An overview on Medicated Chewing Gum and its Applications

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ABSTRACT

Medicated chewing gum has a history for about a century. Now-a-days it is considered to be a potential and convenient modified release drug delivery system which can be used in pain relief medication, smoking cessation, travel illness, freshening of breath, prevention of dental caries, alleviation of xerostomia, vitamin or mineral supplementa-tion etc. Medicated chewing gums are prepared by using a water insoluble gum base with water soluble bulk portion. This formulation offers both local and systemic effects and has a range of advantages over conventional oral solid dosage forms. USP currently has no in vitro release testing apparatus for the evaluation and determination of drug release from the prepared chewing gums. But European Pharmacopoeia adopted a compendial apparatus to do so. Medicated chewing has drawn attention to the researchers as potential drug delivery system and it could be a commercial success in near future.

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Introduction:
It is well known fact that the right drug delivery system is critical to the success of a pharmaceutical product. Pharmacological active agents or drugs are formulated into variety of dosage forms like tablets, capsules, injectables, inhalers, ointments etc considering physicochemical properties, pharmacokinetic and pharmacodynamic parameters and biopharmaceutical aspects of drugs. In addition to its confectionary role, Chewing Gum (CG) also has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients[1]. Medicated Chewing Gum (MCG) is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. The introduction and subsequent success of nicotine chewing gum in the 1980s paved the way for a more general acceptance of chewing gum as a drug delivery system. Unlike chewable tablets
medicated gums are not supposed to be swallowed and may be removed from the site of application without resort to invasive means and MCGs are solid, single dose preparations. As for as patient convenience is concerned it is discrete and easy administration without water promotes higher compliance. Since it can be taken anywhere, a chewing gum formulation is an excellent choice for acute medication. The advantages for children and for patients who find swallowing tablets difficult are obvious. This review mainly tells about history, composition of MCG, in vitro drug release testing apparatus and future trends. A novel drug delivery system creates additional patient benefits that will add new competitive advantages for a drug and thus increase revenue. Oral route is the most preferred route amongst the patient and clinicians due to various advantages it offers. One of the reasons that the oral route achieved such popularity may be in part attributed to its ease of administration[2]. Medicated chewing gum (MCG) is the gum base incorporating drug(s)[3]. Chewing gum is being used worldwide since ancient times after man experienced the pleasure of chewing a variety of substance. One thousand years ago the Mayan Indians chewed tree resin from the sapodilla tree in order to clean their teeth and freshen their breath. Shortage of natural gum bases during World War II enhanced development of the synthetic gum bases that are used today. Chewing gum can be used as a convenient modified release drug delivery system. Medicated chewing gums are currently available for pain relief, smoking cessation, travel illness, and freshening of breath. In addition, a large number of chewing gum intended for prevention of caries, xerostomia alleviation and vitamin / mineral supplementation are currently available. Chewing gum is a pleasure that almost everyone enjoys[4]. Chewing gums are mobile drug delivery systems[5]. Chewing gum usually consists of a gum core, which may or may not be coated. The water content of chewing gum is very low and requires no preservatives. Medicated chewing gums are defined by the European Pharmacopoeia and the guidelines for pharmaceutical dosage forms issued in 1991 by the Committee for Medicinal Products for Human Use (CPMP) as ‘solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not to be swallowed, providing a slow steady release of the medicine contained[6]. Generally, chewing gum is a combination of a water-insoluble phase, known as gum base and some other ingredients. These include powdered sugar whose amount and grain size determine the brittleness of the resulting gum, corn syrup and/or glucose which serve as humectants and coat the sugar particles to stabilize their suspension and keep the gum flexible, various softeners, food colorings, preservatives, flavorings etc. Chewable tablets and Chewing Gum permits more rapid therapeutic action compared to per-oral dosage form[7]. In Children particularly may consider chewing gum as a more preferred method of drug administration compared with oral liquids and tablets. It had shown that people chewing gum was better at keeping awake and alert, and that gum chewing eased tension. The anecdotal effect of chewing gum on weight loss has also been studied recently. Though there are many other interesting anecdotal effects that result from gum chewing, such as the easing of
blocked ears. It can be used either for local (mucosal) treatment of mouth disease or for systemic (transmucosal) delivery by direct intraoral absorption through the buccal mucosa[8].

