AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Medicated Chewing Gum-An Emerging Intra- Oral Dosage Form

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ABSTRACT

Medicated chewing gum, in addition to its confectionary role also has a proven value as a drug delivery vehicle for pharmaceuticals, over the counter medicines and neutraceuticals ingredients. In 1991, the European pharmacopoeia defined the intended use of medicated chewing gum as non-dissolving intra-oral drug dosage form for local treatment of mouth diseases or for systemic delivery after absorption through buccal mucosa or from the gastrointestinal tract. Moreover, medicated chewing gums require the active and continuous masticatory activities for activation and continuation of drug release. In addition, drug that is not absorbed by the oral cavity membranes can be dissolved in the saliva before being swallowed thus leading to a more rapid onset of action. Medicated chewing gums are used 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. Thus chewing gum proves to be an excellent drug delivery system for self-medication as it is convenient and can be administered discretely without the aid of water. The present article highlights medicated chewing gum drug delivery system concepts including its advantages and disadvantages, composition, manufacturing processes, factors affecting drug release, its evaluation parameters, applications and worldwide marketed preparations.

Keywords: Medicated chewing gum, Intra-oral dosage form, Masticatory gum base, Drug release, Directly Compressible gums, and Patient compliance

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Received 7 February 2013, Accepted 25 February 2013

Please cite this article in press as: Deshpande TM *et al.*, Medicated Chewing Gum-An Emerging Intra-Oral Dosage Form American Journal of PharmTech Research 2013.

INTRODUCTION

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 and most important is its ease of administration. The intra-oral route is one of the more preferred routes of the drug administration as it is convenient and, with certain drugs, may provide a more rapid onset of action. Intra-oral dosage forms deliver the drug to the target sites for local or systemic drug delivery in the oral cavity. 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 Gums permit more rapid therapeutic action as compared to per-oral dosage forms. Chewable tablets and chewing gums have been very well received by the parents for their use in children with full dentition. Children in particular may consider chewing gum as a more preferred method of drug administration compared with oral liquids and tablets. The use of Medicated Chewing Gum is feasible in local treatment of diseases of oral cavity as well as treatment of systemic conditions.

Owing to new social and behavioral 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.

Medicated Chewing Gum represents the newest system with potential uses. The drugs intended to act in oral cavity often have low water or saliva solubility and chewing gum constitutes a valuable delivery system for such drugs.

Historical Development of Medicated Chewing Gum:[6,13]

Chewing Gum contains masticatory gum base with pharmacologically active ingredient and intended to be used for local treatment of mouth diseases or systemic absorption through oral mucosa. Chewing gum is a pleasure that almost everyone enjoys. 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 medicament contained. The drug product is intended to be chewed in the oral cavity for a specific period of time, after which the insoluble gum base is

discarded. Chewing gum is being used worldwide since ancient times after man experienced the pleasure of chewing a variety of substance. It can be used as a convenient modified release drug delivery system. Chewing gum has been used for centuries to clean the mouth and for freshening their breath. One thousand years ago the Mayan Indians chewed the tree resin (Chicle) from the sapodilla tree to clean their teeth and for freshening their breath.

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. The first Medicated chewing gum product 'As per gum' containing acetylsalicylic acid for headache was launched in 1928. The success story of nicotine chewing gum in the 1980s has led to more general acceptance of chewing gum as a drug delivery system. Moreover, there is need of reformulation of existing drugs into New Drug Delivery Systems (NDDS) to extend or protect product patents thereby delaying, reducing or avoiding generic erosion at patent expiry. Today improved technology and extended know how have made it possible to develop and manufacture medicated chewing gums with pre-defined properties. Regarding local actions, it is possible to achieve beneficial effects with medicated chewing gum that might be superior to those achieved with lozenges. Medicated chewing gum is a valid alternative to standard, chewable or orally disintegrating tablet. Recently, the chewing gum bases are widely used in controlled drug delivery systems. Chewing gum drug delivery systems 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 circulation. Medicated chewing gums are more effective in the removal of the extrinsic tooth stain. These days, the chewing gum 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 pharmaceuticals.

