Review Article *Gupta et al.*, 10(7-8): July/Aug, 2019:6319-6330]
CODEN (USA): IJPLCP ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

Medicated Chewing Gum – A Modernistic Drug Delivery System

Priya Gupta*, Madhvi Jain, Sonu Sharma, Arya Vidhyadhari, Sandeep Singh and Deepak Sharma
School of Pharmaceutical Sciences, Jaipur National University, Jaipur (RJ) - India

Abstract

Medicated chewing gum is an innovative approach which is used as a drug delivery vehicle for pharmaceutical and nutraceutical ingredients. Medicated chewing gum is a solid, single dosage form which release drug slowly in oral mucosa by the help of mechanical strength of chew. Medicate chewing gum does not dissolve in mouth but it release therapeutic agent in oral mucosa. Distinct from chewable tablet, medicated chewing gum have to remove from mouth so medicated chewing gum always labeled as not to be swallowed. Medicated chewing gum contains gum base with one or more than one active ingredients and suitable excipients. Medicated chewing gums are brilliant mobile drug delivery systems for self-medication and it can be administered discretely without water. Medicated chewing gum is used in systemic as well as local disease condition like Smoking cessation, travel illness, freshening of breath, vitamin or mineral supplementation, vomiting, pain relief etc. Other than therapeutic benefits medicated chewing gum offers many advantages like it give attractive and elegant look, acceptable taste and odour, it can formulate in many flavours which give joy to patients and most important it is highly acceptable by children and patients who have problem to swallow tablet.

Key-words: Oral mucosa, chewable tablet, self medication, mobile drug delivery system.

Introduction

Medicated chewing gum is a pliable dosage form that is designed to be chewed rather than swallowed. Medicated chewing gums release the drug substance(s) into the saliva. Medicated chewing gums can deliver therapeutic agents for local action in the mouth or for systemic absorption via the buccal or gastrointestinal routes (e.g., nicotine or aspirin). Most gums are manufactured using the conventional melting process derived from the confectionary industry or alternatively may be directly compressed from gum powder. Medicated chewing gums are formulated from insoluble synthetic gum bases such as polyisoprene, polyisobutylene, isobutylene isoprene copolymer, styrene butadiene rubber, polyvinyl acetate, polyethylene, ester gums, or polyterpenes. Plasticizers and softeners such as propylene glycol, glycerin, oleic acid, or processed vegetable oils are added to keep the gum base pliable and to aid in the incorporation of the drug substance, sweeteners, and flavoring agents.

*** Corresponding Author**
E.mail: priyanshi1209@gamil.com

Sugars as well as artificial sweeteners and flavorings are incorporated to improve taste, and dyes may be used to enhance appearance. Some Medicated chewing gums are coated with magnesium stearate to reduce tackiness and improve handling during packaging. A preservative may be added. [1]

The first medicate chewing was launched in 1928 under the the name Aspergum which contains acetylsalicylic acid, this medicated chewing gum is still available in the market. In 1991, chewing gum was approved as a term for pharmaceutical dosage form by the commission of European council. Medicate chewing gum did not gain acceptance as a reliable drug delivery system until 1978, when nicotine chewing gum became available. This medicated chewing gum used in smoking cessesion, which is most demanding medicated chewing. [6]

The European Pharmacopoeia defines medicated chewing gum as ‘‘solid, single-dose preparations with a base consisting mainly of gum that are intended to be chewed but not swallowed’’.

A novel drug delivery system creates additional patient benefits that will add new competitive advantages for a drug.

In recent years scientific and technological advancements have been made in the research and development of oral drug delivery system. It offers

