



## CHEWING GUM: A MOBILE DRUG DELIVERY SYSTEM

Bhaskar D. Ingole\*, Amit S. Daga, Unmesh M. Joshi, Kailash R. Biyani

Department of Pharmaceutics, Anuradha College of Pharmacy, Chikhli, Buldhana, M.S, India.

\*Corresponding author's E-mail: [bdingole888@gmail.com](mailto:bdingole888@gmail.com)

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### ABSTRACT

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. MCGs are solid, single dose preparations with a base consisting mainly of gums that are intended to be chewed but not swallowed. They contain one or more active substances which are released by chewing and are intended to be used for local treatment of mouth diseases or systemic delivery after absorption through the buccal mucosa.

**Keywords:** Chewing gums, mobile drug delivery system, dental caries, local disinfectant, mouth diseases.

### INTRODUCTION

Chewing gum is being used worldwide since ancient times after man experienced the pleasure of chewing a variety of substance. One thousand years ago the Mayan Indians chewed tree resin from the sapodilla tree in order to clean their teeth and freshen their breath. Shortage of natural gum bases during World War II enhanced development of the synthetic gum bases that are used today. Chewing gum can be used as a convenient modified release drug delivery system.

Chewing gum is a pleasure that almost everyone enjoys<sup>1</sup>. Chewing gums are mobile drug delivery systems<sup>2</sup>. 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 a 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<sup>3</sup>. 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, flavourings.

A large number of chewing gum intended for prevention of caries, xerostomia alleviation and vitamin / mineral supplementation are currently available. 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. The first Medicated chewing gum "Aspergum" was launched in 1928. This chewing gum is still available and contains acetylsalicylic acid. Another commercially available medicated chewing gum is dimenhydrinate – containing chewing gum for motion sickness. However, chewing gum did not gain acceptance as a reliable drug delivery system until 1978, when nicotine chewing gum became available<sup>3,4</sup>.

Chewing gum is considered a valid drug delivery system that releases the active ingredient by chewing. Chewing gum has been proven as a great delivery vehicle for nutrients and drugs. There are several advantages to using chewing gum to administer drugs. It is non-invasive, readily accepted, and can be given at almost any time and everywhere. Stability of the therapeutic agent is easily maintained during storage because of packaging that keeps it away from oxygen, light, and water. Gum chewing can have local effects in the mouth and also systemic effects after the active agents have been swallowed, or absorbed through the oral mucosa. Drug absorbed directly via the buccal membrane avoids metabolism in the GI tract and the first-pass effect of the liver; it might therefore be to administer a reduce dose in chewing gum Compared to other oral delivery system<sup>5</sup>.

#### (A) Local effect

Chewing gum is an obvious drug delivery system for local treatment of diseases in oral cavity and in the throat, as sustaining the release of active substances may deliberately prolong exposure. Chewing gum is an ideal drug delivery system for this treatment area; the active substances are released as the gum is chewed, thus providing the potential for a high level of active substance to obtain local effect in the oral



cavity. It is possible to design a chewing gum that releases active substances over a prolonged period<sup>6</sup>.

### (B) Systemic effect

Systemic effects of active substances released from chewing gum can be achieved in two ways: in the "traditional" way, by swallowing the active Substance, or buccally via absorption through the oral mucosa. The latter is of special interest. As buccal absorption avoids first-pass hepatic metabolism of the active substance, it could provide better bioavailability. The buccal absorption of nicotine has been studied extensively and is, therefore, a good example of buccal absorption obtained when using chewing Gum as a drug delivery system<sup>7</sup>.

