**International Journal of Pharma and Bio Sciences** **ISSN 0975-6299**

# CHEWING GUM AS A DRUG DELIVERY SYSTEM

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## ABSTRACT

In present era, many research and technological advancements are made in the field of oral drug delivery as it is highly accepted amongst patients.. Chewing gum is one of the very popular oral confectionery products. Medicated chewing gums are prepared by using a water insoluble gum base, elastomers, emulsifiers, fillers, waxes, antioxidants, softeners, sweeteners, food colourings, flavoring agents and drug. This formulation offers both local and systemic effects and has a range of advantages over conventional oral solid dosage forms. It is found effective in the treatment of smoking cessation, pain, obesity, xerostoma, acidity, allergy, nausea, motion sickness, anxiety, dyspepsia, cough. Sustained release of drug can also be achieved by fewer formulary changes during preparation. Medicated chewing gums are an excellent drug delivery system that is convenient, easy to administer anywhere, anytime discretely without water. So, in the near future, one may expect to see major categories of drugs formulated into chewing gum.

**KEY WORDS: Chewing Gum, Confectionary, Conventional Manufacturing Methods, Dental Caries, Chlorhexidine**

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# INTRODUCTION

Chewing Gum (CG) has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients[1]. Today CG is a convenient drug delivery system which is appropriate for a wide range of active substances[2].Chewing gum as a drug delivery system holds tremendous potential not only in smoking cessation and oral health care arenas but also in other indications[3]. Medicated chewing gum is solid, single-dose preparations that have to be chewed & not swallowed; chewing gums contain one or more active ingredient that is released by chewing. It also could be defined as both solid and semi solid preparations based on the art of manufacturing, i.e using conventional melting procedures or direct compression of tailored gum base powder. Chewing gums are not to be swallowed and the remaining mass after chewing has to be discarded. The drug released during chewing may either be absorbed through the oral mucosa or may reach the stomach for GI absorption. So, medicated chewing gums offers both local and systemic effect. The water content of chewing gum is very low and no preservatives are needed. The gum base determines the basic characteristics of the product, e.g. the texture. The gum base also determines the release profile of active substances, and changing the gum base composition may therefore change the release profile.

### *History of medicated chewing gum*

Chewing gum has been has been used worldwide since ancient times after man experienced the pleasure of chewing a variety of substance. Chewing gum has been used for centuries to clean the mouth and freshen the breath[3]. 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. A medicated chewing gum containing Acetyl Salicylic Acid was commercially introduced in 1928[4]. Another commercially available medicated chewing gum is dimenhydrinate containing chewing gum for motion sickness. In 1991, Chewing Gum was approved as a term for a pharmaceutical dosage form by the commission of European Council[5]. However, chewing gum did not gain acceptance as a reliable drug delivery system until 1978, when nicotine chewing gum became available[6]. People chew gum for a variety of reasons, including modulating psychological states, for example to aid concentration and to help relieve stress[7]. The notion that chewing gum may relieve stress was investigated in a controlled setting. In December 1999, The New England Journal of Medicine[8] revealed that chewing gum, energy expenditure increases from 58 kcal per hour to 70 kcal per hour – an increase of 19%.

### *Clinical benefits of chewing gum*

1. Improves memory.
2. Reduces symptoms of stress.
3. Helps to manage weight.
4. Improves digestion.
5. Improves oral health.

### *Advantages of chewing gum[9-11]*

1. Fast/rapid onset of action
2. High bioavailability
3. Pleasant taste
4. Easy for administration without water promotes higher patient compliance
5. High acceptance of children and for patients who find swallowing tablets difficult are obvious
6. Fewer side effects
7. Systemic effect and Local effects can be acheived
8. Product distinctiveness from a marketing perspective.
9. Reduce dry mouth (xerostomia)
10. Suitable for acute medication.
11. Gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients.
12. Fraction of the product reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased.

### *Disadvantages[9-11]*

1. Causes unnecessary wear and tear of the cartilage.
2. Risk of over dosage with MCG compared with chewable tablets or lozenges that can be consumed in a considerable

number and within a much short period of time.
3. Chewing gum adheres to different degrees to enamel dentures and fillers.