various advantages over conventional drug delivery systems. Unlike chewable tablets medicated gums are not supposed to be swallowed and may be removed from the site of application without resorting to invasive means. Over the years, patient convenience and patient compliance-oriented research in the field of drug delivery has resulted in bringing out potential innovative drug delivery options. Out of which, medicated chewing gum offers a highly convenient patient-compliant way of dosing medications, not only for special population groups with swallowing difficulties such as children and the elderly, but also for the general population, including the young generation. Medicated chewing gum delivery system is convenient, easy to administer - anywhere, anytime - and is pleasantly tasting making it patient acceptable. It offers a wide range of advantages that make it an excellent alternative. It can be used to prevent or cure the dental caries, smoking cessation, pain, obesity, xerostoma, acidity, diabetes etc. A novel drug delivery system creates additional patient benefits that will add new competitive advantages for a drug and thus increase revenue. During chewing the drug contained in the gum is released into the saliva. The released drug has got two fates; either it could be absorbed through the oral mucosa or may reach the stomach for GI absorption. In fact both these two fates may occur simultaneously. So, medicated chewing gums offer both local and systemic effect. This drug delivery system offers two absorption pathways. Drug absorbed directly via the buccal membrane avoids metabolism in the gastrointestinal tract and thus the chance of first pass effect of the liver. As a result drug formulation as medicated chewing gum may require reduced dose compared to other oral drug delivery systems. [5] Application of bio-adhesive semisolid gels creates considerable tech nical problems in the buccal absorption. Although me dicated chewing gums pose difficulties in regulating the dose administered, they still have some advantages as drug delivery devices, particularly in the treatment of diseasesin the oral cavity and in nicotine replacemet therapy. Some commercially available chewing gums are Caffeine chewing gum, (Stay Alert®) and Nicotine chewing g ums (e.g. Nicorette® and Nicotinell®). The permeability of nicotine across the buccal mucosa is faster than acros the skin. However, chewing gum slowly generates a steady plasma level of nicotine rather than a sharp pe ak as experienced when smoking. Possible swallowing of considerable amount of nicotine during chewing may lead to decreased effectiveness of the chewing gum d ue to first pass metabolism and gastrointestinal disco mfort. It is a major challenge to optimize the dose-response relationship of nicotine administered in a chewing gm. [6]

Varying the formulation and manufacturing process, chewing gum as a drug delivery system can be formulated for an extended period of time. There is no doubt that chewing gum is an important factor in confectionery and that it can be expected to have an influence on dental health. Chewing gum was initially sweetened with sugar, which contributed to dental caries. Today, however, more than 50% of chewing gum sold in Europe is sweetened with sugar substitutes (polyols). Clinical evidence shows that sugar substituted chewing gum does not lead to caries, because the polyols do not lead to a clinically relevant production of metabolic acids in dental plaque. At the same time, however, chewing stimulates the flow of saliva, thus strengthening its protective properties, i.e., its buffering capacity, mineral supersaturating, and cleansing, antimicrobial, and agglutinating actions. Clearly, this suggests a beneficial effect from the chewing of sugar-free gum.

MERITS OF MEDICATED CHEWING GUM (PHARMACOLOGICAL) [2, 3, 39, 43]

- Relaxes and eases tension.
- Increase concentration.
- Makes wakeful.
- Freshens the breath.
- Helps in ear ache and decrease ear discomfort when flying.
- Satisfies snack craving.
- Reduces appetite.
- Exercise of facial muscle.
- Cleans teeth and remove plaque.
- Gives fun and joy.

MERITS OF THE MEDICATED CHEWING GUM (OVER OTHER DOSAGE FORMS)

- Dose not requires water or any other liquid to swallow. So can be taken anywhere conveniently.
- Patients who are suffering from and swallow difficulty problems can be use medicated chewing over than any oral dosage form.
- It is invasive route of administration.
- Supervision is not required.
- Excellent for acute medication.
- Counteracts dry mouth, prevents candidiasis and caries.

- Highly acceptable by children and youth specially girls.
- High bioavailability of drug.
- Removal of drug from site of administration is possible.
- The active therapeutic moiety absorbed in oral mucosa avoids the enterohepatic circulation and the associated metabolism.
- Gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients.
- Fast onset of action due to rapid release of the drug.
- Oral mucosa is rich in blood circulation which increases the absorption of drug. Hence provide fast onset of action.
- Many drugs show faster absorption through medicated chewing gum than tablet like Aspirin, Dimenhydrinate & caffeine.

DEMERITS OF MEDICATED CHEWING GUM

- Unnecessary wear & tear of the cartilage.
- It can produce headache.
- Wastage of energy.
- Long term frequent use causes increase release of mercury vapour from dental amalgam filling.
- 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 Liquorice cause Hypertension.
- Chlorhexidine oromucosal 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.

COMPONENTS OF MEDICATED CHEWING GUM [5, 51]:

Table No. 1 Components of Medicated Chewing Gum

S No	Ingredients	Concentration	Characterization	Example
1	Active pharmaceutical ingredient	0.5-30%	Provide therapeutic effect	Vitamins, Nicotine, Analgesic, Antacid, Anti tussive, Antihistamines,
Gum Base (water insoluble)				
2	Elastomers	40-70%	Provide elasticity and gummy texture	Nature rubber like latex or natural gum such as jelutong, lechi caspi, puerile, chicle .
3	Plasticizers	3-20%	Regulate cohesiveness of product	**Natural plastisizers-** Natural resin esters like glycerol esters or partially hydrogenated resin, polymerized glycerol esters etc. **Synthetic plasticizers-** Terpene resins**.**
4	Fillers or texturizers	2-60%	Provides texture, improve chewability, and provide reasonable size	Magnesium and calcium carbonate, ground limestone, clay, alumina, talc, titanium oxide .
Water Soluble Ingredients				
5	Softners and Emulsifiers	0.5 -15 %	Optimize chewability and mouth feel of the gum. Provide softness to the mixture.	Glycerin, lecithin, tallow, hydrogenated tallow, mono/di/tri glycerides, stearic acid, palmitic acid, oleic acid, linoleic acid etc.