Advantages of Medicated Chewing Gums:[9,11,12]

- Fast/rapid onset of action.
- Improved bioavailability.
- Pleasant taste.
- Ease of administration without water promotes higher patient compliance.
- Ready for use.
- High acceptance by children and for patients having swallowing difficulties.

- Fewer side effects.
- Systemic effect.
- Local effect.
- Effect on dry mouth (xerostomia).
- Product distinctiveness from a marketing perspective.
- 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 by the gastric mucosa.
- Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly, therefore, duration of action is increased.
- Less first-pass metabolism.
- Improved focus and concentration.
- Stress relief.
- Increase the rate of saliva secretion. Stimulated saliva has a buffering capacity and may therefore help reduce acidity of gastric fluid.

Disadvantages of Medicated Chewing Gums:[13,16]

- Risk of over dosage with medicated chewing gum compared with chewable tablets or lozenges that can be consumed in a considerable number and within much shorter period of time.
- Sorbitol present in medicated chewing gum formulation may cause flatulence, diarrhea.
- Additives in gum like flavoring agent, Cinnamon can cause Ulcers in oral cavity and Liquorices causes Hypertension.
- Chlorhexidine or mucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue.
- Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers.
- Prolonged chewing of gum may result in pain in facial muscles and ear ache in children.

Anatomy and Physiology of Oral Mucosa:[12,14,19]

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

1. The Oral Epithelium
2. The Lamina Propria

3. The Sub Mucosa

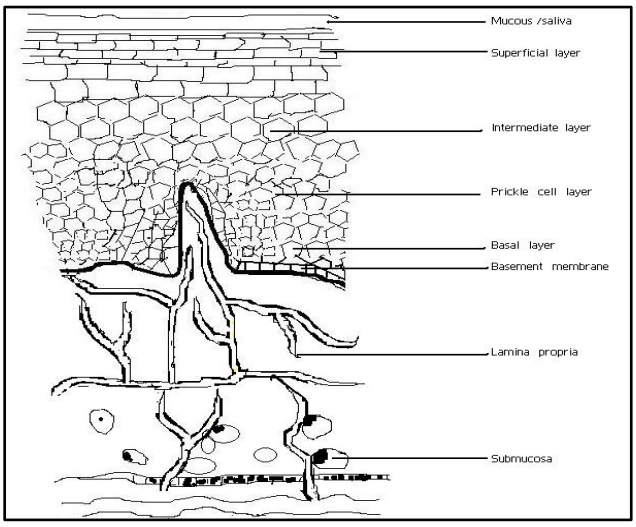

Figure 1: Generalized structure of oral mucosa

The Oral Epithelium:

The epithelium of mouth consists of stratified, squamous epithelium, which can be keratinized or non-keratinized. Keratinized epithelium is dehydrated, mechanically tough and chemically resistant. It is found in oral cavity subject to mechanical stress such as mucosa of gingival and hard palate (roof of mouth). Non-keratinized epithelium is relatively flexible and is found in areas such as the soft palate, the floor of mouth, the lips and the cheeks. The epithelium of the oral cavity is supported by the basement membrane, which separates the epithelium from the underlying connective tissue layer (the lamina propria). Oral epithelium broadly similar to stratified squamous epithelia found elsewhere in the body, for example the skin , in that cells are produced by mitosis in the basal layer of the epithelium and these proliferating cells push existing cells towards the surface. The phase of this process is represented in four morphological layers:[12]

1. Basal layer;
2. Prickle cell layer;
3. Intermediate layer;
4. Superficial layer: Structural changes that occur during this upward transit, from basal to superficial layer, include the cells becoming

a) Larger in size;

b) More flattened: The cuboidal cells of the basal layer are more polygonal shape in prickle cell layer , become slightly flattened in the intermediate layer and more flattened in the superficial layer .

c) More proteinaceous: Increasing amount of protein are found in the cells (for both keratinized and non-keratinized epithelium) toward the epithelial surface, in the form of protein monofilaments;

d) Less viable: There is an absence of organelles in superficial cells, indicates that these cells are no longer viable.

