do not exist in nature, whereas in the European Union, E numbers are used for all additives, both synthetic and natural, that are approved in food applications. In the US, the following seven coal tar dyes are permitted as of 2007:

- FD&C Blue No. 1 -- Brilliant Blue FCF, E133 (blue)
- FD&C Blue No. 2 -- Indigotine, E132 (dark blue shade)
- FD&C Green No. 3 -- Fast Green FCF, E143 (bluish green)
- FD&C Red No. 40 -- Allura Red AC, E129 (red)
- FD&C Red No. 3 -- Erythrosine, E127 (pink)
- FD&C Yellow No. 5 -- Tartrazine, E102 (yellow)
- FD&C Yellow No. 6 -- Sunset Yellow FCF, E110 (orange).

But, as FD&C Yellow No. 5 (Tartrazine) causes hives in < 0.0001% of those exposed to it and provokes asthma attacks in aspirin-intolerant individuals, most pharmaceutical companies have eliminated the use of this colorant in their products. Owing to safety concerns of artificial dyes, natural colorants obtained from plant and animal sources have become more popular. Plant extracts such as chlorophyll-green, annatto-yellow, curcumin-yellow, saffron yellow and animal extracts such as cochineal red are incorporated to enhance a pleasing appearance or hide the colors of drugs or excipient in the final product. Opacifiers such

as titanium dioxide and magnesium oxide are also included to provide whiteness to the final product.

Glidants: Improve the flow property of material from hopper to the die cavity by reducing interparticulate friction. Colloidal silica, that is, syloid, pyrogenic silica (0.25%), hydrated sodium silicoaluminate (0.75%) and corn starch (3 -- 10%) are used successfully as glidant to induce flow. Anti-adherants avoid sticking of material to die walls and picking of material by punches. These materials themselves undergo deformation easily on compression. Talc (1 -- 5%) and corn starch (3 -- 10%) are very good examples of anti-adherants. Lubricants are added to reduce the friction between the cylindrical surface of the compressed dosage form and the die wall during compression and ejection. Metallic stearates (0.25 -- 1%) (magnesium and calcium stearate) and high-molecular-mass polyethyleneglycol (PEG 4000 and PEG 6000) are commonly used as water-insoluble lubricants. Boric acid (1%), DL-leucine (3 -- 10%), sodium benzoate (5%), sodium acetate (5%) and sodium lauryl sulfate (1 -- 5%) are successful examples of water-soluble lubricants.

Active Component: In medicated chewing gum active pharmacological agent may be present in core or coat or in matrix. 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 absorbed³¹. Methods to increase the rate and extent of release of APIs include the addition of buffering agents or solubilizing agents and coating/encapsulating the API.

Manufacturing processes:

1. **Conventional/Traditional Method:** Components of gumbase 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 form into a thin, wide ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to

enhance the flavor. In a carefully controlled room, the gum is cooled for upto 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.

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

- Cooling and Grinding:** The CG composition (base) is cooled to a temperature at which the composition is sufficiently brittle and would remain brittle during the subsequent grinding step without adhesion to the grinding apparatus. The temperature required for cooling is determined in part by the composition of the CG and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperatures of the refrigerated mixture are 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 malto dextrin can be incorporated. However practical use of these substances is limited because these substances are highly alkaline and hence would be incompatible with acidic ionisable therapeutic agents. They also tend to remain in the composition and final chewing gum tablet and thus may be problematic for therapeutic and safety point of view. 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.

b. 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 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, 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: Recently, free flowing directly compressible co-processed gum materials such as Pharmagum developed by SPI Pharma³² and Health in gum developed by CAFOSA³³, 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 lowcost 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.

Important formulation aspects for MCG:

- 1. Ion exchange resin complexation:** Complexation of lipophilic active ingredients to ion exchange resins such as polacrillin potassium provides sustained drug delivery. Also, this approach is useful to mask the taste of bitter drugs. As most drugs possess ionic sites in their molecule, the resin's charge provides a means to bind such drugs loosely and this complex prevents drug release in the saliva, thus masking the taste. For the purpose of masking the taste, weak cation exchange or weak anion exchange resins are used, depending on the nature of the drug.
- 2. Cyclodextrin complexation:** Cyclodextrin complexes have been used to increase the solubility, stability and bioavailability of a variety of active ingredients in formulations and also explored for masking the taste of certain active ingredients³⁴. The naturally occurring cyclodextrins are α , β and γ types containing six, seven and eight glucopyranose units, respectively. Water soluble cyclodextrin derivatives of commercial interest include the hydroxypropyl derivatives of β CD, randomly methylated β -cyclodextrin (RM β CD) and sulfobutylether β -cyclodextrin sodium salt (S β EbCD). Hydrophilic cyclodextrin derivative

such as 2-hydroxypropyl β -cyclodextrin (HP β CD) are considered non-toxic at low to moderate oral dosages and so it is used to increase aqueous solubility of poorly watersoluble drugs. Lipophilic cyclodextrin derivatives, such as the methylated cyclodextrins and sulfobutylether cyclodextrin are to some extent absorbed from the gastrointestinal tract into the systemic circulation, but oral administration of it is limited by its potential toxicity.