			Promote uptake of saliva.	
6	Colorants and whiteners	Less than 1%	Provide colour and	FD & C type dyes and lakes
7	Sweeteners	50-65%	Provide sweetness of the product	sorbitol, mannitol, glycyrrhizin, sucrose,maltose, xylose, glucose, galactose, frictose , com syup, sucralose, aspartame, saccharin etc.
8	Bulking agent	qs	Use when low calorie gum is required	Polydextrose, oligofructose, lnulin, fructooligosaccharides, guargum hydrolysate, indigestible dextrin.
9	Flavoring agents	1-5%	Enhance flavor and consumer acceptability	Citrus oil, peppermint oil, spearmint oil, mint oil, clove oil, and oil of wintergreen.
10	Anti caking agents	0.2-1%	Prevent formation of agglomerate of ground chewing gum particles	Silicon dioxide, magnesium oxide.
11	Grinding agents	0.2-1%	Prevent sticking	Alkaline metal phosphate, Alkaline earth metal phosphate.
12	Antioxidants	0.02%	Prevent oxidation	BHT, tocopherol, propyl gallate etc.

Table No 2: Optimal properties of drug [37]

Physicochemical properties	Patient related factor
• Molecular wt. – less than 1000 dalton • Lipid solubility – high lipid soluble • Ionization - less • Solubility - High Salivary Solubility, pH independent solubility • Organoleptic properties - acceptable	• Non-toxic to oral mucosa and salivary Ducts • Non-carcinogenic • Non irritant • Should not cause tooth decay • Should not cause oral mucosa and teeth staining • Should not affect salivary flow rate

MANUFACTURING PROCESSES [7,52]: Different methods employed for the manufacturing of medicated chewing gum can be broadly classified into three main classes as follows:

1) Conventional/ traditional (melting) method
2) Cooling, grinding and tabletting method
3) Direct Compression method

1. Conventional/ traditional Method: 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 upto 48 hours. This allows the gum to set properly. Finally the gum

is cut to the desired size and cooled at a carefully controlled temperature and humidity.

Limitations: Elevated temperature used in melting restricts the use of this method for thermolabile drugs. Lacks of precise form, shape or weight of dosage form are other limitations.

2. Cooling, grinding and tabletting method: This method can be divided into two steps:

(a) Cooling and Grinding: 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 medicated 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°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 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 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 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 evaporation. Alternatively it has been found that such a powdered mass when warmed to room temperature from the refrigerated state, it becomes cross linked or self adhere together to form an integrated body which incorporates minute air bubbles in the texture between the particles. This provides a chewing gum product that is light and gives a soft chewing impression when chewed.

(b) Tabletting: After, the coolant has been removed from the powder, the powder is 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 and staged for compression. Compression can be carried out by any conventional process like punching.

3. Direct Compression Chewing Gum: 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. This method has been used by few industries and for specialized gums only. Examples of gums: Lactose, Pharmagum.

Problems associated with manufacturing chewing gums [50]:

Following are the problems associated with manufacturing chewing gums:

- Capping, lamination, picking, and sticking are the most common processing problems.
- In the first method, one of the problems is that the inordinate content of moisture in the matrix may cause a low viscosity which reduces the shear and compressive forces, indeed more gum base particles are more likely to dissociate and float.
- Heating and melting can make controlling the accuracy and uniformity of the drug difficult.
- It is hard to provide sanitary conditions to make medicated chewing gum.
- In the second method, moisture content of chewing gum may cause the gum jam to the blades and punches of apparatus, screens, surfaces, and chamber's wall.

- In the second method caking and balling of the gum prevent formation of gum fragments.

