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## CHEWING GUM: A MODERN APPROACH TO ORAL MUCOSAL DRUG DELIVERY

**Ami Makwana<sup>1\*</sup>**;

Krunal Sameja<sup>1</sup>; Vishva Raval<sup>1</sup>; Harshad Asodiya<sup>1</sup>; Dhaval Patadiya<sup>1</sup>

<sup>1</sup>Department of Pharmaceutics, C U Shah College of Pharmacy & Research, Opposite: IBP Petrol Pump, Surendranagar- Ahmedabad Highway, Wadhwan-363030

### ABSTRACT

*In recent years scientific and technological advancements have been made in the research and development of oral drug delivery system. The medicated chewing gum has through the years gained increasing acceptance as a drug delivery system. Chewing gum is a combination of a water-insoluble phase, known as gum base (insoluble gum base resin), elastomers, emulsifiers, fillers, waxes, antioxidants, softeners, sweeteners, food colourings, flavouring agents, and in case of medical chewing gum, active substances are added. 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. The absorption of active substances through the buccal mucosa can be examined by both In-vitro and In-vivo methods. There is not any official apparatus described in USP for dissolution of chewing gum however, An In-vitro apparatus was specially designed and constructed for release testing of medicated chewing gums. It has many advantages like fast onset of action, no first pass metabolism, patient's compliance, taste masking, reduced risk of erosion of gastric mucosa, overdose related & some marketing related advantages. It was concluded that Chewing gum is an excellent drug delivery system for self-medication as it is convenient and can be administered directly without water.*

**Key words:** Chewing gum, Oral mucosal drug delivery, Buccal Delivery, Masticatory base.

### Correspondence to Author



**Ami Makwana**

Department of Pharmaceutics, C U  
Shah College of Pharmacy &  
Research, Opposite: IBP Petrol Pump,  
Surendranagar- Ahmedabad Highway,  
Wadhwan-363030

**Email:** amimakwana89@gmail.com

## 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.<sup>[1]</sup> Many therapeutic agents are absorbed in the oral cavity. For the drugs having significant buccal absorption, dosage forms such as Lozenges, Chewable tablets and Chewing Gum permits more rapid therapeutic action compared to pre-oral dosage form. Chewable tablets and chewing gum have been very well received by the patients for use in children with full dentition. In Children particularly may consider chewing gum as a more preferred method of drug administration

compared with oral liquids and tablets. The use of MCG is feasible in local treatment of diseases of oral cavity as well as treatment of systemic conditions. Moreover there is need of reformulation of existing drug into New Drug Delivery Systems (NDDS) to extend or protect product patents thereby delaying, reducing or avoiding generic erosion at patent expiry. To provide additional patient benefit, meet competitive challenges and to conserve revenues, the research on NDDS is gaining importance now a days. Medicated Chewing Gum (MCG) is one of them. Owing to new social and behavioural trends in the past modern age, such as the growing consumer health awareness and increasing attention to safety products, chewing gum has been known for a new image and potential. Chewing gum today is gaining consideration as a vehicle or a delivery system to administer active principles that can improve health and nutrition.<sup>[2]</sup>