History[9]

Chewing gum has an old and long history, in 50 AD, the Greeks sweetened their breath and cleansed their teeth by using mastiche, a resin from the bark of mastic tree. (The English word "masticate" is derived from the root word mastic.) At the beginning of its history this product was not so much accepted by the public. The social acceptance of chewing gum, however, has increased dramatically over the years. As chewing gum has become more widely accepted and practiced, songwriters, film makers and authors have incorporated related themes into their works. One thousand years ago, the ancient Mayan Indians of Yucatan chewed tree resin (chicle) from the Sapodilla tree. Spruce gum, which was manufactured in 1848, became the first chewing gum product to be manufactured commercially called "STATE OF MAINEPURE SPRUCE GUM." However, its use was eventually replaced by paraffin, which is still being chewed in some areas. During the 1860's, a New York photographer named Thomas Adams, realized the potential market for chewing gum products. He wrapped pieces of pure, flavorless chicle in colored tissue paper, packaged them in boxes, and left them on consignment with numerous drugstore owners. The gum was named Adams New York No.1. Public response to the product was very favorable. The first patent for chewing gum, U.S. number 98,304 was filed on December 28, 1869 by Dr. William F. Sample, a dentist from Mount Vernon, Ohio. This product, consisting of liquorice and rubber dissolved in alcohol and naphtha, was initially intended to be used as a dentifrice. In 1891, William Wrigley Jr., arrived in Chicago with $32 in cash with a desire to market his special variety of soap. Eventually, he switched from soap to baking powder sales and offered chewing gum premiums to merchants who became his customers. By 1892, when the premiums had become more popular than the baking powder, Wrigley launched his first chewing gum products, LOTTA and VASSAR. A year later, he developed JUICY FRUIT, and shortly thereafter, WRIGLEY'S SPEARMINT gum. Sugarless gum made its debut in the early 1950s, generally used sorbitol as a sugar substitute. The first brand to be marketed was Harvey's followed by Trident and Carefree. In 1975, the Wm. Wrigley Jr. Company introduced the arrival of a new chewing gum product, Freedent, designed especially for denture wearers, which did not stick to most dentures as ordinary gum did.

Merits of MCG [10-14]

1) Does not require water to swallow. Hence can be taken anywhere.
2) Advantageous for patients having difficulty in swallowing.
3) Excellent for acute medication.
4) Counteracts dry mouth, prevents candidiasis and caries.
5) Highly acceptable by children.
6) Avoids first pass metabolism and thus increases the bioavailability of drugs.
7) Fast onset due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation.
8) Gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients.
9) Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa.
10) Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased.
11) Aspirin, Dimenhydrinate and Caffeine shows faster absorption through MCG than tablets.
12) Stimulates flow of saliva in the mouth.
13) Neutralizes plaque acids that form in the mouth after eating fermentable carbohydrates.
14) Helps whiten teeth by reducing and preventing stains.

Demerits of MCG[15-19]
1. Risk of over dosage with MCG compared with chewable tablets or lozenges that can be consumed in a considerable number and within much shorter period of time.
2. Sorbitol present in MCG formulation may cause flatulence, diarrhea.
3. Additives in gum like flavoring agent, Cinnamon can cause Ulcers in oral cavity and Liquorice cause Hypertension.
4. Chlorhexidine oromucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue.
5. Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers.
6. Prolonged chewing of gum may result in pain in facial muscles and ear ache in children.

Chewing Gum and Saliva[20]
Chewing gum stimulates one of the most powerful defense mechanisms in the body – saliva. Saliva is vital to good oral health. Saliva has three main protective (anti-caries) functions:
1 Dilutes and washes away food debris.
2 The bicarbonate neutralizes and buffers plaque acids.
3 The calcium and phosphate ions contribute to remineralization of early dental caries lesions.
Saliva also contains antibacterial agents. Saliva alone is a powerful protector of the oral cavity. And, chewing gum is an efficient and pleasant way to increase saliva without drugs. Increasing saliva in the mouth is accomplished by the stimulation of flavors and the gustatory action of chewing. Together these forces stimulate the salivary glands to increase their flow rate by about 10 times the resting state during the first few minutes of chewing and keep it significantly elevated for as long as one chews.