### *Mechanism of Drug Transport*[12]

Major pathways of drug transport across the buccal mucosa follow simple fickian diffusion. Passive diffusion occurs in accordance without the pH partition theory. Some carrier mediated transport also observed. Equation for drug flux is:

$J = DK_p/\Delta C_e$

Where,

J = drug flux

D = diffusivity

$K_p$ = partition coefficient

$\Delta C_e$ = concentration gradient

h = diffusional path length

According to the equation, the flux may be increased by :

- Decreasing the diffusional resistance of the membrane by making it more fluid,
- Increasing the solubility of the drug in the saliva immediately adjacent to the epithelium
- Enhancing the lipophilicity through pro-drug modification.

  Because of the barrier properties of the tight buccal mucosa, the rate limiting step is the movement of the drug molecules across the epithelium.

## FORMULATION

Chewing gum consists basically of a neutral and tasteless masticatory gum base (15-40%) and several non-masticatory ingredients such as fillers, softeners, sweetening agents, flavouring agents and texture regulating agents. The water insoluble portion includes elastomers, fillers , plasticizers whereas the water soluble portion includes softners, emulsifiers, colorants, sweetners.

**Table 1**
***Components employed in formulation of medicated chewing gum*** [13,14,15]

| Ingredient | Purpose | Examples | Concentration |
|---|---|---|---|
| **Elastomers** | To provide elasticity and cohesion to the chewing gum. | ○ Natural rubbers like Latex<br>○ Natural gums such as Jelutong, Lechi Caspi, Perillo, Chicle .<br>○ Synthetic elastomers like polyisobutylene and butyl rubber. | 40-70% by wt. of gum base |
| **Resins**: | ○ Act as mastication substance<br>○ As binding agent between elastomers and fillers.<br>○ They contribute to the balance between the properties of elasticity and plasticity. | ○ Natural – glucerol esters from pinene resins.<br>○ Synthetic - polyvinyl acetate | |
| **Emulsifiers and fats** | ○ Soften the mixture and give required chew during mastication.<br>○ Optimize the chewability and mouth feel of the gum. | Monoglycerides, diglycerides and partly hardened vegetable and animal fat | 3-20% by wt. of gum base |
| **Plasticizers** | Used to regulate cohesiveness of product. | ○ *Natural Plasticizers :*<br>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.<br>○ *Synthetic Plasticizers:*<br>Terpene Resins derived from a-pinene and/or d-limonene. | 0.5 to 15% |
| **Antioxidants** | Protects the gum base and flavors from oxidation. | Ascorbic acid, tocopherol, butylhdroxytoluene | 0.02% by weight of gum base |
| **Fillers** | They provide the right texture for the gum base, provide texture, improve chewability, and provide reasonable size of the gum lump with low dose drug. | Magnesium and Calcium Carbonate, Ground Limestone, Magnesium and Aluminum Silicate, Clay, Alumina, Talc, Titanium Oxide & Mono/ di/ tri Calcium Phosphate.Talc, calcium carbonate . | 2-60% by weight of gum base |
| **Colorants and Whiteners** | To impart color to the preparation. | FD & C type dyes, fruit and vegetable extracts, Titanium Dioxide. | Less than 1% |
| **Sweeteners** | These are of two types, *Aqueous* and *Bulk*.<br>○ Aqueous Sweeteners can be used as softners to blend the | ○ *Aqueous Sweeteners:*<br>Sorbitol, hydrogenated Starch hydrolysates and Corn Syrups.<br>○ *Sugar Components* | 50-65% |

| | | | |
|---|---|---|---|
| | ingredients and retain moisture.<br>o Bulk Sweeteners include Sugar and Sugarless components | Saccharides like Sucrose, Dextrose, Maltose, Dextrin, Fructose, Galactose, and Corn Syrup.<br>o *Sugarless Components*<br>sugar alcohols such as Sorbitol, Mannitol, Xylitol, hydrogenated starch hydrolysate.<br>o *Artificial sweetners :*<br>Sucralose, Aspartame, salt of Acesulfame, Alitame,Saccharin | |
| **Flavouring Agents** | used to improve flavour in chewing gum | Essential oils, such as Citrus oil, fruit essences, Peppermint oil, Spearmint oil, Mint oil, Clove oil & Oil of Wintergreen. | 1-5% |
| **Bulking agents** | These are used if low calorie gum is desired. | Polydextrose, Oligofructose, Inulin, Fructooligosaccharides, Guargum hydrolysate, Indigestible Dextrin. | |