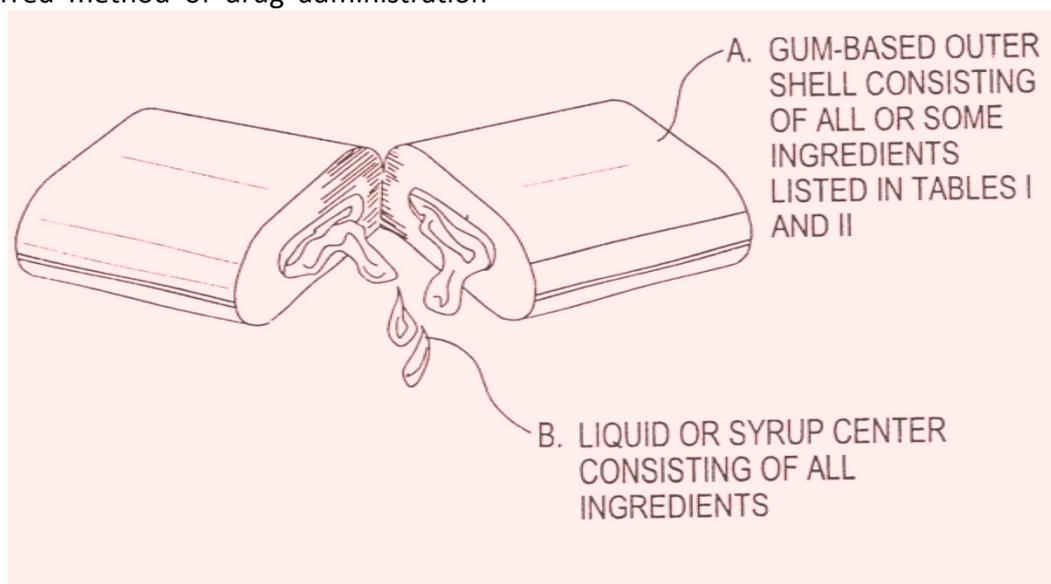


Figure 1 Schematic diagram of drug release from a chewing gum

## AIM AND OBJECTIVES:

The aim of this review article is (1) to discuss the advantages and limitation of chewing as drug delivery system, (2) to describe the methods of preparation, evaluation, stability, release of drugs, factors affecting release, safety aspects and development with respect to the medicated chewing gums.

## HISTORY<sup>[3]</sup>

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One thousand years ago, the Mayan Indians chewed tree resin from the sapodilla tree in order to clean their teeth and freshen the breath. Shortage of natural gum bases during World War II enhanced development of the synthetic gum bases that are used today. Chewing gum has been used for centuries to clean the mouth and freshen the breath. The first commercial chewing gum "State of Maine pure spruce gum" was marketed in 1948 in

the U.S.A. The first patent for the production of chewing gum was filed in 1869 and was issued to Mr W. F. Semple in Ohio under U. S. Patent No. 98,304.

The first medical chewing gum, Aspergum<sup>®</sup>, was launched in 1928. This chewing gum contains the analgesic substance acetylsalicylic acid known from Aspirin<sup>®</sup> tablets. Chewing gum did not gain acceptance as a reliable drug delivery system until 1978, when nicotine chewing gum became available. The introduction and success of nicotine chewing gum in the 1980's paved the way for a more general acceptance of chewing gum as a drug delivery system. Another commercially available medical chewing gum is dimenhydrinate-containing chewing gum for motion sickness. Improved technology and extended know-how, together with the inclusion of medical chewing gum in the European Pharmacopoeia in 1998, have further contributed to the acceptance of this method of drug delivery.

A MCG containing Acetyl Salicylic Acid was commercially introduced in 1928. In 1991, Chewing Gum was approved as a term for pharmaceutical dosage form by the commission of European Council.<sup>[4]</sup> Empiric findings had shown that people chewing gum was better at keeping awake and alert, and that gum chewing eased tension. The acceptance of this somewhat anecdotally understood effect achieved a better scientific basis in the summer 2002 when L Wilkinson and co-workers published a study of 75 healthy volunteers who were led through a number of cognitive, recognition, and memory tests. The results provided the first evidence that the chewing of gum can improve episodic memory and working memory.<sup>[5]</sup>

#### **MEDICATED CHEWING GUM:**

Medicated Chewing Gums are solid or semi-solid, single dose preparations that have to be chewed but not swallowed. They containing masticatory gum base with one or more pharmacologically active substances which are released by chewing. A medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose, after which the

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remaining mass is discarded. During the chewing process the drug contained in the gum product is released from the mass into saliva and could be absorbed through the oral mucosa or swallowed reaching stomach for gastrointestinal absorption. Mostly the chewing gum is spit out after the medicament is released out. They are intended to be used for local treatment of mouth diseases or systemic delivery after absorption through the buccal mucosa.<sup>[6]</sup> MCG represents the newest system with potential uses in pharmaceuticals, over the counter medicines and neutraceuticals. The drugs intended to act in oral cavity often have low water/saliva solubility and chewing gum constitute a valuable delivery system for such drugs.

#### **CHEWING GUM 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 bioadhesive 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<sup>®</sup>), and Nicotine chewing gums (e.g. Nicorette<sup>®</sup> and Nicotinell<sup>®</sup>). 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.