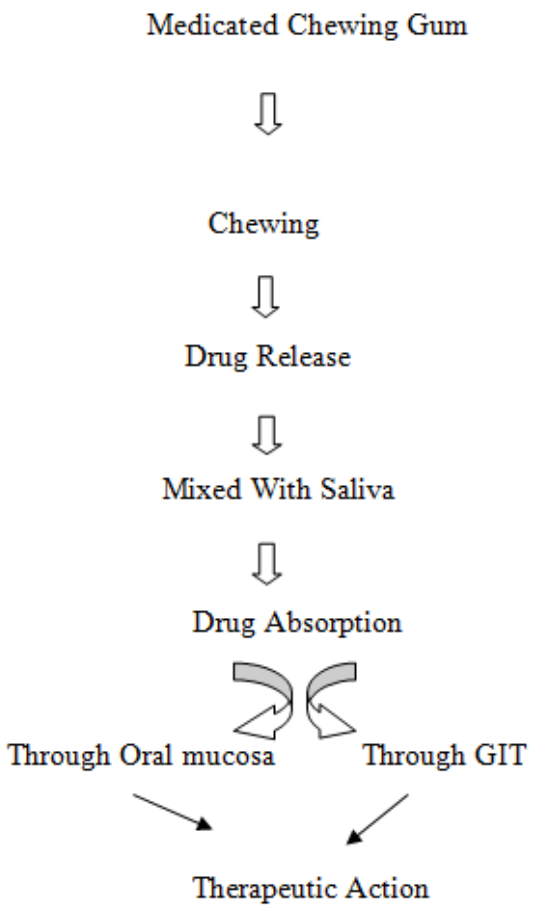

Figure No.1 Drug Release from Medicated Chewing Gum

EVALUATION OF MEDICATED CHEWING GUM [1,11,26,28,50]:

1. Content uniformity

Ten medicated chewing gums are selected randomly then their contents are measured, if each single content is between 85% and 115% of average content, it will comply with the test, but if one single preparation is out of this range the preparation will not comply with the test.

2. Mass uniformity

Twenty medicated chewing gums are selected randomly and weighed, not more than two single mass should vary the average mass.

3. Evaluation of organoleptic properties

Organoleptic properties refer to those which affect sense, taste and feelings of people who use a product, so the vital role of these properties should not be disregarded because they impress acceptance by individuals and even marketing. The organoleptic characteristics of prepared gums comprise softness/stiffness, adherence to teeth, taste, bulk volume and perdurability of taste. A Latin-square designed should be held on 10 volunteers to score their points of view. The Latin-square design is a statistical method; this means that testing units (volunteers and formulations) are divided into two blocking factors. For differentiation, we allocate rows to volunteers and columns to formulations or contrariwise. In this case no testing unit should be repeated in each row and column.

4. Evaluation of chewing gums taste

A Latin-square design should be carried out using a taste panel of some trained and healthy volunteers and then asking them to score to their points of view according to a series of scales like Likert scale. To finally diagnose the best and most desirable flavor among volunteers; a further taste panel test can be performed.

5. Evaluation of mechanical properties of chewing gums

Tensile test

Simply that is a test in which the chewing gum specimens are subjected to a tension until such time as failure occurs. The load required for elongation before fracture is recorded by computer. The tensile testing machine is set for the determination of force-elongation properties. Engineering stress and strain are obtained as describe below:

Stress = $\sigma = P/A_o$ (Load/Initial cross-sectional area).

Strain = $e = \Delta l/l_o$ (Elongation/Initial gage length).

The first part of the curve obeys Hook's law where the ratio of stress to strain is constant, and a linear relationship can be observed.

The shape, size, width, thickness, and gauge length are to be specified precisely because we wish to avoid having a break or nonuniformity within the area being gripped. Hence, the specimen should be suitably prepared for gripping into the jaws of the testing machine according to the standards.

The major parameters obtained from the test and the explanations of the stress-strain curve are tensile strength, yield strength, and fracture strength as expressed by percent elongation and reduction in area, the highest stress the specimen sustains during the test and before failure is typically recorded as ultimate tensile stress. After yield strength, we enter

the plastic region where the chewing gum will not revert to its first shape by removing the load.

6. Dissolution

Principle

The test is used to determine the dissolution rate of active substances in medicated chewing gums. This is done by applying a mechanical kneading procedure to a piece of gum placed in a small chamber designed to simulate the process of chewing.

Apparatus-I

The chewing apparatus (Figure) consists of:

- 1 chewing chamber,
- 1 vertical piston,
- 2 horizontal pistons with O-rings and sealing rings.

The chewing chamber consists of 4 individual parts:

- 1 central chamber,
- 1 funnel (Figure),
- 2 guides with bushes (Figure).

Funnel and guides are mounted on the central chamber. The O-rings are incorporated in the piston recess with the sealing ring round it; the sealing rings ensure that the chamber is watertight. The horizontal pistons are placed in the chewing chamber through the guides.