The Lamina Propria:

The lamina propria contains a sheet of connective tissue containing collagen elastic fiber and cellular components in hydrated ground substance. It also carries blood capillaries and nerve fibers that serve the mucosa. It is through the blood vessels in the lamina propria that drug moieties can gain the entry in systemic circulation.[12]

The Salivary Glands:

Saliva is a hypotonic, watery secretion containing variable amount of mucus, enzyme, antibodies and inorganic ions. The surface of mucus membrane is constantly washed by a stream of about 0.5 to 2L of saliva daily produce in the salivary gland the chief secretion is supplied by three pairs of glands, the parotid, the sub maxillary , and the sublingual glands.[12]

The presence of saliva in mouth is important for two main reasons:

1. Drug permeation across moist membranes occurs much more readily than across non mucous membranes; compared to drug absorption across the GI tract and skin.

2. Drugs are commonly administered to mouth in solid dosage form. The drug must therefore first dissolve in saliva before it can be absorbed across the oral mucosa; that is the drug cannot be absorbed directly from the tablet.

Absorption of drug through Oral Mucosa:

The oral cavity is point of entry for oral drug formulations but their contact with the oral mucosa is brief. So in order to take advantages of these properties or to treat the mucosa locally, these delivery system have been designed to prolong residence in this area. The total surface area available for drug absorption is quite limited being only approximately 100 cm^2. The oral cavity is rich in blood vessels and lymphatic, so rapid onset of action and high blood levels obtained quickly. In many cases oral dosage form can result in the same availability as the same intravenous formulation, without need of aseptic preparation. Finally they share with transdermal system the advantages that treatment can be rapidly stopped by removing dosage form. Ideally the plasma concentration versus time profile should resemble a square wave, similar to that seen after application of glycerol trinitrate patches, but this is not always achievable. In order to absorb orally, the drug must be dissolve in saliva. Extremely hydrophobic materials will not

dissolve well and are likely to be swallowed intact unless a specialized delivery system is used to prevent them to mucosa.[11,12]

FACTORS AFFECTING DRUG RELEASE:[8]

Membrane factor:

Regional difference in both permeability and thickness affect both the rate and the extent of drug reaching the systemic circulation. Keratinization and composition also affect systemic mucosal delivery. Additional factors such as absorptive membrane thickness, blood supply, blood/ lymph drainage, cell renewal rate, and enzyme content will also govern the rate and extent of drug absorption.

Environmental factor:[12]

1. Saliva:

It is composed of 99% water and its pH varies between 6.5 to 7.5 depending on the flow rate and location. Increase in the salivary flow rate leads to the secretion of watery saliva. Stimulated salivary secretion affects the film thickness and aids in the easy migration of the test compounds. Salivary pH is also important for the passive diffusion of the unionized drug.

2. Salivary Glands:

The medicated chewing gum should be placed either over or adjacent to the salivary duct because it may result in excessive washout of drug or rapid dissolution of the system making it difficult to achieve high local drug concentration.

Chewing Time and Chewing Rate:

The chewing time should be around 20 to30 minutes. The rate of chewing also affects the drug release. The average chewing rate is about 60 chews / minute.

Aqueous Solubility of the drug:

Release of the water soluble drug(solubility > 1:10) about 75% or more during 5 minutes of chewing and 90% or more during 15 minutes of chewing at a rate of 60 chews per minute. Drug with the aqueous solubility between 1:10 and 1:300 demonstrate up to 60% and 90% when the gum is chewed for 15 minutes. The release of the drug which is only slightly water soluble can only be expected to be small i.e. less than 5% even if the gum is chewed for 30 minutes.

Contact Time:

The local or systemic effect is dependent on time of contact of medicated chewing gum in the oral cavity. In clinical trial chewing time of 30 minutes is considered close to ordinary use.

Physicochemical properties of active ingredient:

Physicochemical properties of active ingredient plays very important role in release of drug from

medicated chewing gum(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.

Inter individual variability:

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

Formulation factor:

Composition and concentration of gum base affects rate of release of active ingredient. If lipophilic fraction of gum is higher, the release rate is lower.

COMPOSITION OF MEDICATED CHEWING GUM:[3,13]

Table 1:Excipients used in Medicated Chewing Gums.