The advantages of utilizing a chewing gum drug delivery system are highlighted by T Imfield in

his 1999 review of gum chewing and oral health. There are two absorption pathways which are possible to introduce the active ingredient into the systemic circulation giving rise to a systemic effect. 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>[7]</sup>

**(a) Local effect:**

To obtain the optimal local effect to treat a health condition requires that the relevant active substance be available at a therapeutic level near or within the tissue being treated, regardless of the delivery system. For the treatment of oral cavity conditions, it is a beneficial to achieve a therapeutic level of active substance in the saliva, and different formulations (e.g. oral, gel, mouth rinse) have been created to meet this goal. 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 aa chewing gum that releases active substances over a prolonged period. The “oral health and caries prevention” and “oral fungal infection” provide a more comprehensive review of the advantages of chewing gum drug delivery system for the local treatment of oral health conditions.<sup>[8]</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 buccal 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. Buccal absorption may also lead to fast onset of the active substance as the vascular supply of the buccal mucosa is rich and lead directly into the systemic circulation. Chewing gum promotes buccal absorption by releasing active substance at carefully controlled rates, thus allowing for extended exposure of in Available online on [www.ijprd.com](http://www.ijprd.com)

the oral cavity. There are several methods for examining buccal absorption; these methods are described by Mr Rassing and co-workers. 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>[9]</sup>

**OTHER ASPECTS OF CHEWING GUM**

As suggested above, obvious that the length of time that patients chew becomes important when using chewing gum as a drug delivery system. In order to receive the full benefit from either buccal absorption or local effect, a certain concentration level in the oral cavity has to be maintained for a period of time.<sup>[10]</sup> The question is, therefore, what prescribed chewing duration will the typical patient accept; A study of 4,064 Americans between the ages of 12 and 55 answered this question to some degree. Participants were asked about their gum chewing habits, and results showed that mean chewing time was 36 minutes – a sufficient time to obtain local effect or buccal absorption of an active substance.

**CONCEPT OF FORMULATION DEVELOPMENT:**

A piece of chewing gum usually consists of gum core, which may or may not be coated. The core is composed of an insoluble gum base resin, elastomers, emulsifiers, fillers, waxes, antioxidants and softeners, sweeteners, flavouring agents, and in case of medical chewing gum, active substances. The water content of chewing gum is very low and no preservative is needed. As many active substances are lipophilic, they will adhere to the gum base and may therefore be released slowly and incompletely. The rate and extent of the drug release can be increased by the addition of buffering agents or solubilizing agents and coating/encapsulating the active substances. In contrast, hydrophilic active substances are rapidly released and it may therefore be necessary to slow down the release rate by encapsulating the active substances or by increasing the amount of gum base. The water content of gum base is very low and the gum binds lipophilic substances very firmly. In order to obtain the optimal formulation it is possible to decrease the release rate, choose highly

lipophilic substances and increase the release rate of lipophilic substances.<sup>[11]</sup> To succeed in the market, a chewing gum formulation must have a pleasant taste and texture. The gum base determines the basic characteristics of the product like the texture, its softness, hardness, elasticity, crumbliness, stickiness, mouth feel etc. It also determines the release profile of active ingredients and flavours.

Chewing gum is a mixture of natural or synthetic gums and resins, sweetened with sugar, corn syrup, artificial sweeteners and may also contain colouring agents and flavour. The basic raw material for all CG 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 polyvinyl acetate and similar polymers can be used as gum base.

**Gum base:** Gum base is an inert and insoluble non-nutritive product used as a support for the edible and soluble of the chewing gum.<sup>[18]</sup> Today, gum base is made of man-made latex and divided into two major categories: chewing and bubble gum, with the latter having more elasticity. In recent years, non-stick gum bases for chewing and bubble gums have been formulated to satisfy the needs of more consumers.

Typically Chewing Gum comprises two parts

1. Water insoluble chewable gum base portion.
2. Water-soluble bulk portion.

**1. Water insoluble gum base generally comprises Elastomers, Resins, Fats and Oils, and Inorganic fillers:**<sup>[12]</sup>

**a) Elastomers:** Elastomer provides elasticity and controls gummy texture.

These are used to aid in softening the elastomer base component.

They include terpinene resins, modified resins and gums

The elastomer solvents employed in 45-70% by weight of its gum base.

Natural elastomer: Natural rubbers like Latex or Natural gums such as Jelutong, LechiCaspi, Perillo, Chicle.

**b) Plasticizers:** These are softeners such as lanolin, Palmitic acid, Oleic acid, Stearic acid, Potassium

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Stearate, Microcrystalline waxes, Propylene glycol, incorporated to obtain variety of desirable textures and consistency properties. These are used to regulate cohesiveness of product. These are again divided into **Natural and Synthetic**.

Natural Plasticizers include Natural rosin esters like Glycerol Esters or Partially hydrogenated Rosin, Glycerol Esters of Polymerized Esters, Glycerol Esters of Partially dimerized Rosin & Pentaerythritol Esters of Rosin.