### *Drugs incorporated in Chewing gum[16]*

### *1. Chlorhexidine*

Dental plaque, a bacterial biofilm, is one of the major etiologic agents involved in the initiation and progression of dental caries, gingivitis and periodontal disease. The recognition of the role of microorganisms as the major cause of chronic gingivitis was early established[17-19]. Chlorhexidine was the first antimicrobial agent shown to inhibit dental plaque formation and the development of chronic gingivitis[20]. CHX is a cationic chlorophenyl bisbiguanide antiseptic. Bisbiguanides are the primary second-generation antiplaque agents exhibiting considerable substantivity and very broad antibacterial properties. CHX is a strong base and at physiologic pH is a large dicationic molecule [1,6-di(4-chlorophenyl-diguanido) hexane] with two positive charges distributed over the nitrogen atoms on either side of the hexamethylene bridge[21,22]. By virtue of its positive charge, CHX has the ability to bind to negatively charged surfaces such as the bacterial cell wall[23]. Since most intraoral surfaces are negatively charged the drug gets well distributed in the oral cavity and is not easily displaced[24]. Once bound, it can exert its bacteriostatic and bactericidal effects. The substantivity of CHX is given by the fact that once adsorbed to intraoral surfaces, it gets only slowly displaced by calcium ions from saliva. The dicationic nature, making CHX extremely interactive with anions is not only relevant to its efficacy, safety, but also to local side effects and difficulties with product formulation.CHX is available as digluconate, acetate or hydrochloride salt. Digluconate and acetate salts are water soluble, CHX hydrochloride is weakly soluble in water. CHX, developed by Imperial Chemical Industries, GB, after intensive investigations of the biological properties of polybiguanide compounds, was first marketed as an antiseptic for skin wounds in 1953. It has undergone extensive laboratory testing. In dental medicine, CHX was initially used for presurgical disinfection of the mouth and in endodontology. Plaque inhibition by CHX was already investigated in 1962[24] but the first controlled clinical study was performed by LÖE & SCHIOTT (1970). This study showed that rinsing for 60 sec, twice per day with 10 ml of a 0.2% (20 mg dose) CHX gluconate solution, in the absence of normal tooth cleaning inhibited plaque re-growth. Numerous studies have followed such that CHX is one of the best investigated compounds in dentistry and to date still remains the gold standard to which other antiplaque and antigingivitis agents are compared[26-27]. For purposes of dental medicine, CHX is marketed and routinely used in various galenic forms such as mouth rinse, toothpaste, spray, gel, varnish and pastille or lozenge.

### *2. Fluoride*

Fluoride plays a major role in oral health and in the prevention of tooth decay, as it has the following effects[29]:

• Inhibition of demineralization
• Enhancement of remineralisation
•Inhibition of bacterial activity in dental plaque

Several studies have been conducted in which fluorides have been administered in a chewing gum formulation. J Ekstrand and co-workers[30] compared chewing gum containing 0.25 mg of fluoride with a placebo chewing gum in 20 healthy volunteers in a double-blind crossover study. The results from the study indicated that slightly elevated levels of fluoride in the saliva, achieved by repeated intake of fluoride gum for seven days, are sufficient to influence the acidogenicity of dental plaque. A similar study conducted at the same Swedish institute[31] concluded that chewing gum

containing fluoride is a convenient and safe way to administer fluoride – it elevates fluoride concentration and as a positive "side effect", stimulates salivary secretion. A larger study compared the salivary concentration of fluoride after intake of different fluoride tablets and fluoride chewing gum in 55 subjects (20 children age 10-12 years, 20 healthy adults and 15 patients suffering from dry mouth)[32]. The main conclusion from the study was that the saliva clearance patterns and salivary stimulating effects of all the products were approximately the same. There were great variations among the subjects, however. Another study compared fluoride chewing gum with a sorbitol chewing gum and a control group, looking specifically at there mineralization of root lesions[33]. It was shown that the frequent administration of low fluoride doses was able to produce high fluoride incorporation in root surfaces. In the conclusion, the authors indicated that the "findings present encouraging results in fluoride uptake and remineralization using fluoride chewing gum", and "it is also expected that patient compliance should be high since the chewing habit is generally accepted by many people." Comparison between different methods of applying fluoride (e.g. lozenges, chewing gum, and mouth rinse) have also been carried out[33].Toothpaste and mouth rinse increased the concentration of fluoride significantly more than lozenges and chewing gum. However, the authors pointed out in the discussion that the differences are small and not crucial in terms of caries prevention efficacy. Consequently, the most important issue is that the formulation be acceptable and convenient to the patient for regular use. A multinational group[35] studied the safety of fluoride chewing gum by measuring the uptake of fluoride in humans after chewing fluoride chewing gum. Though there was a 1.7 fold increase in fluoride levels on plaque, the plasma fluoride levels were negligible indicating that fluoride chewing gum is safe.