Component	Function and percentage range used	Examples
Water insoluble excipients gum base		
Elastomers	Provides elasticity and Controls gummy texture 15 to 45%	Natural (Chicle gum, nispero, rosadinha, jelutong, periollo, lechi capsi, sorvaetc.) and synthetic rubbers(butadiene, styrene copolymers, polyisobutylene, polyethylene mixtures, polyvinylalcoholetc.)
Elastomer Solvents	Softening the elastomer base component45 to 70%	Terpinene resins(polymers of alpha-pineneor beta pinene),modified resins or gums(hydrogenated, dimerized or polymerized resins)
Plasticizers	To obtain a variety of desirable textures and consistency properties	Lanolin, palmitic acid, oleicacid, stearic acid, glyceryl triacetate, propylene glycol monostearate, glycerine, natural and synthetic waxes, hydrogenated vegetable oils, paraffin waxes, fatty waxes, sorbital monostearate, propyleneglycol
Fillers or mineral adjuvant	Provide texture, improve chewability, Provide reasonable size of the gum lump with low dose drug up to 50%	Calcium carbonate, magnesium carbonate, aluminum hydroxide, talc, aluminum silicate
Water soluble excipients: Portions		
Softeners and emulsifiers	They added to the chewing gum in order to optimize the chewability and Mouth feel of the gum 0.5 to 15%	Glycerin, lecithin, tallow, hydrogenated allow, mono/di/tri glycerides
Colorants and whiteners	Gives the formulations soothing color and Improves acceptability of the formulation 0.1%	Titanium dioxide, natural food colors and dyes suitable for food, drug and cosmetic applications

Sweeteners	To provide the desired wetness of the Product Up to 50%	Water soluble sweetening agents(xylose, ribulose, glucose, mannose, galactose, sucrose, fructose, maltose, monellin, sugar alcohol slike sorbitol, mannitol etc.),water soluble artificial sweeteners(sodium or calcium saccharin salts, cyclamate salts etc.),di-peptide based sweeteners (aspartame, alitameetc),naturally occurring water soluble sweeteners, chlorinated derivative so ordinary sugar (sucralose), protein based sweeteners (thaumatin I and II)
Antioxidants	Prevents any possible microbial growth	Butylated hydroxyl toluene, butylated hydroxyl anisole, propyl gallate
Flavoring agents	To enhance consumer acceptability 0.01 to 1%	Essential oils(citrusoil, fruit essences, peppermint oil, spearmint oil, mint oil, clove oil and oil of wintergreen) and synthetic or artificial flavors
Bulking agents	Used flow calorie gum is desired Q.S.	insulin, fructose oligosaccharides, Guar gum hydrolysate ,indigestible dextrin
Compression Aid	To ease the compression process 0.5 to 2%	Silicon dioxide, magnesium stearate, calcium stearate, talc

Active component:[3]

In medicated chewing gum the active pharmacological agent may be present in core or coat or in matrix. The proportion of which may vary from 0.5 to 30%of final gum weight. A small, unionized, lipophilic and enzymatically stable active agent is likely to be absorbed faster. A saliva soluble ingredient will be completely released within 10 to 15 minutes of chewing whereas lipid soluble ingredient will dissolve in the gum base and thereafter be slowly and completely absorbed. Methods to increase the rate and extent of release of active pharmaceutical ingredients include the addition of buffering agents or solubilizing agents and coating/encapsulating the active component.

MANUFACTURING PROCESSES:[1,3,7,11,12]

Different methods employed for the manufacturing of medicated chewing gum can be broadly classified into three main classes namely:

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

1.**Conventional/Traditional method(Melting**):

Components of gum base are softened or melted and placed in a kettle mixer to which sweeteners, syrups, active ingredients and other excipients are added at a definite time. The gum

is then sent through a series of rollers that forms into a thin, wide ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavor. In carefully controlled room, the gum is cooled for upto 48 hours. This allows the gum to set properly. Finally the gum is cut in 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 the molabile 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 the moisture content(2-8%).If attempted to grind and tablet such ac composition would 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. The medicated 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 temperature of the refrigerated mixture is around-15^{o}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^{o}C,it sublimes 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 the first step. Additional solid carbon dioxide and silica are added to the ground composition, and the composition is further ground in the second 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 to 8% by weight of grinding aid such as alkaline metal phosphate, an alkaline earth metal phosphate or maltodextrin can be incorporated. However practical use of these substances is limited because these substances are highly alkaline and hence would be incompatible with acidic ionizable 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.