Synthetic Plasticizers include Terpene Resins derived from  $\alpha$ -pinene and/or d-limonene.

**c) Fillers or Texturizers or Mineral adjuvants:** Provide texture, improve chewability, provide reasonable size of the gum lump with low dose drug. Commonly used fillers are Magnesium and Calcium Carbonate, Ground Limestone, Magnesium and Aluminium Silicate, Aluminium Hydroxide, Clay, Alumina, Talc, Titanium Oxide & Mono/di/tri Calcium Phosphate.

**2. Water soluble portions contains Bulk Sweeteners, High intensity Sweeteners, Flavouring agents, Softeners, Emulsifiers, Colours & Antioxidants:**<sup>[12]</sup>

**a) Softeners and Emulsifiers:** These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. Softeners include Glycerine, Lecithin, Tallow, Hydrogenated Tallow, Mono/di/tri-Glycerides, Fatty acids like Stearic acid, Palmitic acid, Oleic acid and Linoleic acid.

**b) Colorants and Whiteners** may include FD & C type dyes and lakes, fruit and vegetable extracts, Titanium Dioxide.

It include pigments which may be incorporate in amounts up to about 6% by weight of the gum composition, titanium dioxide may be incorporated in amount up to 2%. The colorants may also include natural food colours and dyes.

**c) Sweeteners :** These are of two types, Aqueous and Bulk.

**Aqueous Sweeteners** can be used as softeners to blend the ingredients and retain moisture. These include Sorbitol, hydrogenated Starch hydrolysates and Corn Syrups. Corn syrup keeps gum fresh and flexible.

**Bulk Sweetners** include Sugar and Sugarless components. Sugar Components include Saccharides like Sucrose, Dextrose, Maltose, Dextrin, Fructose, Galactose, Corn Syrup.

**Sugarless Components** include sugar alcohols such as Sorbitol, Mannitol, Xylitol, hydrogenated Starch hydrolysate. High intensity artificial Sweeteners can also be included to provide longer lasting sweetness and flavour perception.

e.g. Sucralose, Aspartame, salt of Acesulfame, Alitame, Saccharin, Glycerrhizin, Dihydrochalcones.

**d) Bulking agents:** These are used if low calorie gum is desired. Examples of low caloric bulking agents include Polydextrose, Oligofructose, Inulin, Fructooligosaccharides, Guar gum hydrolysate, Indigestible Dextrin.

**e) Flavouring Agents:** A variety of flavouring agents are used to improve flavour in chewing gum includes essential oils, such as Citrus oil, fruit essences, Peppermint oil, Spearmint oil, Mint oil, Clove oil & Oil of Wintergreen. Artificial flavouring agents can also be used.

**f) Active Component:** In medicated chewing gum active pharmacological agent may be present in core or coat or in both. The proportion of which may vary from 0.5-30% of final gum weight. A small, unionized, lipophilic and enzymatically stable active agent is likely to be absorbed more readily. A saliva soluble ingredient will be completely released within 10-15 minutes of chewing whereas lipid soluble ingredient will dissolve in the gum base and thereafter be slowly and completely absorbed.

**g) Antioxidants:** -Butylated hydroxytoluene, Butylated hydroxyl anisole, propylgallate.

**h) Compression adjuncts:** -Silicon dioxide, magnesium stearate, talc can be used in medicated chewing gum. The alkaline earth metals, metal phosphates prevent caking and balling of high i.e. 2-8% moisture containing chewing gum composition during grinding, maltodextrane enhances the grinding of high moisture containing chewing gum composition. If oil lubricants are used, it is preferred to be 0.4-1% by weight of tableted chewing gum composition. The glidant composition

is about 0.5-5% by weight of tableted chewing gum composition.

#### **MANUFACTURING PROCESSES:**

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

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

#### **1. Conventional/ traditional Method** <sup>[13]</sup>:

Three 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 flavour. 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:**

1. Elevated temperature used in melting restricts the use of this method for thermolabile drugs.
2. Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult.
3. Lack of precise form, shape or weight of dosage form.
4. Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.
5. Such a chewing gum composition is difficult to form into chewing gum tablets because of their moisture content (2-8%). If attempted to grind and tablet such a composition would jam.
6. 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:** <sup>[14]</sup>

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  $-15^{\circ}\text{C}$  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  $-78.5^{\circ}\text{C}$ , 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

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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.