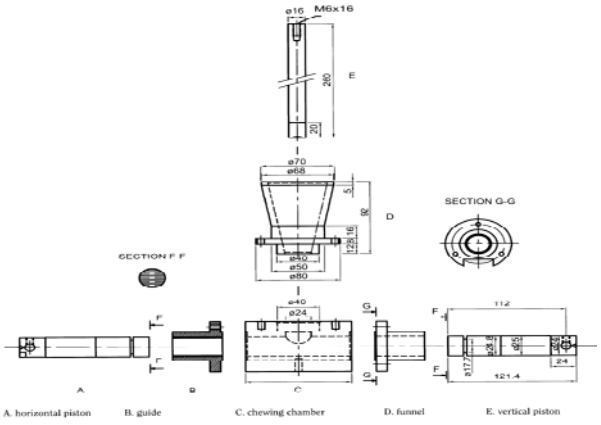

Figure No.2 Apparatus-I

The gum is artificially chewed by the horizontal pistons, and the vertical piston ensures that the gum stays in the right place between chews. Machine speed is controlled to ensure a constant cycle. One cycle (chew) is defined as follows: the horizontal pistons start from their outermost position, move to their innermost position and back to their outermost position. Within one cycle, the vertical piston moves from its lowest position to its uppermost position and back to its lowest position. Each horizontal piston has a stroke of 25.0 mm. The maximum distance between these 2 pistons is 50 mm. The minimum distance between the 2 horizontal pistons is 0.1 mm to 1.0 mm. The vertical piston has a stroke of 22.0 mm. Horizontal piston movement is controlled, so that the 2 pistons are at their innermost position at the same time. Vertical piston movement is controlled, so it does not conflict with the movement of the horizontal pistons. If necessary, the machine can be constructed so that the horizontal pistons rotate around their own axes in opposite direction to each other by the end of the chew in order to obtain maximum chewing. All parts of the apparatus that may come in contact with the preparation or the dissolution medium are chemically inert and do not adsorb, react or interfere with the sample.

Procedure

For each determination, the following information is needed:

- composition, volume and temperature of the dissolution medium,
- number of chews per minute,
- time and sampling method,
- whether the analysis is performed on the gum residue or on the dissolution medium,

Method of analysis.

Place the prescribed volume of dissolution medium in the chewing chamber, usually 20 ml of phosphate buffer solution pH 6.0 . Maintain the medium temperature at 37 ± 0.5 °C using an electrical device with external control. Set the piston speed at the prescribed number of chews per minute (usually 60). Accurately weigh a portion of gum or the whole gum, put it into the chewing chamber and start the machine.

Sampling and evaluation

Stop the apparatus at the prescribed time. Remove the gum residue and take a sample of the dissolution medium. Determine the content of active substance by a suitable method. Medium replacement may be made after each sampling procedure; compensation by calculation of medium volume change or sample dilution is needed. Alternatively, determine the content of active substance remaining in the gum residue. Carry out the test successively on 6 medicated chewing gums.

The quantity of active substance dissolved in a specified time is expressed as a percentage of the content stated on the label.

Apparatus II. Alternative Chewing Gum Apparatus, Noncompendial — Wennergren One of the noncompendial apparatus commercially available was designed by Wennergren. The schematic

representation of the Wennergren chewing apparatus is shown in Figure below. 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°) 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 Wennergren *et al*. The influences of different operational parameters of the chewing gum apparatus on drug release have been carefully investigated.(8)

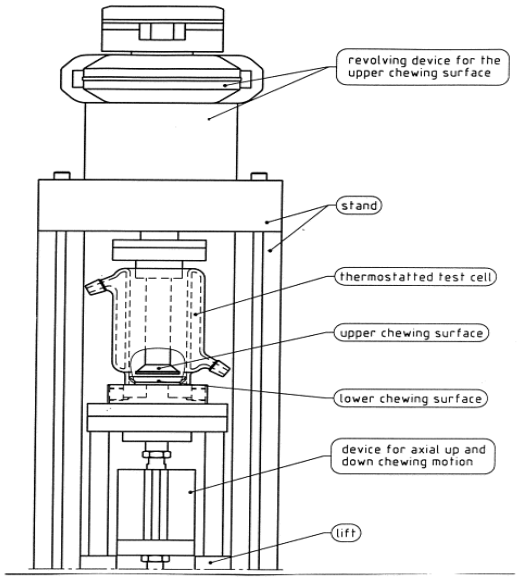

Figure No.3 Apparatus-II

Table No.: 3 List of marked medical chewing gum

S.No.	API	Trade name	Therapeutic effect
1	Fluoride	Fluorette	Cariostatic- re-elevates plaque pH which lowers intensity and frequency of dental caries
2	Calcium as a tricalcium phosphate	Orbit white Happydent white Trident white Recaldent	Dental hygiene and for tooth whitening
3	Chlorhexidine	Vitaflo CHX Advanced + HEXIT	Antibacterial agent – preventing tooth decay & to treat gingivitis, periodontitis, oral and pharyngeal infections
4	Aspirin	Aspergum	Pain relief- in treatment of minor pains, headache and muscular aches
5	Nicotine	Nicorette Nicotinelle NiQuitin CQ	Smoking cessation
6	Calcium carbonate	Chooz	Stomach & neutralization
7	Vitamin C	Endykay Stamil Source	General health
8	Docosahexaenoic acid & CCE	Brain	Enhanced brain activity
9	Caffeine	Stay alert Café coffee	Alertness and lipolysis and have a thermo genic effect (increased energy expenditure) and reduce feeling of hunger
10	chromium	Chroma slim	Diet