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 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 with a coating agent thereby minimizing undesirable particle agglomeration. The granules so obtained can be mixed with anti-adherents like talc. The mixture can be blended in a V type blender, screened and 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. **Use of Directly Compressible Chewing Gum Excipients:**[3,4,5]

The manufacturing process can be accelerated if a directly compressible chewing gum excipient is available. Gums formed using compressible formulation are 10 times harder and crumble when pressure is applied resulting in faster release than conventional methods. The limitations of conventional manufacturing methods for medicated chewing gum such as melting & freezing can be overcome by the use of directly compressible gums. Pharmagum 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® is available in three forms namely S, M and C. Pharmagum® M has 50% greater gum base compared to Pharmagum®S. Pharmagum®S consists primarily of gum base and sorbitol. Pharmagum®M contains gum base, mannitol & Isomalt. Also another directly compressible gum which has made the production of medicated chewing gum easier is the Cafosa's Health in Gum (HiG), an innovative concept for the pharmaceutical industry. Health in Gum is an excipients, a directly compressible powder gum containing a mixture of ingredients, to which you only need to add APIs. Health in Gum is specially designed for in-house use in pharmaceutical facilities and does not require specific chewing gum production equipment. It can be compressed easily using standard tablet press. Health in Gum offers an innovative drug delivery system that benefits from all the advantages of chewing gum and also contributes to improved compliance. It has been created to simplify the manufacturing process of chewing gum in a quick and cost-effective way. It is directly compressible and works at room temperature, which allows the use of thermo-sensitive APIs. It is also available in three grades HiG 01, 02 and 03. HiG 01 and HiG 02 have same composition i.e. gum base, sorbitol, xylitol, ant caking agent and plasticizer; only difference is that concentration of gum base in HiG 02 is slightly more than HiG 01.HiG 03 contains higher percentage of gum base than HiG 01 and 02 and also contains isomalt, sorbitol and anticaking agent.

REGULATORY ISSUES:[11]

The first monograph on medicated chewing gum was published in the European Pharmacopoeia in1998.Use of a solid tasteless masticatory gum base and coating, if necessary, to protect from

humidity and light, is described. Being a single dose preparation, medicated chewing gum has to comply with tests for uniformity of content and uniformity of mass. In addition, the microbial quality has to be ensured. Release testing is prescribed to control the bioavailability of the drug(s).In the year 2000 the first monograph on a principle chewing apparatus and a procedure for the determination of drug release from medicated chewing gum was published in the European Pharmacopoeia. Chewing gum must be chewed to release the drug(s) and it is accepted that a residual of the drug(s) may be left in the chewing gum after drug will remain after finishing chewing. Generally a reproducible residual of a lipophilic drug will remain after chewing a gum at a constant rate for a predetermined period of time. In some cases, e.g. smoking cessation, one only chews the gum until the desired effect is obtained, hence the expelled gum will contain inter-individual variations in the amount of residual drug.

EVALUATION PARAMETERS:

1) **Test for Uniformity of Content:**

Unless otherwise prescribed or justified and authorized medicated chewing gum with content of2 mg or less than 2 percent of the total mass of gum comply with test.

2) **Uniformity of mass:**

Uncoated medicated chewing gum and unless otherwise justified and authorized coated medicated chewing gum comply with the test for uniformity of mass of single-dose preparations.

3) **Drug release from medicated chewing gum:**[22,23,24]

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

Apparatus I. Chewing Gum Apparatus, Compendial—Ph. Eur.[25]

The chewing apparatus for medicated chewing gum was adopted by Ph. Eur. in 2000.58 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. The working procedure of this chewing apparatus is described in Ph. Eur.58,59 Several studies have been carried out using the Ph. Eur. Apparatus and the results indicate the methodology is rugged and reproducible.