#### **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 tableting equipment and requires careful monitoring of humidity during the tableting process.

**3. Direct Compression Using Directly Compressible Chewing Gum Excipients <sup>[15]</sup>:**

The manufacturing process can be accelerated if a directly compressible chewing gum excipient is available. The limitations of melting & freezing can be overcome by the use of these. PHARMAGUM<sup>®</sup>, is one such compactable gum system developed by SPI Pharma. Pharmagum is a mixture of polyol(s) & or sugars with a chewing gum base. It is available as directly compressible powder, free flowing powder which can be compacted into a gum tablet using conventional tablet press thus enabling rapid and low cost development of a gum delivery system. It is manufactured under CGMP conditions and complies with Food Chemicals Codex specifications as well as with FDA, so they can be considered as "Generally regarded as safe" (GRAS). Pharmagum<sup>®</sup> is available in three forms namely S, M and C. Pharmagum<sup>®</sup> M has 50% greater gum base compared to Pharmagum<sup>®</sup>S. Pharmagum<sup>®</sup>S consists primarily of gumbase and sorbitol. Pharmagum<sup>®</sup>M contains gumbase, mannitol&Isomalt. Release of nicotine from directly compressible nicotine gum formulations and from Nicorette<sup>®</sup> prepared by conventional methods have shown that use of Pharmagum in formulation showed a faster release rate. Formulations made with Pharmagum<sup>®</sup> M & S are similar to tablet in appearance. Gums formed using compressible formulation are 10 times harder and crumble when pressure is applied resulting in faster release than conventional methods. Use of Pharmagum S, M and C enables formulators to

utilize a gum delivery system quickly & more cost effectively than by traditional methods.

**PROBLEMS OCCURRED DURING MANUFACTURING OF CHEWING GUM <sup>[16]</sup>**

- 1) Generally the chewing gum will jam the grinding machine, sticking to blades, screens and other surfaces if the moisture level is not controlled.
- 2) Many pharmaceutically active agents possess unpleasant taste or odour that results in the undesirable chewing gum products. Many active agents also tend to irritate the mucosa and few others degrade rapidly, making impractical to include them in chewing gum.
- 3) Another problem associated with the above methods is that the gum base is heated to a fluid mass to facilitate mixing of other ingredients. Such elevated temperatures can cause degradation of heat sensitive compounds, including active agents and flavours.
- 4) In manufacturing of chewing gum, sometimes organic solvents are used to dissolve the active agents. It is difficult to eliminate these organic solvents from the final product and may present certain health risks if even trace amounts remain in the final dosage forms.
- 5) Water can also be utilized in gum preparations, but it is difficult to eliminate at low temperature. Heating the gum mass to eliminate water is not advisable because the gum will then become stickier, which makes handling difficult and interferes with large-scale production.

**FACTORS AFFECTING RELEASE:**

The release rate of an active substance is determined not only by the formulation of the chewing gum but also by the properties of the active substance and of the individual chewing the gum. The chewing gum – The water content of gum base is very low and the gum binds lipophilic substances very firmly. In order to obtain the optional formulation it is possible to

1. Decrease the release rate of highly hydrophilic substances

2. Increase the release rate of lipophilic substances.
3. Achieve a more complete release of lipophilic substances.
4. Contact Time: The local or systemic effect is dependent on time of contact of MCG in oral cavity. In clinical trial chewing time of 30 minutes was considered close to ordinary use.
5. Physicochemical properties of active ingredient: Physicochemical properties of active ingredient plays very important role in release of drug from MCG. The saliva soluble ingredients will be immediately released within few minutes whereas lipid soluble drugs are released first into the gum base and then released slowly.
6. Formulation factor: Composition and amount of gum base affect rate of release of active ingredient. If lipophilic fraction of gum is increased, the release rate is decreased.<sup>[17]</sup>
7. Changing the water solubility of the active substance will increase or delay the release. A similar effect may be obtained by changing the hydrophilic/lipophilic balance of the chewing gum formulation. The simplest way of achieving this is to increase or decrease the amount of gum base. An increase in the gum base will make the formulation more lipophilic and thus

reduce the release rate of a given active substance.

8. The active substance: The release rate of an active substance depends on the solubility of the active substance in water and saliva. Highly hydrophilic substance will be almost completely released within 10 to 15 minutes. Substances with solubility in water or less than 0.1 – 1 g/100 ml are lipophilic components of the gum base and thereby show a slow and incomplete release.