~ 100 μ m. Both of these can be solved by microencapsulation.

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 ³⁵

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:

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 ³⁶. 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.

Official MCG chewing apparatus: The official modified dissolution apparatus for assessing drug release from MCG, as per European Pharmacopoeia, is depicted in **Figure 2** ³⁷. 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.

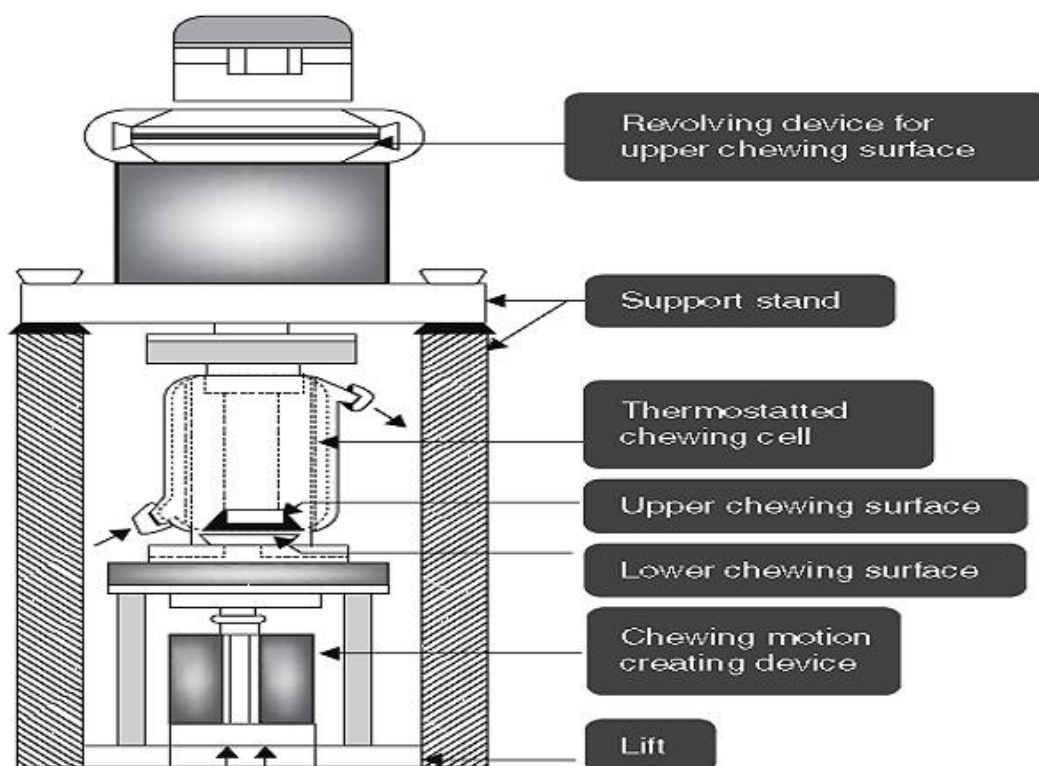


FIG. 1: SCHEMATIC REPRESENTATION OF UNOFFICIAL SINGLE MODULE CHEWING APPARATUS

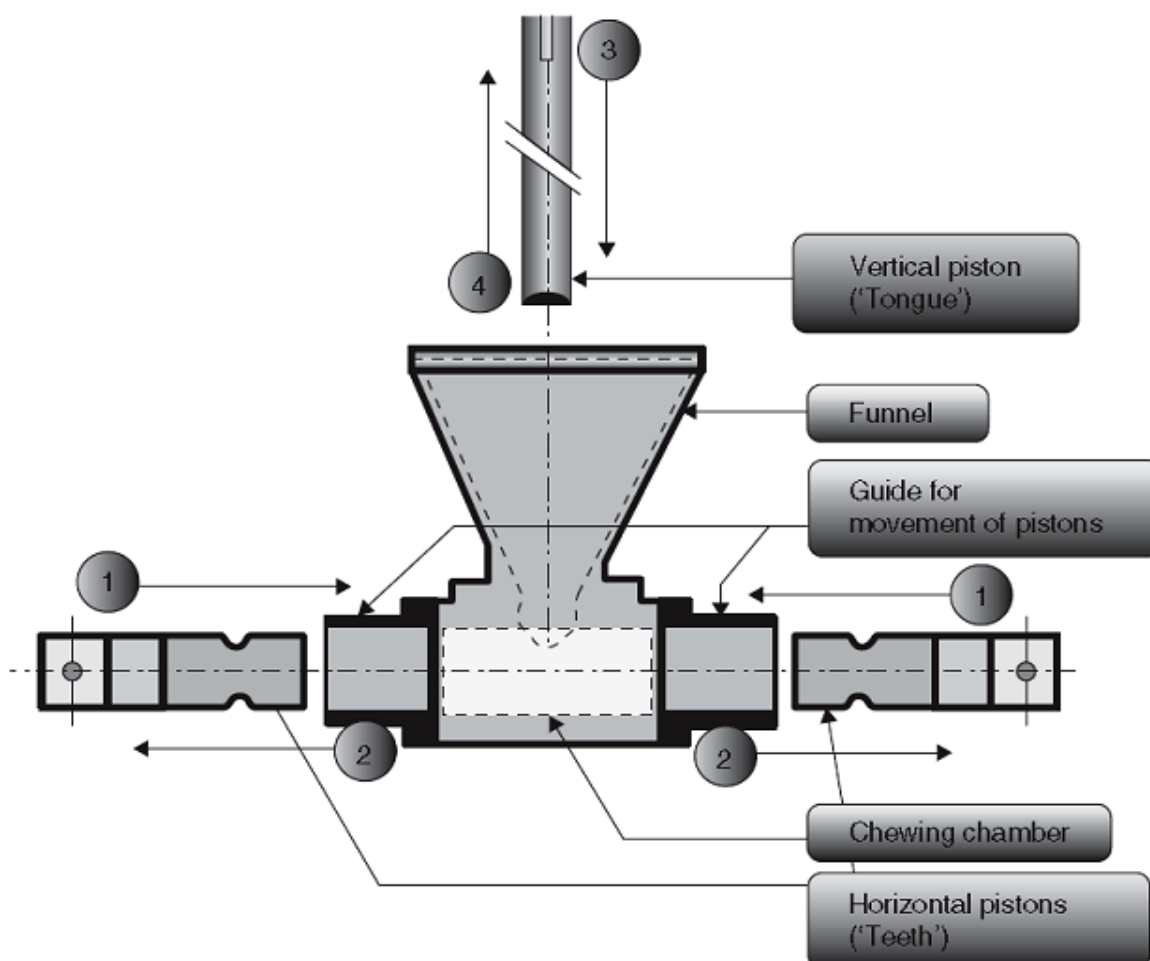


FIG. 2: SCHEMATIC REPRESENTATION OF MODIFIED DISSOLUTION APPARATUS AS PER EUROPEAN PHARMACOPOEIA, WHERE NUMBERED ARROWS INDICATE SEQUENCE OF MOTION

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 $37\pm0.5^{\circ}\text{C}$ 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.

***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 method³⁸.

- 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)³⁹. 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.

Factors affecting release of active ingredient from MCG:

softening agents may affect the rate of release of the active ingredient from MCG.

1. Person-to-person variability: One of the reasons why MCG has not yet been fully exploited is because of the therapeutic uncertainty related to the drug delivery method that is, a patient's mechanical chewing action. The gum's therapeutic effect depends on chewing and as each person has his/her own chewing force, frequency and chewing time, which may lead to variation in results. The rate at which the subject chews gum also affects the amount of drug released. The average chewing rate is ~ 60 chews every minute. For this purpose, the release of nicotine from Nicorette chewed at different rates has been investigated. In that study it was found that a chewing rate of 1 chew every second gave a significantly ($p < 0.05$) higher release than a chewing rate of 1 chew every 8 s. An in vitro study prescribed by European Pharmacopoeia suggests 60 strokes a minute are sufficient for proper release of active ingredient.