### *3. Xylitol*

Xylitol (a polyol sugar alcohol – also referred to as birch sugar because it can be produced frombirch trees) is used frequently, especially in Finland, and has been used for oral health care. Theregular use of xylitol chewing gum[36] leads to a reduction in the acidogenic potential of dentalplaque, and studies[37-39] have shown that xylitol reduces enamel demineralization and inhibits caries. One study even claimed that xylitol is cariostatic and can reduce the risk of mother-child transmission of mutans streptococci[40]. This is an important factor in oral health, as the prevention of colonisation of mutans streptococci in early childhood has been shown to lead tothe prevention of dental decay. That mother-child transmission of streptococci can be reduced was proven in another study that included 195 mothers with mutans streptococci[41]. The mothers in this study were randomized to either receive chewing gum containing xylitol, fluoride varnish, or chlorhexidine varnish. At age 5, the children of the mothers chewing xylitol had a reduction in dental caries of 70% when compared to the other treatment groups. Other long term studies show that daily use of xylitol chewing gum by children significantly lowered their caries score, and that this decrease could still be seen five years after discontinuation of therapy[42]. The best result was achieved if xylitol chewing gum treatment was initiated at least one year prior to eruption of permanent teeth[43]. Finally, a review of cariologic aspects of xylitol concluded that a daily intake of two to three pieces of xylitol chewing gum resulted in a defined reduction of caries[44]. Regular and prolonged use of xylitol chewing gum may have a caries-preventive effect[45].

### *4. Urea*

Studies have also been performed to test if chewing gum containing urea could have a caries preventive effect. A study was carried out on schoolchildren in Madagascar[46]. The study included 376 children who were asked to chew gum containing urea and 326 children of the same age in a control group that received no chewing gum. At the end of the three-year follow up period, a positive effect on DMFS was seen on the children chewing gum containing urea as compared with the controls. Though this was not a significant difference, a statistically significant reduction of occlusal dental caries was seen in a subgroup of the gum-chewing children. It was concluded that "the present investigation indicated a positive clinical effect of using chewing gum", and "the use of such chewing gum may be considered a supplement to the

control of occlusal dental caries in permanent teeth of young schoolchildren, particularly in developing countries with limited resources for formal oral health care."In Lithuania, a similar study[47] was performed on 602 children. The children were given sorbitol/urea chewing gum, sorbitol chewing gum, xylitol chewing gum, control chewing gum, or no chewing gum. The children were monitored for three years. At the end of the trial period, there were significantly lower caries increments in the groups receiving sorbitol chewing gum, xylitol chewing gum and the control chewing gum than in the no chewing gum group. There wasNo statistically significant difference between the control group and the group receiving sorbitol/urea chewing gum. The authors concluded that there is an indication that though caries cannot be further prevented by sweeteners or additives such as polyoland urea, they can be prevented by chewing sugar free gum.A study performed on Swedish adults[48] compared chewing gum containing urea with a placebo chewing gum with regard to formation of calculus. Little effect was seen, and the main conclusion was that, three months of frequent use of sugar-free chewing gum – with or without urea – neither promotes nor inhibits calculus formation.

### *5. Vitamin C*

A group from the Royal Danish School of Pharmacy[49] compared the excretion of ascorbic acid in urine after administration via chewing gum and chewable tablets. Six healthy volunteers were included. The study showed a higher recovery of vitamin C in the urine after administration of the chewing gum formulation when compared to the chewable tablet indicating a better bioavailability for the chewing gum formulation. Another study with vitamin C was performed in Sweden [50]. The aim of the study was to evaluate the effect of frequent use of a sugar free chewing gum containing vitamin C (60 mg) on calculus formation and other oral parameters. The study showed that frequent use of chewing gum containing vitamin C reduces not only calculus formation, but also gingival bleeding and plaque formation. The reductions were significant when compared to a group receiving no chewing gum. Though chewing gum without vitamin C also created reductions in the same study, these reductions were not significant.

### *6. Zinc*

Zinc in a chewing gum formulation has been compared to zinc in a mouth rinse formulation[51]. The study was set out to examine whether zinc could be made available in the oral cavity and inhibit the production of volatile sulphur-containing compounds. The "morning breath" of 11 healthy subjects was tested. The mouth rinse and chewing gum had similar effects resulting in a 45% reduction in volatile sulphur-containing compounds.