#### IN VITRO DRUG RELEASE:

Number of apparatus for studying in-vitro drug release from medicated chewing gum has been developed. An apparatus for in vitro drug release testing of medicated chewing gums has been developed by Kvist C et al.<sup>[18]</sup> They have studied the effect chewing surfaces, twisting movements of surfaces and temperature of test medium on release rate of drug from MCG. Another novel dissolution apparatus has been developed for MCG by Rider JN et al.<sup>[19-20]</sup> The apparatus consist of conical Teflon base and a rotating, ribbed Teflon plunger suspended in a dissolution vessel. The rotation speed, plunger frequency, medium volume, medium type, medium sampling location, number of plunger ribs and number of gum pieces were studied by them.

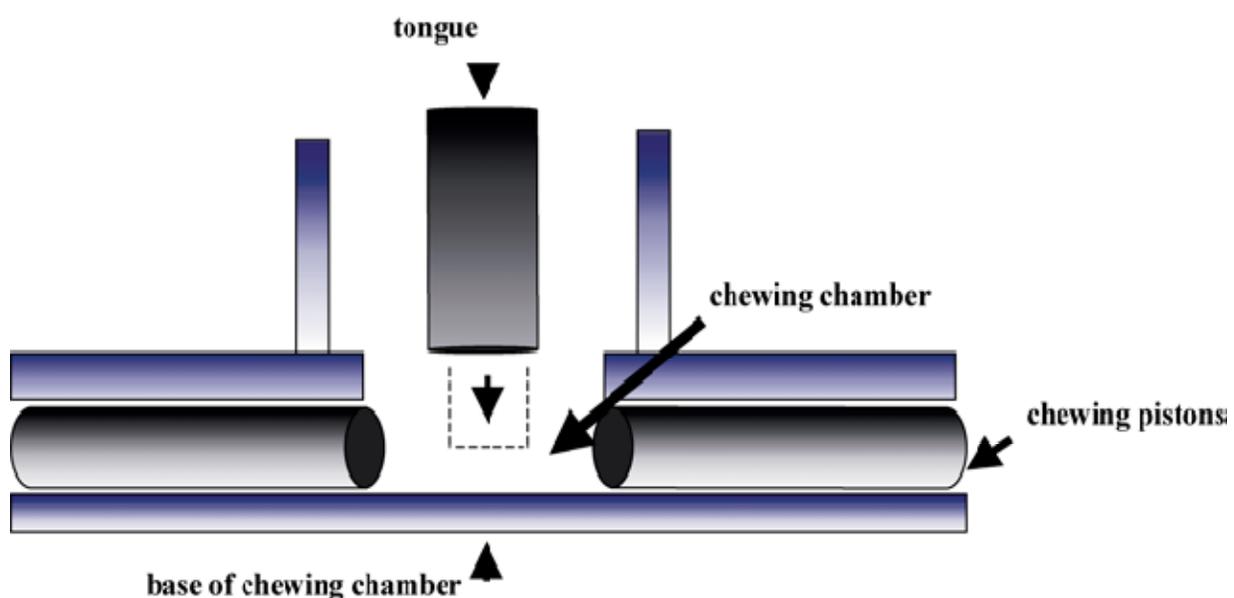


Figure 2 : Schematic diagram of the chewing chamber of in vitro chewing apparatus used [21]



Figure 3 apparatus for invitro dissolution of chewing gum

In 2000, European Pharmacopoeia<sup>[22-23]</sup> published a monograph describing a suitable apparatus for studying the in-vitro release of drug substances from MCG. The chewing machine consists of a temperature-controlled chewing chamber in which the gum piece is chewed by two electronically-controlled horizontal pistons driven by compressed air. The two pistons transmit twisting and pressing forces to the gum, while a third vertical piston, (“tongue”) operates alternately to the two horizontal pistons to ensure that the gum stays in the appropriate position. The temperature of the chamber can be maintained at  $37\pm 0.5^{\circ}\text{C}$  and the chew rate can be varied. Other adjustable settings include the volume of the medium, the distance between the jaws and the twisting movement. The European Pharmacopoeia recommends using 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 per minute.<sup>[24]</sup>

#### PHARMACEUTICAL SIGNIFICANCE OF MEDICATED CHEWING GUMS<sup>[25]</sup>

Prevention and cure of oral disease are obvious targets for chewing gum formulations. Chewing gum can release an active substance at a controlled rate over an extended period of time providing a prolonged local effect.