### CHEWING GUM AS DOSAGE FORM FOR BUCCAL DELIVERY

Dosage forms such as mouthwashes, erodible/ chewable buccal tablets, and chewing gums allow release of drugs for only a short period and thus the reproducibility of drugs absorption is comparatively poor. Application of bio-adhesive semisolid gels creates considerable technical problems in the buccal absorption. Although medicated chewing gums pose difficulties in regulating the dose administered, they still have some advantages as drug delivery devices, particularly in the treatment of diseases in the oral cavity and in nicotine replacement therapy. Some commercially available chewing gums are Caffeine chewing gum, (Stay Alert®) and Nicotine chewing gums (e.g. Nicorette® and Nicotinell®). The permeability of nicotine across the buccal mucosa is faster than across the skin. However, chewing gum slowly generates a steady plasma level of nicotine rather than a sharp peak as experienced when smoking. Possible swallowing of considerable amount of nicotine during chewing may lead to decreased effectiveness of the chewing gum due to first pass metabolism and gastrointestinal discomfort. It is a major challenge to optimize the dose-response relationship of nicotine administered in a chewing gum.<sup>1,8</sup>

**Table 1:** Marketed available chewing gums

Product	Drug	Indications
Nicorette® <sup>10</sup>	Nicotine	Smoking cessation
Nicotinell®	Nicotine	Smoking cessation
NiQuitin CQ®	Nicotine	Smoking cessation
Fluorette®	Fluoride	Prevention of caries
Vitaflo CHX®	Chlorhexidine	Antibacterial
Advanced+® <sup>11</sup>	Chlorhexidine	Prevention of caries
HEXIT® C	Chlorhexidine	Antibacterial
Stay Alert® <sup>12</sup>	Caffeine	CNS stimulant
Travvell®	Dimenhydrinate	Motion sickness
Aspergum® <sup>9</sup>	acetylsalicylic acid	NSAIDS

### Why use chewing gum as drug delivery system?

Chewing gum provides new competitive advantages over conventional drug delivery system:

#### Advantages of chewing gum<sup>13-19</sup>

1. Fast/rapid onset of action.

2. High bioavailability.
3. Pleasant taste.
4. Easy for administration without water promotes higher patient compliance
5. Ready for use.
6. Highly acceptances by children and for patients who find swallowing tablets difficult are obvious.
7. Fewer side effects.
8. Systemic effect
9. Local effect
10. Effect on dry mouth (xerostomia)
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 bioavailability.
16. Improved focus and concentration.
17. Stress relief.
18. Increase the rate of saliva secretion, stimulated saliva has a buffering capacity and may be helpful to reduce acidity of gastric fluid.

#### Disadvantages of chewing gum<sup>20-23</sup>

1. Risk of over dosage with chewing gum 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 chewing gum formulation may cause flatulence, diarrhoea.
3. Additives in gum like flavouring agent, 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.

#### Physicochemical properties of drug<sup>24</sup>

Physicochemical property deals with the physical and chemical property of drug. Physicochemical property of drug as given in table 2.



**Table 2:** Optimal Properties of Drugs

<b>Physicochemical Properties of Drug</b>	High Salivary Solubility
	pH independent 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

**COMPOSITION OF CHEWING GUMS**

Chewing gum is a mixture of natural or synthetic gums and resins, sweetened with sugar, corn syrup, artificial sweeteners and may also contain coloring agents and flavour (table 3). The basic raw material for all chewing gum is natural gum Chicle, obtained from the sapodilla tree. Chicle is very expensive and difficult to procure therefore other natural gum or synthetic materials like polyvinylacetate and similar polymers can be used as gum base.

**Table 3:** Excipients Used In Chewing gum<sup>26</sup>

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, a-pinene, b- 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

Typically Chewing Gum comprises two parts;

1. Water insoluble chewable gum base portion.
2. Water-soluble bulk portion<sup>25</sup>.

**1. Gum Base:** Gum base is an inert and insoluble nonnutritive product used as a support for the edible and soluble of the chewing gum (sugar, glucose, poly oils and flavors)