**Table 2**
***Dosage of drugs formulated as chewing gum***

| Drug | Generally employed dose in chewing gum |
|---|---|
| Chlorhexidine | 5mg |
| Aspirin | 227mg |
| Fluoride | 0.1 to 0.5 mg |
| Urea | 3% |
| Vitamin-C | 6omg |
| Zinc | 2mg |
| | 20mg |
| Calcium carbonate | 500mg (200mg of calcium) |
| Caffeine | 10-50mg |
| Nicotine | 2-4mg |
| Xylitol | 1 gm |

### *Chewing Gums Types[16]*

Chewing gums come in a variety of flavors, shapes and sizes. There is no standard type of gum, but mostly is a small stick or wad of gum. Chewing gum is basically made by combining a water-insoluble phase with a water-soluble phase of sweeteners, flavoring and food coloring.

Today the basic types of chewing gums are

- **Bubble gum** - Bubble gum have property of blowing bubbles because film-forming characteristics.
- **Sugar-free gum** - Instead of sugar, sugar-free gum has artificial sweeteners to provide the taste.
- **Center-filled Gum** – Center-filled gum in his center has a soft mass, usually filled with some tasty liquid.
- **Dragee gum** – Dragee gum has the most popular format for chewing gum, dragee gum is a pillow-shaped coated pellet, often packed in blister packs.
- **Medicated gum** – Medicated gum is a chewing gum with a purpose to introduce medicated substances into blood stream faster than pills. Based on the shapes, they are named as:
- **Stick gum -** Stick gum is a thin, flat, slab of gum usually in rectangular shape.
- **Ball Gum** – This gum has shape like ball. It is one of the most popular chewing gums.
- **Ribbon Gum -**Ribbon gum is like the stick gum, it is longer, coiled up in a cylindrical container, and the consumer tears off a piece of the size he wants.
- **Wrap gum** – Wrap gum and cut gum is usually in the form of a chunk, cube or cylindrical shape, depending of the machine that wraps it.
- **Tab gum** – Tab gum is shorter than stick gum and also thicker.
- **Tube gum -**Tube gum or spaghetti gum comes in a tube and gum inside tube is a very soft bubble gum.

***Method of preparing chewing gum*[52-55]**

Three types of manufacturing processes are available for the production of chewing gum.

**a)*Melting method or conventional production process***

Today the majority of chewing gum systems are manufactured using conventional confectionery production process .The gum base is first melted in a steam jacketed mixer. The active medicament, the sweetener and other ingredient are added to the melted phase according to specific time schedule, with flavor added at the last. 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 upto 48 hours. The mixer is then scored and cut into pieces to produce sticks.

## Limitations

- The main disadvantage of this process is the thermal instability of many active ingredients (vitamins, vegetable extract etc.)Precludes traditional chewing gum production methods because the temperature profiles, associated with this type of production, may reach 90°C.
- Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult.
- Lack of precise form, shape or weight of dosage form.
- Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.
- Such a chewing gum composition is difficult to form into chewing gum tablets because of their moisture content (2- 8%). If attempted to grind and tablet such a composition would jam the grinding machine, stick to blades, screens adhere to punches and would be difficult to compress.

**b)*Cooling,Grinding and Tabletting Method***

This method has been developed with an attempt to lower the moisture content and alleviatethe problems faced in conventional method. The Chewing Gum composition (base) is cooledto a temperature at which the composition is sufficiently brittle and would remain brittle duringthe subsequent grinding step without adhesion to the grinding apparatus. The temperaturerequired for cooling is determined in part by the composition of the Chewing Gum and iseasilydetermined 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. Amongstthe various coolants like liquid nitrogen, hydrocarbon slush, use of solid carbon dioxide ispreferred as it can give temperatures as low as 78.5°C. The solid carbon dioxide sublimesreadily on warming the mixture and is not absorbed by the