1. Sugar free chewing gum is known to be beneficial to dental health. It has been shown that use of sugar free chewing gum after meals re-elevates plaque. pH plays an important role in the development of dental caries. Therefore, in caries prevention programs, sugar-free chewing gum is recommended after meals and snacks as a supplement to tooth brushing.
2. Indications for fluoride chewing are prevention of dental caries in children in fluoride deficient areas, in adults with a high incidence of caries and in patients with xerostomia.
3. Chlorhexidine chewing gum can be used for alleviations of gingivitis, periodontitis and other oral and pharyngeal infections. It can also be used for inhibition of plaque growth and has proven valuable in oral health care of the elderly. Furthermore, chlorhexidine in a chewing gum formulation gives less staining of the teeth and is more convenient to use than a chlorhexidine mouth rinse. The chlorhexidine released by chewing is distributed evenly in the oral cavity and is present there for a prolonged time. The bitter taste of chlorhexidine can be masked quite well in achieving gum formulation.
4. Smoking cessation- Chewing gum formulation containing nicotine<sup>49</sup>, lobeline and silver

acetate have been clinically tested as aids to smoking cessation. Nicotine is a natural alkaloid occurring in the leaves of tobacco plant. It is a therapeutic agent intended to help smokers break the psychological habit of smoking by reducing the nicotine withdrawal symptoms normally experienced when smoking is stopped. The formulation nicorette available as mint and classic with different flavour and dosage, is developed with ion- exchange resin, released 90% of drug after 30 min chewing. The release rate was controlled by the rate and vigour of chewing. Thus the patient can control the drug intake to match his needs. Increasing the pH of the medium in which it is dissolved can enhance nicotine absorption.

5. Clinical trials involving patients with oral candidiasis have shown that miconazole chewing gum is at least as efficient as miconazole oral gel in the treatment of fungal infections in the mouth. Furthermore, patients preferred chewing gum to oral gel due to convenience and fewer side effects.
6. Chewing gum as a drug delivery system also provides benefits to systemic drug delivery, especially if the active substance is absorbed through the buccal mucosa, fast and acute treatment, convenience, no need for water and thereby easy administration – anytime anywhere – reduced risk of gastrointestinal side effects. These benefits apply not only to the treatment of adults, but also to the treatment of children and adolescents. Systemic effect of active substances released from chewing gum can be achieved in two ways. In the “traditional” way by swallowing the active substances, or 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. Buccal absorption may also lead to fast onset of the action and lead directly in to systematic circulation. Chewing gum promotes buccal absorption by releasing active substances at carefully controlled rates, thus allowing for extended exposure in the oral cavity.
7. A study of pharmacokinetics of nicotine chewing gum indicated that some of the nicotine was not absorbed through route but was swallowed and underwent first-pass metabolism. It was estimated that approximately 80% of the nicotine released from the chewing gum was absorbed through buccal route.
8. Successful treatment of minor pains, headaches, pains of colds, muscular ache, etc. requires rapid absorption of therapeutic doses of active substance. Chewing gum as a drug delivery system could be beneficial in minor pain treatment, when buccal absorption results in fast onset of action and reduces the risk of gastrointestinal side effects.
9. The bioavailability of acetylsalicylic acid in a chewing gum formulation relative to an unbuffered tablet formulation has been determined. Absorption from the chewing gum formulation was shown to be faster than absorption from the tablet, and consequently, a chewing gum formulation may provide faster pain relief.
10. Several chewing gum formulations containing caffeine, guarana or chromium are available. Caffeine and guarana are central stimulating anorectic agents that have been proved to increase the metabolic rate. Moreover, they stimulate lipolysis, have a thermogenic effect (increase energy expenditure) and reduce the feeling of hunger.
11. Chromium is claimed to reduce the craving for food due to an improved blood glucose balance. Chewing gum has been proven efficient in the treatment involving instant raving and “oral habits”. Hence there is a rationale for administering weight reducing active substance in a chewing gum formulation.
12. Allergy, nausea, motion sickness, diabetes, anxiety, dyspepsia, osteoporosis, and cough and cold are all indications for which chewing gum as a drug delivery system could be beneficial.