**2. Elastomers:** including natural and synthetic rubbers. The gum base composition may contain conventional elastomer solvents to aid in softening the elastomer base component. Such elastomer solvents may comprise terpinene resins such as polymers of alpha-pinene or beta-pinene, methyl, glycerol or pentaerythritol esters of resins or modified resins and gums, such as hydrogenated, dimerized or polymerized resins or mixtures. The elastomer solvents may be employed in amounts from 5.0% to 75.0%, by weight of the gum base, and preferably from 45.0% to 70.0%, by weight of the gum base. Synthetic elastomers such as butadiene, styrene copolymers, polyisobutylene, isobutylene isoprene copolymers, polyethylene mixtures, and non-toxic vinyl polymer, such as polyvinyl alcohol are widely used bases. The molecular weight of the vinyl polymer may range from 3,000 to 94,000. The amount of gum base employed varies greatly depending upon various

factors such as the type of base used, the consistency of the gum desired and the other components used in the composition to make the final chewing gum product. In general, the gum base will be present in amount from 5% to 94%, by weight of the final chewing gum composition. Preferably, the gum base is used in amounts from 15% to 45% and more preferably in amounts from 15% to 35% by weight of the final chewing gum composition.

**3. Plasticizers:** waxes, vegetable oils, glycerides. Plasticizers or softeners such as lanolin, palmitic acid, oleic acid, stearic acid, sodium stearate, potassium stearate, glyceryl triacetate, glyceryl lecithin, 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.

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



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

**6. Compression adjuvants:** Suitable compression adjuvant such as silicon dioxide, magnesium stearate, calcium stearate and talc can be used in medicated chewing gum for ease of compression. The alkaline earth metal phosphates and alkali metal phosphates prevent caking and balling of High" i.e. 2 to 8% moisture-containing chewing gum compositions during grinding. Additionally, it has been discovered that maltodextrin enhances the grinding of "high" moisture-containing chewing gum compositions by absorbing moisture to allow lubrication in the gum as it separates into granules. If oil lubricants are used, it is preferred to be 0.4% to 1% by weight of the tabletted chewing gum composition. The amount of glidant present in the tabletted chewing gum composition is from 0.5% to 5% by weight of the tabletted chewing gum composition. Those glidants useful are selected from the group consisting of alkali metal salts, talc, starch, polyhydric alcohols and mixtures. Anti-adherents 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 tabletted chewing gum composition and preferably about 0.3 to about 0.6% by weight. Generally anti-adherent is a finely divided low bulk density powder, which is preferably water insoluble. The preferred anti-adherents are fumed silica and talc. The term-fumed silica is meant to include pyrogenic silicas, micron sized silicas and hydrated silicas<sup>27-29</sup>.

#### 7. Sweeteners:

a) *Water-soluble sweetening agents:* xylose, ribulose, glucose, mannose, galactose, fructose, sucrose, maltose, invert sugar partially hydrolyzed starch, dihydrochalcones, monellin, steviosides, glycyrrhizin, and sugar alcohols such as sorbitol, mannitol, hydrogenated starch hydrolysates.

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

c) *Dipeptide based sweeteners:* L- aspartic acid derived sweeteners such as Aspartame, Alitame, methyl esters of L-aspartyl-L phenyl-glycerine and L-aspartyl- L 2,5-dihydrophenylglycine, L-aspartyl 2,5-dihydro-L phenylalanine – L aspartyl – L (1-cyclohexen) alanine.

**8. Coloring Agents:** The coloring agents include pigments, which may be incorporated in amounts up to about 6% by weight of the gum composition; titanium dioxide may be incorporated in amounts up to about 2%.

The colorants may also include natural food colors and dyes suitable for food drug and cosmetic applications.<sup>26</sup>

- ✓ 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).

**9. Flavouring Agents:** Flavouring agents (table 4) 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.

**Table 4:** Flavoring Agents for Specific Taste-Masking<sup>26</sup>

Taste of drug	Flavors used for taste-masking
Sweet	Fruit and berry, honey, vanilla, bubble gum, Wild cherry, raspberry, coffee, chocolate, mint
Bitter	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
Salty	Butterscotch, maple, apricot, meion

### MANUFACTURING PROCESSES

Different methods employed for the manufacturing of CHEWING GUM can be broadly classified into three main classes namely;<sup>30,31</sup>

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

#### 1. Conventional/ traditional Method<sup>32</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 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 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.