chewing gum composition. It doesnot interact adversely with the processing apparatus and does not leave behind any residuewhich may be undesirable or potentially hazardous. The refrigerated composition is thencrushed 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. The grinding apparatus itself is cooled by keeping the grinding apparatus incontact with a coolant or byplacing the grinding apparatus in a cooling jacket of liquidnitrogen or other cold liquid. For more efficient cooling, the chewing gum composition can bepre cooled prior to cooling to the refrigeration temperature. Sometimes a mixture of chewing gum composition, solid carbon dioxide and precipitatedsilica is ground in a mill grinder in a first grinding step. Additional solid carbon dioxide andsilica are added to the ground composition, and the composition is further ground in a secondgrinding step. This two step grinding process keeps the chewing gumcomposition 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 byincorporating additional carbon dioxide and/or precipitated silica at each step.Certain additives can be added to the chewing gum composition to facilitate cooling, grindingand to achieve desired properties of chewing gum. These include use of anti-caking agent andgrinding agent.Once the coolant has been removed from the powder, the powder can be mixed with otheringredients such as binders, lubricants, coating agents, sweeteners, etc. all of which arecompatible with the components of the chewing gum base, in a suitable blender such as sigmamill or a high shear mixer.Alternatively a Fluidized Bed Reactor (FBR) can also 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 obtained granules are mixed with extragranular ingredients and are then compressed into tablet by normal punching. Thus this technique overcomes the limitations of conventional method. The disadvantage of this method is that it is expensive and moreover strict control of humidity has to e maintained during the entire process

**c) *Direct compression process***

In Directly compressible technique free flowing powdered gums have been developed which contains mixtures of polyols and/or sugars with gum base. Such a obtained gum base can be compacted in to a tablet form using a conventional tablet press. The finally obtained chewing gums are harder than their counter-parts and texture analysis shows that they crumble under applied pressure. These chewing gums include higher levels of active ingredients than traditional extruded gums.Low temperature protects sensitive bioactivity and phytochemical components, moreover lower moisture content also improves shelf life of active molecules. Release is faster than from the conventional gums.

## Limitations

The main disadvantage is its sticking effect to the punches of the tableting equipment. This effect is due to the adhesive nature of the gum, which is the main component of the formulation.For this reason, the procedure becomes difficult and needs slower production speed and cooling operations to prevent the tableting machine.

### *EVALUATION OF MEDICATED CHEWING GUM*

Being a single dose preparation, medicated chewing gum has to comply with the tests for uniformity of content and uniformity of mass. In addition, the microbial quality has to be ensured

***1. Drug content and in-vitro release***

Chewing gums unlike tablets cannot be assayed by the conventional method of crushing and weighing the medicament. For estimation of drug content in chewing gums and study of drug release an apparatus called ERWEKA's DRT 6 chewing apparatus is widely used which mimics the natural chewing action.

***For estimation of drug content***

The test cell is filled with 50 ml of simulated salivary fluid. The chewing gum is placed in

the equipment and the instrument is operated for a period of 60 min. From the dissolution medium 5 ml is withdrawn and its absorbance is read.

***For in-vitro release studies***

The test cell is filled with 50 ml of simulated salivary fluid. The chewing gum is placed in the equipment. 5ml of dissolution medium is withdrawn at regular intervals of 5, 10,15,20,25 and 30 minutes. Equivalent volume of fresh medium is replaced. The absorbances of samples collected are read.

***2. Uniformity of content***

Ten medicated gums are selected randomly. Each gum is first dissolved in 50 ml chloroform. The drug is extracted into the aqueous phase using suitable buffer. (For example, for nicotine, phosphate buffer pH 6.8 is used). The amount of drug is determined by measuring the drug absorbance. The experiment is repeated three times.

*Test Limits:* Unless otherwise prescribed or justified and authorized, medicated chewing gum with content of 2 mg or less than 2 percent of total mass comply with the test. If the preparation contains more than one active substance, the requirements apply only to those active substances, which correspond to the above condition.

***3. Uniformity of mass***

The weight of Ten medicated gums, which are selected randomly is to be determined.

*Test limits :* Uncoated medicated chewing gum and, unless otherwise justified and authorized, coated medicated chewing comply with the test for uniformity of mass of single dose preparations. If the test uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required.

***4. In vivo 'chew-out' studies[56]***

The invivo 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 into the saliva and then it is either absorbed through oral mucosa or, if swallowed, it is absorbed through the gastrointestinal tract.

***a) Release of drug in saliva***

Panel of volunteers is asked to To estimate the drug release in saliva, 4 human volunteers are selected and are asked to chew the formulation for 15 minutes. Samples of saliva are taken for every 2 minutes interval till 15 minutes and are analyzed spectrophotometrically. Selection of human volunteers helps in studying the influence of salivary secretion, salivary pH and oral mucosa on the release pattern.