11	Extracts of Ashwagandha, Passion Flower and Jujube Fruit and Calcium carbonate	Zoft stress gum	Reduces the symptoms associated with stress, anxiety and depression
12	Extracts of Dong Quai Root, Black Cohosh Root, Damiana Leaf, Mexican Wild Yam Root	Zoft menopause gum	Symptomatic relief from postmenopausal syndrome
13	Extracts of Hoodia gordonni -- nature's calcium channel blocker	Slim n trim Chew away gum	Appetite suppressant for weight loss

REGULATORY ISSUES [2]

The first monograph on medicated chewing gum was published in the European Pharmacopoeia in 1998. 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.

STABILITY

Stability study of chewing gum was studied to obtain a stable product which assures safety and efficacy, till shelf life, at defined storage and package conditions. Stability study was done according to ICH guidelines to assess the combined effect of drug, gum base, and excipients on the stability of the formulation. Optimized formulation was placed in vials and stored in stability chamber at 30°C ± 2°C/65% RH ± 5% RH. The samples were evaluated for the color, taste, drug content, *in vitro* drug release study and growth of microorganisms after 7, 15, and 30 days and 3 months.

The stability of chewing gum is comparable to that of most other solid delivery systems. Chewing gum contains little water (2–5%) and the water can be bound to other components in the formulation and is therefore not very reactive. The water activity in chewing gum is normally below 0.6 and typically 0.4– 0.5. If the water content is very critical for the stability of a drug, the chewing gum can be manufactured without water (less than 0.2%). However, it will often make the product hygroscopic and affect the texture. The low water content also inhibits microbial growth in the chewing gum during storage. Antioxidants are normally added with the gum base. Furthermore, the product can be protected against oxidation by a sealed coat and by an appropriate packaging. For very temperature-labile components, e.g., enzymes, during mixing, the process temperature of 50–60 ° C may create a stability problem. However, it is possible to operate the process at a lower temperature to avoid this issue. [2]

CHALLENGES IN FORMULATION OF MEDICATED CHEWING GUM

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. It is necessary to meet these challenges for the success of this drug delivery system.

FUTURE TRENDS

Medicated chewing gum is the potential drug delivery system to treat the disease by its local and systemic action of drug. It can be utilized for its systemic drug delivery where the rapid onset of action is needed like motion sickness, pain, nausea, allergy, infection and hypertension provided that the drug is easily absorbed through oral mucosa. For local action of drug in oral cavity it has various applications like the treatment of toothache, periodontal disease, bacterial and fungal infections

which require a long period of drug release to the oral cavity.

As chewing gum is needed to be retained in mouth for long time, persistent feel of flavor and taste masking becomes the biggest challenge for formulation. The expediency and high acceptability of chewing gum along with better flavoring, sweetening and taste masking will lead to improved compliance. New gum base formulations that are compressible, digestible and potential biodegradable will extend applications for chewing gum, but the influence of these bases on drug release must be well investigated. Drug entrapment and release is still being developed on a product–by-product basis. By using optimal release systems and an appropriate combination of flavors, more drugs will be successfully formulated in chewing gum in the future.

The problem with consumption of chewing gum is it sticks to the surface where it is thrown after chewing. Moreover Chewing gum of the future will most likely be composed such that it can be removed from indoor and outdoor surfaces by conventional cleaning method and technology. It will disappear by means of nature's own remedies like water, light and bacteria.

Various classes of medicaments can be investigated for incorporated in chewing gum. Drugs used for dental care like treatment for sensitive teeth and for tobacco stain prevention, throat diseases, nausea, allergy and pain are being investigated. Food and pharmaceuticals industries have the opportunity to deliver nutraceuticals through this formulation. Chewing gum containing probiotics or soluble fiber have been launched. Highly successful nicotine chewing gum is the evidence of systemic buccal drug delivery giving faster onset of action and overcoming first pass metabolism.

Conclusion

Medicated chewing gum is most convenient, self medicated, easily administered without water and highly patient compliant. It capability to allow local and systemic delivery of drug makes it preferable over other delivery system. Thus in upcoming years it is sure that the medicated chewing gum would be most popular drug delivery system.

References

1) USP Pharmacopoeia, 40- NF 35, 2017.

2) Kinjal R. Shah & Tejal A. Mehta, "Medicated Chewing Gum- A Mobile Oral Drug Delivery System", International Journal of PharmTech Research, Jan-March 2014, Vol.6, No.1, pp 35-48.