*Limitations:*<sup>31</sup>

- 1) Elevated temperature used in melting restricts the use of this method for thermo labile drugs.



2) Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult. Cooling, Grinding and tableting method.

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

## 2. Cooling and Grinding

The chewing gum 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 chewing gum and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperatures 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. 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.

## Tabletting

Once the coolant has been removed from the powder, the powder can be mixed with other ingredients such as binders, lubricants, coating agents, 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 tabletting equipment and requires careful monitoring of humidity during the tabletting process:

## 3. Direct Compression Chewing Gum

Pharmagum is a compatible gum system that has been developed by SPI pharma. Pharmagum is a mixture of polyols and of sugar with gum base. It is a free flowing powder, which is directly compressible. This gum is manufactured under chewing gum MP conditions and complies with food chemicals. Direct compression chewing gum can be directly compressed on a traditional tabletting machine, thus enabling rapid and low cost development of a gum delivery system<sup>31</sup>.

### SOME IMPORTANT FORMULATION ASPECT<sup>33-38</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.

### IN-VITRO APPARATUS

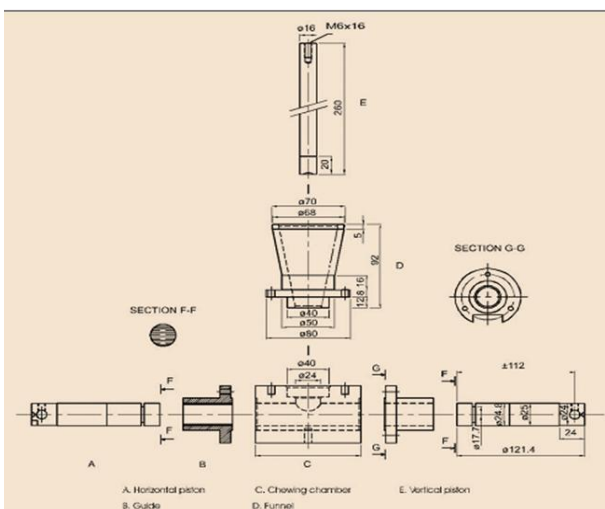
The absorption of active substances through the buccal mucosa can be examined by both *in vitro* and *in vivo* methods. The most common method utilizes using chamber where excised buccal mucosa (either from



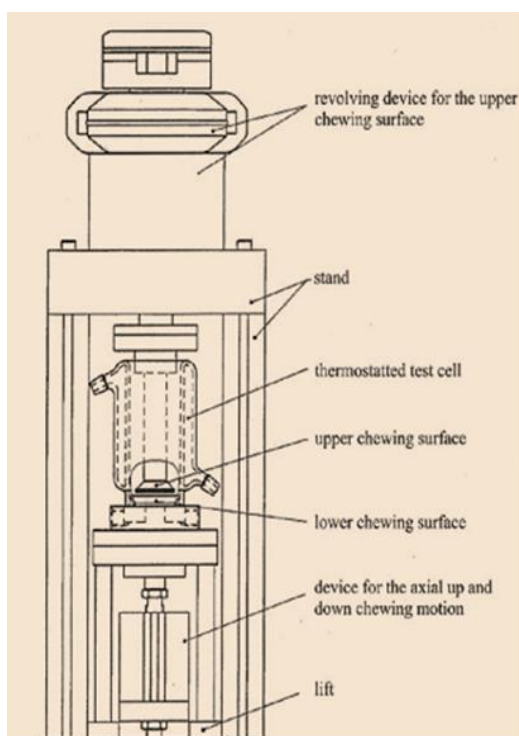
human or animal) is placed as a barrier between two chambers. The transport of active substances across the mucosa is measured by withdrawal of samples from each chamber.