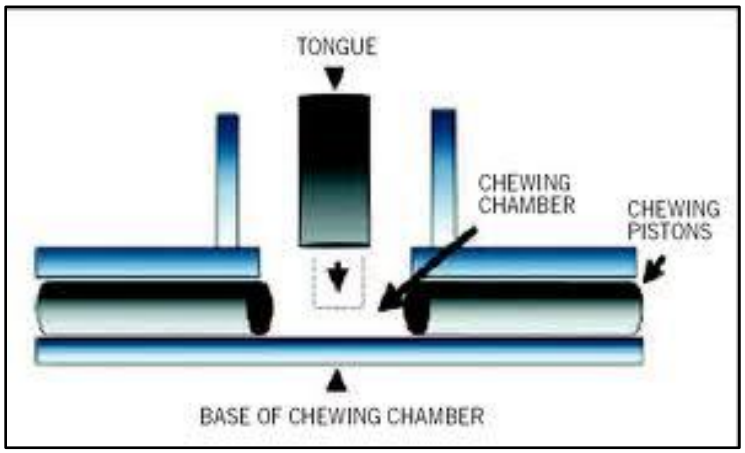

Figure 2: Apparatus for the determination of drug release from medicated chewing gum

Apparatus II. Alternative Chewing Gum Apparatus, Non-compendial—Wennergren[23,24]

One of the non-compendial apparatus commercially available was designed by Wennergren. 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. Investigations of the performance of the chewing apparatus with multiple drug products were published by Wennergrenet al.[23] The influences of different operational parameters of the chewing gum apparatus on drug release have been carefully investigated.

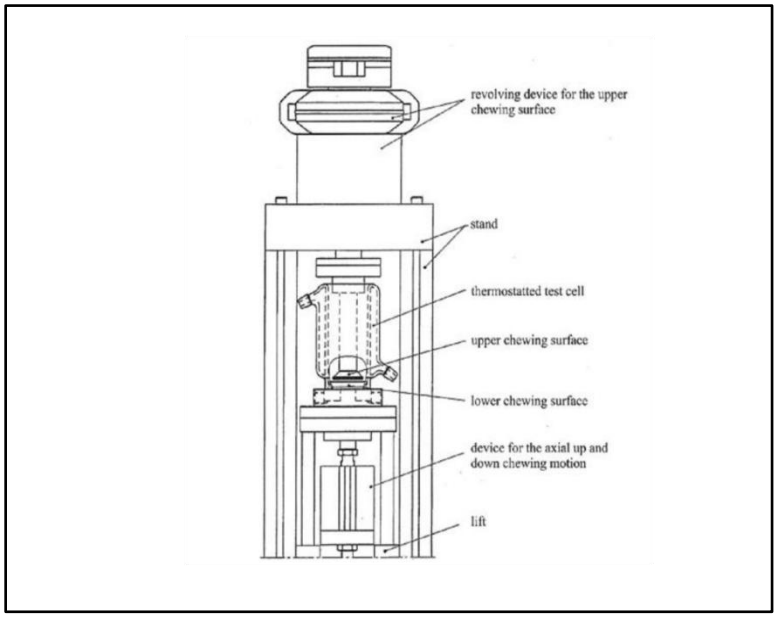

Figure 3: Single-module chewing apparatus from Wennergren

Drug release testing methodology:[20,21]

Ph. Eur. has adopted an apparatus to determine the release rate from chewing gum formulations. The basic principle is a simple masticatory movement employed to simulate the chewing action on a piece of gum placed in a small chewing chamber containing a known volume of buffer solution at a given temperature. The drug release rate is influenced by the chewing rate and angle, which provides the necessary shear force to expose new gum surfaces and is a requisite for further drug release. The mechanism and kinetics of drug release from chewing gums have not yet been completely understood due to the complexity of the formulation itself. The transition from the inactive gum to the active dosage form is influenced by:

1. Mechanical forces
2. Temperature
3. Wettability
4. Water permeation

As a general rule under sink conditions, the rate at which the drug is released is directly proportional to the chewing frequency and aqueous solubility of drug substance and is indirectly proportional to the mass of the gum base.