13. Chewing gum containing antacids or mucolytics also presents advantages for patients.
14. Chewing gum as a drug delivery system offers convenience in the treatment/prevention of motion sickness and nausea. Medicated chewing gum containing dimenhydrinate for motion sickness is already on the market, however, active substances like scopolamine, metoclopramide, ondansetron and dolasetron may be candidates for a chewing gum formulation for the treatment/prevention of motion sickness and nausea.
15. Several chewing gum formulations containing calcium are available on the market. Adolescents constitute a potential target group for a calcium chewing gum as the calcium intake of young people is often very low. Calcium chewing gum with a pleasant flavour is an attractive and convenient alternative to tablets.

#### **SAFETY ASPECTS** <sup>[25]</sup>

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 sugaralcohol containing chewing gum may cause diarrhoea. Long term frequent chewing of gum has been reported to cause increased release of mercury vapours from dental amalgam fillings. However, medicated chewing gum does not normally require extensive chewing, or consumption to great extent. Flavours, 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.

#### **ADVANTAGES OF CHEWING GUM OVER CONVENTIONAL DRUG**

#### **DELIVERY SYSTEM:** <sup>[26-31]</sup>

Available online on [www.ijprd.com](http://www.ijprd.com)

- 1) It is a convenient dosage form, which can be administered anytime, anywhere without need of water.
- 2) Avoid first pass metabolism
- 3) Fast/rapid onset of action due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation.
- 4) High bioavailability
- 5) Taste masking/Pleasant taste
- 6) Reduce risk of erosion of gastric mucosa because gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients. Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa.
- 7) Easy for administration without water promotes higher patient compliance
- 8) Aspirin, Dimenhydrinate and caffeine show faster absorption through Medicated chewing gum than tablets
- 9) Ready for use
- 10) The treatment can, if required, be terminated at any time
- 11) High acceptance by children and for patients having difficulties in swallowing tablets.
- 12) Fewer side effects
- 13) In addition, the drugs that are released from chewing gum and swallowed, will be introduced in the gastrointestinal tract either dissolved or suspended in saliva and thus the drug will be presented in a readily bioavailable form.
- 14) Convenient-promoting higher compliance
- 15) Discrete-less stigmatization
- 16) Excellent for acute medication
- 17) Systemic effect OR It may prove to be particularly suitable for the systemic delivery of drugs, which are susceptible to metabolism in the gut wall or liver.
- 18) Local effect
- 19) Counteracts dry mouth (xerostomia) through stimulation of the salivary secretion, thereby preventing candidiasis and caries.
- 20) Product distinctiveness from a marketing perspective.

As a delivery systemic administration of drug via the oral mucosa it has the potential to overcome the problems of short lived action and variations in drug release and retention times.

#### DISADVANTAGES OF THE CHEWING GUM: [6,35-38]

- 1) Chewing gum has been shown to adhere in different degrees to enamel dentures and fillers.
- 2) The drug released into saliva disappears rapidly from the oral cavity because of involuntary swallowing.
- 3) Prolonged chewing of gum may result in pain in facial muscles and ear ache in children.
- 4) Additives in gum like flavouring agent, Cinnamon can cause Ulcers in oral cavity and Liquorice cause Hypertension.
- 5) The concentration of drug in the oral cavity always tends to decrease as a result of salivary dilution.
- 6) 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.

- 7) Drug release from chewable formulations has shown to be strongly influenced by the way patient chews the formulation. Administration of such dosage form is restricted to short period of time because the presence of the delivery system in the oral cavity causes disturbance in drinking, eating and speaking.
- 8) Chlorhexidineoromucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue .
- 9) Sorbitol present in MCG formulation may cause flatulence, diarrhoea.

Despite these limitations, chewing gum formulation affords extended delivery period compared to solution and fast dissolving tablets.

**Some commercially available chewing gum are as follows:**

**Table 1:**commercially available products

Trade Name	Active drug	Use
Nicorette	Nicotine	Smoking cessation
Nicotinell	Nicotine	Smoking cessation
NiQuitin CQ	Nicotine	Smoking cessation
Fluorette	Fluoride	Dental flourosis
HEXIT	Chlorhexidine	Preventing tooth decay
Vitaflo CHX	Chlorhexidine	Preventing tooth decay
Advanced+	Chlorhexidine	Preventing tooth decay
Stay Alert	Caffeine	Stimulant
Travvell	Dimenhydrinate	Motion sickness
Chooz	Calcium carbonate	Antacid
Stamil vitamin C	Vitamin C	Anti-oxidant



### Future Trends:

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

Finally, it is concluded that Chewing gum is an excellent drug delivery system for self-medication so in the future, we may see 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 improves patient compliance. Hence in forth coming years it will be a much more common and popular drug delivery system.

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