***b) Dissolution test of residual medicated chewing gum***

In this experiment, gums are tested by a panel of volunteers to verify the drug release process from the drug delivery system. Each person chews one sample of the tableted gum for different time periods (1, 5, 10, 15 min) 39. The residual gums are cut into small pieces, frozen and then ground till obtaining a fine powder. The residual drug content is determined by using the suitable analytical method. The amount of drug released during mastication is calculated by subtracting the amount of residual active ingredient present in the gum from the total content, whereas pharmacokinetics can be determined from withdrawn blood samples at specific time intervals. The prerequisites of human volunteers, person-to-person variability in the chewing pattern, chewing frequencies, composition of individual salivary fluid and flow rate of saliva are a few limitations of chew-out studies.

***c) Urinary excretion profile of medicated chewing gum***

This method can be applicable only to those drugs which are excreted via urine. In that minimum four healthy human volunteer are selected for the study of formulations. Volunteers are strictly instructed that they should not take any medicine in the last 48 hour. They are fasted overnight, and emptied their bladder in the volumetric flask. Sample collection starts from blank of zero hour urine. Then sample collection is done on the 15 min, 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 24 hour intervals after administration of medicated chewing gum. The volunteers are asked to drink water at regular intervals of 30 min. and urine samples are analyzed by suitable analytical methods.

***d) Buccal absorption test***

Human volunteer swirled fixed volume of drug solution of known concentration at different pH value of 1.2, 5, 6, 6.5, 7, 7.5, 7.8, 8, in the oral cavity for 15 min and then expelled out. The expelled saliva is analyzed for drug content and back calculated for buccal absorption.

***Formulation techniques for sustained release*** [7]

The sustained release of the drug can be achieved by one of the following methods:

1. ***Particle size of the drug***
2. ***Drug-Ion exchange complex***

Complexing a drug with ion exchange resin slows the release of drug g\from gum base. Nicotine is a liquid with boiling point 247°C, basic nature, pKa of 3.12 freely soluble. Nicotine chewing gum, which is used for smoking cessation must be able to release nicotine for about 30 min . But when nicotine is incorporated into an ordinary gum composition, its release occur rapidly to avoid this nicotine is complexed with cation exchanger amberliteIRP 64, a weak acidic methacrylic acid polymer

3. ***Coating and embedding***

Coating of drug with various coating agents like PVP, celluloses and Embedding a drug in hydrophobic matrix consisting of lecithin, synthetic waxes or mixtures was found to reduce the release rate of drug from chewing gum.

4. ***Adsorption***

Adsoprtion of a flavoring agents onto silica gel could reduce the release rate of drug from chewing gum.

**Table 3**

***Commercially available medicated chewing gum*** [15,56]

| Drug Employed | Trade Name |
|---|---|
| Aspirin | Aspergum |
| Dimenhydrinate | Travell, Superpep |
| Nicotine | Nicorette, Nicotinelle, Niquitin CQ, Nulife, Nicotex |
| xylitol | V6,Bfresh, Xylichew , Xylifresh, Mentos |
| Calcium carbonate | Chooz |
| Vitamin C | Peelu, Stamil Vit C, Endykay, Stamil Source |
| Caffeine | Alert energy gum, Stay Alert, Café Coffee |
| DHA and CCE | Brain |
| Fluoride | Fluorette, Fludent, Fluogum, Sensodyne fluor, Lacalut fluor |
| Tricalcium phosphate | Orbit White, Happydent White, Trident White, Recaldent |
| Chlorhexidine | Vitaflo CHX, Advanced +, Hexit |
| Guaran | Buzz Gum, Go Gum |
| CR | Chroma Slim |
| Zinc acetate | zenser |
| Zinc, Q10 | Dental health |
| Zinc | Discus dental |
| Zinc chloride | Breath RX |
| Bicarbonate | Dental care, Oral B, Arm and hammer dental, Trident advantage, Ice white |

**Table 4**
***Chewing gums containing plant extracts*[7]**

| | |
|---|---|
| Zoft Stress Gum | Extracts of Ashwagandha, Passion Flower and Jujube Fruit and Calcium carbonate |
| Zoft Menopause Gum | Extracts of Dong Quai Root, Black Cohosh Root, Damiana Leaf, Mexican Wild Yam Root |
| Slim n Trim, Chew Away Gum<br>Zoft Vertility Gum | Extracts of Hoodia gordonni -- nature's calcium Slim n trim channel blocker<br>Extracts of Hawthorn Berry, Horny Goat Weed, Damiana Leaf, Muira Puama Root, Ginkgo Biloba Leaf, Ginseng Root, Catuaba Bark Extract, Saw Palmetto Berry |
| Zoft Stress Gum | Extracts of Ashwagandha, Passion Flower and Jujube Fruit and Calcium carbonate |