***In Vivo* 'Chew-Out' Studies:**[24]

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.

1) **Release of drug in saliva:**

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

saliva are taken after 2, 4, 6, 8, 10, 12, 14 and 15 minutes. The saliva samples are made diluted in required solvent and absorbance is measured using suitable analytical method.

2) **Dissolution test of residual medicated chewing gum:**[3,15,17,20]

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

3) **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 hours. They are fasted overnight, and emptied their bladder in the volumetric flask. Sample collection starts from blank of zero hour urine. Then sample collection is done on 15 minutes, 1, 2, 3, 4, 6, 7, 8, 10, 11, 12 and 24 hour intervals after administration of medicated chewing gum. The volunteers are asked to drink water at regular intervals of 30 minutes. and urine samples are analyzed by suitable analytical methods.

4)**Buccal absorption test:**

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

APPLICATIONS OF MEDICATED CHEWING GUM BASES:[11,12,16]

Dental caries:

1. Prevention and cure of oral disease are targets for chewing gum formulations.
2. It can control the release rate of active substances providing a prolonged local effect.
3. It also re-elevates plaque pH which lowers intensity and frequency of dental caries.
4. Fluoride containing gums have been useful in preventing dental caries in children and in adults with xerostomia.

5. Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oral and pharyngeal infections.
6. It can also be used for inhibition of plaque growth.
7. Chlorhexidine chewing gum offers numerous flexibility in its formulation as it gives lessstaining of the teeth and is distributed evenly in the oral cavity.
8. The bitter taste of Chlorhexidine can be masked quite well in a chewing gum formulation.

Systemic therapy:

Pain:

chewing gum can be used in treatment of minor pains, headache and muscular aches.

Smoking cessation:

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

Obesity:

Active substances like chromium, guaran and caffeine are proved to be efficient in treating obesity. Chromium is claimed to reduce craving for food due to an improved blood-glucose balance. Caffeine and guaran stimulate lipolysis and have a thermo genic effect(increased energy expenditure) and reduce feeling of hunger.

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.

Table 2:Worldwide Marketed Medicated Chewing Gums:[9,11,12]

Trade Mark	Active substance	Aim	Commercially available
Aspergum	Aspirin	Pain relief	North America
Nicorette	Nicotine	Smoking cessation	Worldwide
Nicotinelle	Nicotine	Smoking cessation	Western Europe
Trawell	Dimenhydrinate	Travel illness	Italy, Switzerland
Superpep	Dimenhydrinate	Travel illness	Germany, Switzerland
Chooz	Calcium carbonate	Stomach & neutralization	USA
Endykay	Vitamin C	General health	Middle east, UK
Stamil	Vitamin C	General health	Australia
Source	Vitamin C	General health	Australia
Brain	DHA & CCE	Enhanced brain activity	Japan
Stay alert	Caffeine	Alertness	USA
Café coffee	Caffeine	Alertness	Japan
Buzz gum	Guaran	Alertness	UK
Go gum	Guaran	Alertness	Australia
Chroma slim	CR	Diet	USA
Fluorette	Fluoride	Cariostatic	USA

Vitaflo CHX	Chlorhexidine	Preventing tooth decay	USA
Travel	Dimenhydrinate	Motion sickness	USA, Australia
V6	Xylitol	Dental caries	UK

CONCLUSION:

Despite the aforementioned benefits, the potential of medicated chewing gums has not yet been fully explored. The manufacture of chewing gum requires different technology to that used in pharmaceutical production. Standard chewing gum manufacturing requires specific equipment and facilities involving hot-melt processes, which are usually rare in the pharmaceutical industry. Another reason why medicated chewing gum has not yet been fully explored is because of therapeutic uncertainty related to the drug delivery method namely, a patient's mechanical chewing action. The gum's therapeutic effect depends on chewing, and as each person has their own chewing force, frequency and time, the results can vary. Manufacturers must also take into account that chewing gum has new parameters to monitor such as desired taste, texture, mouth-feel, appearance, interaction between ingredients, flavoring etc. which influences the final product.

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