**Apparatus I. Compendial chewing gum apparatus**

The chewing apparatus for medicated chewing gum was adopted by Ph. Eur. in 2000. Figure 1 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 chews. If necessary, it is feasible to construct the machine so that at the end of the chew the horizontal pistons rotate around their own axes in opposite directions to each other to obtain maximum chewing.<sup>39-44</sup>



**Figure 1:** Compendial chewing gum apparatus



**Figure 2:** Noncompendial chewing gum apparatus

**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 2. 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.<sup>45-50</sup>

**IN VIVO 'CHEW-OUT' STUDIES<sup>51,52</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 CHEWING GUM is released in the saliva and then it is either absorbed through oral mucosa or, if swallowed, it is absorbed through the gastrointestinal tract.

**a. Release of drug in saliva**

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

**b. Dissolution test of residual 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 tabletted gum for different time periods (1, 5, 10, 15 min)<sup>39</sup>. 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 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<sup>53, 54</sup>

1) **Contact Time:** The local or systemic effect is dependent on time of contact of CHEWING GUM 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 CHEWING GUM. The saliva soluble ingredients will be immediately released within few minutes whereas lipid soluble drugs are released first into the gum base and then released slowly.

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

4) **Formulation factor:** Composition and amount of gum base affect rate of release of active ingredient. If lipophilic fraction of gum is increased, the release rate is decreased.

## APPLICATIONS<sup>55-60</sup>

### 1. Dental caries

The Chewing gum can control the release rate of active substances providing a prolonged local effect.

Fluoride containing gums have been useful in preventing dental caries in children and in adults with xerostomia. It can also be used for inhibition of plaque growth.

### 2. Oral Fungal Infection

Chewing gum has advantages as a drug delivery system for active substances where a local effect is the object of treatment. Several studies have been performed regarding the possibility of obtaining a constant, prolonged level of active substance locally for the treatment of oral fungal infections.

### 3. Pain

chewing gum can be used in treatment of minor pains, headache and muscular aches. The oldest medical chewing gum available is Aspergum®, a chewing gum containing ASA (aspirin or acetylsalicylic acid).

### 4. Smoking cessation

Chewing gum formulation containing nicotine and lobeline have been clinically tested as aids to smoking cessation.

### 5. 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.

### 6. Stimulating activating effect

It is a well-known fact that caffeine has stimulating effect. It could, therefore, be interesting to combine it with chewing gum's generally positive effect on memory. The ability of healthy volunteers to stay awake at night was tested in two different experiments.

### 7. Other indications

Xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety, etc are all indications for which chewing gum as drug delivery system could be beneficial.

## SAFETY ASPECTS

Generally, today it is perfectly safe to chew chewing gum. Previously, hard chewing gum has caused broken teeth. Extensive chewing for a long period of time may cause painful jaws muscle, and extensive use of sugar alcohol containing chewing gum may cause diarrhoea. Long term frequent chewing of gum has been reported to cause increased release of mercury vapors from dental amalgam fillings. However, medicated chewing gum does not normally require extensive chewing, or consumption to great extent. Flavors, colour etc. may cause allergic reactions. Overdosing by use of chewing gum is unlikely because a large amount of gum has to be chewed in a short period of time to achieve this. Swallowing pieces of medicated chewing gum will only cause minor release of



the drug because the drug can only be released from the gum base by active chewing. As a general rule, medicated chewing gum (like other medicines) should be kept out of reach of children, if required; drug delivery may be promptly terminated by removal of the gum.

### 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. The potential of chewing gum for buccal delivery, fast onset of action and the opportunity for product line extension makes it an attractive delivery form. Reformulation of an existing product is required for patent protection, additional patient benefits and conservation of revenues.

### CONCLUSION

It can be concluded that the chewing gum can be used, as a carrier for vast categories of drugs where extended release and the local action is desired. Chewing gum can be used without water, at any time. Medicated Chewing gums can produce both local effects as well as systemic effects in the oral cavity. They can be used for the purpose of taste masking of certain drugs too.

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