3) Prashant K. Pagare, *et al*., "Medicated Chewing Gum: A Novel Drug Delivery System" ,Journal of Applied Pharmaceutical Science 02 (06), 2012, 40-54.

4) Manoj Kumar, *et al*., "Chewing Gum: Emerging Technique In Oral Drug Delivery", International Journal of Current Research, July, 2015Vol. 7, Issue, 07, pp.17843-17847,.

5) Sabera Khatun & Kumar Bishwajit Sutradhar, "Medicated chewing gum: An Unconventional Drug Delivery System", International Current Pharmaceutical Journal 2012, 1(4), 86-91.

6) Bhaskar D, *et al*., "Chewing Gum: A Mobile Drug Delivery System", International Journal of Pharmaceutical Sciences Review and Research 14(2), 2012; nº 18, 106-114

7) Rajashree S. Hirlekar and Afan Gadkari,Medicated, "Chewing Gum– A Compliant Drug Delivery", Indian Journal of Pharmaceutical Science & Research, Vol 5, Issue 4, 2015, 233-239.

8) Javachandar Gajendran, Johannes Kraemer, Stig Randers Knudsen, "Product Performance Test for Medicated Chewing Gums", Dissolution Technologies, August ,2010

9) Morjaria Y, Irwin WJ, Barnett PX, Chan RS and Conway BR, "In Vitro Release of Nicotine from Chewing Gum Formulations", Dissolution Technologies, 12-15, May 2004.

10) Athanikar N. K., Gubler S. A., "Process For Manufacturing A Pharmaceutical Chewing Gum", US Patent 6,322,828, 2001.

11) European Pharmacopoeia, Strasbourg: European Directorate for the Quality of Medicines, Chewing Gums: Medicated, 260 & 601, 2013.

12) Lee W. W., "Chewing Gum As A Delivery Vehicle For Pharmaceutical And Nutraceutical Substances", Pharm Tech On-line, 2: 1-11, 2001.

13) Jacobsen J., Bjerregaard S., Pedersen M., Cyclodextrin inclusion complexes of antimycotics intended to act in the oral cavity—drug supersaturation, toxicity on TR146 cells and release from a delivery system, Eur J Pharm Biopharm,48(3):217-24, 1999

14) Addy M, Roberts WR, Comparison of the bisbiguanide antiseptics alexidine and chlorhexidine, II, Clinical and in vitro staining properties, J Clin Periodontol, 8(3):220-30, 1981.

15) Munksgaard EC, Nolte J, Kristensen K," Adherence Of Chewing Gum To Dental Restorative Materials", Am J Dent,8(3):137-9, 1995.

16) Wertalik F, Bonorden R, "Salivary Levels Of Antibiotics From Use Of Neomycin- Gramicidin Chewing Troches", J Pharm Sci, 57(3), 530-1, 1968.