***REGULATORY ASPECTS OF CHEWING GUM***

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. 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 and Bubble gum are regulated as Reg 2.7.3 in FSSAI on 1st Aug 2011. Chewing gum is identified as Food Category 5.3; Hard and soft Candy Under 5.1 and 5.2, respectively, all within the broader category - Confectionery (5.0) .Few formulatory aspects prescribed for chewing gums include :

- Enzymes, baking powder, edible food grains & edible seeds and protein isolates are not allowed.
- Only Modified Starch upto 0.5% is limited for Chewing gum and Bubble gum.
- Sodium bicarbonate is not allowed for chewing gum and bubble gum.
- Combination of sweeteners is not permitted for Confectionery and Chewing gum products.

Current warning & advisory statements:

- This contains (name of the sweetener)
- Not recommended for children
- No sugar added in the product
- Not for phenylketonurics (if aspartame is used)
- Contains artificial sweetener and for the calorie conscious

The Existing standards are not comprehensive as many finished products do not fall into any of the current vertical standards. Many globally approved additives used in gums and confectionery are not approved in current standards

**Table 5**
***Patents filed on medicated chewing gum*[56]**

| Patentee | Title | Filling Number |
|---|---|---|
| TESTA, Emilio | Process for making a medicated chewing gum with a pleasant taste Containing an inclusion complex | EP 0 909 166 B1 |
| BADETTI, Rolando | Composition for medicated chewing gums,process for manufacturing the Same and tablets so obtained | EP 1 162 946 B1 |
| BADETTI, Rolando | A process for the preparation of medicated chewing gums | EP 1 408 769 B1 |
| Kenneth A. Bartlett, Essex, Fells, and William J. Schultz. | Chewing gum tablet | US 2262097 |
| Theodore C. Goggin | Amphetamine chewing gum | US 2536168 |
| Frederick G. Merckel. Laszlo Reiner. | Fluorine chewing gum process | US2627493 |
| Harold M. Sellers | Chewing gum containing gas And a medicament | US 3316154 |
| John H. Litchfield and Victor G. Vely | Anticaries chewing gum | US 3651206 |
| John H. Litchfield and Victor G. Vely | Dlaldehyde-containing anti Caries chewing gum Compositions | US 3679792 |

| | | |
|---|---|---|
| Carsten Andersen and Morten Pedersen | Chewing gum composition with Accelerated, controlled release of active agents | US 5487902 |
| Barbara Eisenstadt, Penny A. Cash and Abraham I. Bakal | Chewing gum containing cough Suppressing agent | US 5846557 |
| Subraman R. Cherukuri, John M. Pinney, Jack E. Henningfield, Aradhana Sasan, Edward J. Cone, Saul Shiffman, Joe Gitchell, Carlos D. Malvestutt | Medicated chewing gum delivery System for nicotine | US 6,344,222 B1 |
| Henry T. TYRPIN, Michael P. Russell, David L. Witkewitz, Sonya S. Johnson, Ronald L. Ream, Christine L. Corriveau | Caffeine coated chewing gum Product and process of making | US 6,444,241 B1 |
| Pardeep NijhaWan | Medicated gum sticks for treatment In anti-inflammatory conditions And prophylaxis against NSAID Gastropathy | US 2007/0003490 A1 |
| Carsten Andersen | Tobacco alkaloid releasing chewing gum | WO 2006000232 A1 |
| Terence Cosgrove, Beth Mary Foster, Erol Ahmed Hasan, Hongli Yang | Medicated chewing gum | WO 2008104547 A1 |

## CONCLUSION

Medicated chewing gum is a valid alternative to standard, chewable or orally disintegrating tablet presentations. Inspite of the benefits offered, the potential of medicated chewing gums has not yet been fully exploited. 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 pharma industry. Another reason is the therapeutic uncertainty. The gum's therapeutic effect depends on chewing, and as each person has their own chewing force, frequency and time, the results can vary. Quality testing procedures are still not well developed. Hence evaluation of gums is a major challenge. While formulating and manufacturing medicated chewing gum, the researchers must try to overcome these problems such that potential of chewing gum as a drug delivery system is expanded into additional therapeutic areas making it a much more common, simple and popular drug delivery system.

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