2. Physicochemical properties of drug: The physicochemical properties of the active ingredient such as its molecular mass, ionized or non-ionized form, lipophilicity or hydrophilicity, stability to salivary enzymes (amylase) and its solubility in salivary fluid play very important roles in the release of drug from MCG and absorption of drug through oral mucosa. For example, the saliva-soluble ingredients will be immediately released within a few minutes, whereas lipid-soluble drugs are released first into the gum base and then slowly into salivary fluid. Aqueous solubility of API plays an important role in the release from chewing gum composition, that is, release of water-soluble drug (aqueous solubility $> 1:10$) is, in general, ~ 75% or more during 5 min of chewing and 90% or more during 15 min of chewing at a rate of 60 chews a minute. Drugs with aqueous solubility between 1:10 and 1:300 demonstrate up to 60% release during 10 min of chewing and between 50 and 90% release after 15 min of chewing.

3. Formulation factors: Composition and amount and type of gum base, solubilizing agents and

Possible absorption pathways

The release of most water-soluble components from chewing gum is relatively rapid⁴⁰. Drug released from the chewing of medicated gum will be either absorbed from the buccal mucosa or, if swallowed, absorbed from the gastrointestinal tract. Drugs that are released from chewing gum and involuntarily swallowed will be introduced to the gastrointestinal tract in dissolved, diluted, or suspended form in saliva and so will be very easily bioavailable with a consequent fast onset of action as compared with solid oral dosage forms. To obtain the optimal formulation it is possible to decrease the release rate of highly hydrophilic substances and increase the release rate of lipophilic substances⁴¹. Antihistamines (chlorpheniramine maleate, cetirizine HCl), appetite suppressants (phenylpropanolamine HCl or caffeine), expectorants (guifensin hydrochloride), antitussives (dextromethorphan, noscapine), opioids (codeine phosphate, codeine sulfate), nasal decongestants (phenylephrine HCl, pseudoephedrine, ephedrine HCl), analgesics and anti-pyretics (aspirin or acetaminophen), anti-inflammatories (ibuprofen, ketoprofen, naproxen), electrolyte and mineral supplements, antacids, laxatives, vitamins, ion exchange resins (cholestyramine), and anti-cholesterolamics such as most prescribed therapeutic categories can be potential possible targets for delivery in the form of MCG owing to its higher patient compliance and quick onset of action⁴².

Applications

1. 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.

- e. Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oral and pharyngeal infections.
- f. It can also be used for inhibition of plaque growth.
- g. Chlorhexidine chewing gum offers numerous flexibility in its formulation as it gives less staining of the teeth and is distributed evenly in the oral cavity.
- h. The bitter taste of chlorhexidine can be masked quite well in a chewing gum formulation⁴³.

2. Systemic therapy:

- a. Pain- chewing gum can be used in treatment of minor pains, headache and muscular aches.
- b. Smoking cessation- Chewing gum formulation containing nicotine and lobeline have been clinically tested as aids to smoking cessation.
- 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 guaran stimulate lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger. *Hoodia gordonii* (hoodia; pronounced hoo-dee-uh) is the most publicized and talked about natural weight loss product in America⁴⁴.
- 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 beneficial⁴⁵.

Future opportunities: Chewing gum not only offers clinical benefits but also is an attractive, discrete and efficient drug delivery system. Nowadays 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 and popularity by the 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. Finally, in the future, we may see that more and more drugs formulated into chewing gum in preference to other delivery systems to deliver drugs locally to the oral cavity. The reason is simple that the chewing gum delivery system is convenient, easy to administer anywhere, anytime and its pleasant taste increases the product acceptability and patient compliance.

CONCLUSION: Chewing gum is an excellent drug delivery system for self-medication, as it is convenient and can be administered discreetly without water⁴⁶. It offers several advantages compared to chewable tablets, lozenges and other related formulations. Hence in forth coming years it will become a much more common and popular drug delivery system. Chewing gum is a viable alternative to traditional dosage forms for drugs intended to cure or relieve diseases in the oral cavity. Local delivery to tissues of the oral cavity has several applications, including the treatment of toothache, periodontal disease, bacterial and fungal infections, aphthous and dental stomatitis, which require a long period of drug release to the oral cavity.

It can be utilized for systemic drug delivery where a rapid onset of action is needed, such as motion sickness, nausea, pain, allergy and infection and hypertension (provided the drug is easily absorbed through the oral mucosa). As chewing gum is intended to be retained in the mouth for a long time, the issue of taste-masking remains an important factor in product development, as does the control of drug release from the gum base. The convenience and acceptability of chewing gums, combined with effective sweetening and taste-masking, may lead to improved compliance. Moreover, MCG also benefits from the rewards that are inherent to chewing gum such as oral care, stress relief, improved concentration and weight management. Reformulation of an existing product is required for patent protection, additional patient benefits and conservation of revenues.

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