17) Zyck D.J., Greenberg; M.J., Barkalow D.G., Marske S. W., Schnell P. G., Mazzone P.: Method of making coated chewing gum products containing various antacids. US Patent 6,645,535, 2003
18) Jacobsen J., Christrup L.L., Jensen N-H, Medicated Chewing Gum: Pros and Cons, Am J Drug Deliv, 2 (2):75-88, 2004
19) Mochizuki Keizo, Yokomichi Fumio, Process for the preparation of chewing gum, US
Patent 4,000,321, 1976.
20) Runwal A.V , V.V Potnis , Lone K. D, Medicated Chewing Gums - A Novel Option, Pharmaceutical Reviews e-journal, Volume 6 Issue 3, 2008
21) Barabolak R.; Hoerman K.; Kroll N., Chewing gum profiles in the US population. Community Dent Oral Epidemiol, 19:125-6, 1991.
22) Yang Robert K., Encapsulation composition for use with chewing gum and edible products, US Patent4,740,376,1988
23) Dodds, M.W.J., Hsieh, S.C., Johnson, D.A., 1991, The effect on increased mastication by daily gum chewing on salivary gland output and dental plaque acidogenicity, J. Dent. Res. 70, 1474–1478.
24) Eisenstadt, B., Cash, A.P., Bakal, I.A., 8 December 1998, Chewing gum Containing cough suppression agent, U.S. Patent 5,846,557.
25) Jayachandar G, Johannes K, Stig RK, Product Performance Test for Medicated Chewing Gums, Pharmacopeial Forum, Vol. 34(3), May–June 2008
26) European Directorate for the Quality of Medicines, Council of Europe, European Pharmacopoeia, General Monograph 2.9.25: Dissolution Test for Medicated Chewing Gums. 6th Ed. Strasbourg,France; 2008:304–306.
27) European Directorate for the Quality of Medicines, Council of Europe, European Pharmacopoeia.Suppl. General Chapter 2.9.25: Chewing Gum, Medicated Release from. 3rd Ed. Strasbourg, France; European Directorate for the Quality of Medicines, Council of Europe; 2000:104.
28) Wennergren B, Kvist C, Andersson SB, Fors S, Berglund J. Apparatus for studying in vitro drug release from medicated chewing gums. Int J Pharm. 1999; 189(1):57–65
29) Imfeld T., Chewing gum—facts and fiction: a review of gum-chewing and oral health, Crit Rev Oral Biol Med, 10(3), 405-19, 1999
30) Siegel IA., Meyer CA and Squier SJ: Permeability of oral mucosa. Pergamon Press, 1984:95-108.
31) Chewing gum, medicated, European, Pharmacopoeia 5th Ed., Supplemented 5.2 Council of Europe, Strasbourg, 2005:3136–3137.
32) Rassing MR: Specialized oral mucosal drug delivery systems: Chewing gum, Adv. Drug Deliv. Rev., 1994; 13:89-121.
33) Jacobsen JJ, Chistrup LL and Jensen NH: Medicated chewing gum: Pros and Cons, Am. J. Drug Deliv 2004; 2:75–88.
34) Logemann J, Smith C, Roa PB, Rademaker A, Lazarus C, Colangelo L, Mittal B, MacCracken E, Gaziano J, Stachowiak L and Newman L: Effects of xerostomia on perception and performance of swallow function, Head and Neck 2001; 23:317–321.
35) Liedberg B and Wall BO: Masticatory ability in experimentally induced xerostomia, Dysphagia. 1991, 6:212–213.
36) Monique E and Bodde EH: Developments in Buccal drug delivery, Crit. Rev. therap. drug carrier syst 1991, 3:271-303.
37)) Nilima Thombre*, Karishma Patel, A review on medicated chewing gum as a novel drug delivery system, Journal of Pharmacy Research 2011,4(3),848-851.
38) Asija R, Patel S, Asija S. Oral dosages forms: Medicine cntaining chewing gum: A review. J Drug Delivery Ther. 2012;2:90–5.
39) Heema N, Stuti G. Medicated chewing gums-updated review. Int J Pharm Res Dev. 2010;2:66–76.
40) Smith AP, Woods M. Effects of chewing gum on the stress and work of university students. Appetite. 2012;58:1037–40.
41) [Last accessed on 2017 April 15]. Available from: http://www.gumassociation.org .
42) Athanikar NK, Gubler SA. Process for Manufacturing a Pharmaceutical Chewing Gum. US Patent. 2001 No. 6,322,828.
43) Khatun S, Sutradhar KB. Medicated chewing gum: An unconventional drug delivery system. Int Curr Pharm J. 2012;1:86–91.
44) Bumrela SB, Kane RN, Dhat SP. Medicated chewing gum: A new reformulation technique. Pharma news. 2005;3:1.
45) [Last accessed on 2017 May 24]. Available from:http://www.dupont.com/products-and-services/plastics-polymers-resins/elastomers/articles.
46) [Last accessed on 2017 May 24]. Available from :http://www.alsiano.com/Food/container/container/Food/Confectionery/Chewing-gum.aspx.
47) Patel MM, Reed MA, Yatka RJ. Environmentally Stable Chewing Gum Composition Containing Xylitol. US Patent. 1990 No. 4,931,294.
48) Rathbone MJ, Hadgraft J, Roberts MS. New York: CRC Press; 2002. Modified-Release Drug Delivery Technology.

49) Jacobsen J, Christrup LL, Jensen NH. Medicated chewing gum. Am J Drug Del. 2004;2:75–88.
50) Abolfazl Aslani and Famaz Rostami, Medicated chewing gum, a novel drug delivery system, Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences 2015 Apr.20(4), 403-411.
51) Shivang chaudahry , aliasgar F Shahiwala, Medicated chewing gum -- A potential drug delivery system , Reasearch gate, https://www.researchgate.net/publication/44685425
52) Mohan A. Ughade *et al*. "Medicated Chewing Gum: Modern Approach to Mucosal Drug Delivery", Asian J. Res. Pharm. Sci. 2012; Vol. 2: Issue 4, Pg 150-159.

How to cite this article
Gupta P., Jain M., Sharma S., Vidhyadhari A., Singh S. and Sharma D. (2019 Medicated Chewing Gum – A Modernistic Drug Delivery System. Int. *J. Pharm. Life Sci*., 10(7-8):6315-6318.
Source of Support: Nil; Conflict of Interest: None declared

Received: 28.05.19; Revised: 20.06.19; Accepted: 20.07.19