Taste and Texture[21]
To succeed in the market, the chewing gum formulation must have a pleasant taste and texture. Most active substances have an unpleasant, bitter or metallic taste. Since the active substance will be released in the oral cavity and remain there for a longer period of time than in the case with ordinary delivery forms (usual chewing time is 10 to 20 minutes), unique expertise in taste definition, taste masking and taste modification are essential for the success of a medical chewing gum product. Moreover, there are no official standards for unpleasant taste, making it necessary to establish information on taste properties for all new active substances. In most cases, it is desirable that the taste fades out when the active substance has been fully released. The release profile of the flavours and sweeteners, therefore, is usually designed to follow the release profile of the active substance. One of the major challenges for the product developer is that any small adjustment in the amount of active substances, flavours and sweeteners often changes the gum base texture, requiring adjustments to tailor-make the gum base to the active substance. During the development process, therefore, it is necessary to test several parameters related to taste and texture continously.

Excipients in MCG formulation:
The fundamental raw (untreated) material for chewing gum is natural gum chicle, obtained from the sapodilla tree, a member of the family Sapotaceae, which is botanically known as Manilkara zapota (L.) van Royen. This
product is harvested in Mexico, Belize and Guatemala during the rainy season from July to February 28. Chemically, chicle is made up of polyterpenes that are composed of thousands of C5H8 isoprene (2-methyl-1, 3-butadiene) subunits. As chicle is very costly and not easy to obtain, other natural gums or synthetic materials such as butadiene-styrene-like basic copolymer, isobutylene-isoprene copolymer (butyl rubber), polyvinyl acetate and identical polymers are used as a chewing gum base. When proper consistency of gum is desired, synthetic elastomers such as butadiene-styrene copolymers, polyisobutylene, isobutyleneisoprene copolymers and polyethylene are very useful. The gum base may include polyvinyl alcohol and polyvinyl acetate of different molecular mass depending on the consistency of gum base desired, which reduces the tendency of the gum to adhere to the teeth (detackifier) and to be divided into pieces during chewing. The gum base determines the basic characteristics of the product, such as texture, softness, hardness, elasticity, crumbliness, stickiness and mouth feel. It also determines the release profile of active ingredients and flavors [22]. Texturizing or filling agents such as talc, magnesium and calcium carbonate, tricalcium phosphate are also included to provide texture and evenhanded size of the gum lump.

Various excipients used in MCG are given in Table 1. The major excipients used in MCG are described below.

**Table 1:** Excipients used in MCG  

<table>
<thead>
<tr>
<th>Category</th>
<th>General range</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elastomers</td>
<td>15-45%</td>
<td>Natural (chicle, crown gum, nispero) and synthetic(butadiene-styrene copolymers, polyisobutylene, isobutyleneisoprene copolymers)</td>
</tr>
<tr>
<td>Elastomers solvents</td>
<td>45-70%</td>
<td>Natural rosin esters such as partially hydrogenated rosin, pentaerythritol esters of rosin or glycerol esters of partially hydrogenated wood or gum rosin and glycerol esters of partially dimerized rosin. Synthetic terpenes (D-limonene, a-pinene, b-pinene)</td>
</tr>
<tr>
<td>Bulking agents</td>
<td>q.s</td>
<td>Guar gum hydrolysates, indigestible dextrin, polydextrose, inulin, oligofructose and fructooligosaccharides</td>
</tr>
<tr>
<td>Softening agents</td>
<td>0.5-15%</td>
<td>Glycerin, lecithin and fatty acids such as stearic acid, palmitic acid, oleic acid and linoleic acid</td>
</tr>
<tr>
<td>Sweetening agents</td>
<td>Up to 50%</td>
<td>Sugars (sucrose, dextrose), sugar alcohols (mannitol, sorbitol), aspartame, neotame</td>
</tr>
<tr>
<td>Flavoring agents</td>
<td>0.01-1%</td>
<td>Natural and artificial volatile essential oils</td>
</tr>
<tr>
<td>Coloring agents</td>
<td>0.1%</td>
<td>Various FD &amp; C-approved colors</td>
</tr>
<tr>
<td>Opacifiers</td>
<td>0.5-2%</td>
<td>Titanium dioxide, magnesium oxide</td>
</tr>
<tr>
<td>Texturizing or Filling agents</td>
<td>Upto 50%</td>
<td>Talc, magnesium and calcium carbonate, tricalcium phosphate, colloidal aluminium silicate (Bentonite) or magnesium aluminium silicate</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>0.02% of gum base</td>
<td>Propyl gallate, butylated hydroxy anisole and butylated hydroxy toluene</td>
</tr>
</tbody>
</table>

**Bulking agents:** Bulking agents are used to produce required bulk of chewing gum when potent drug or low-dose drug is to be incorporated. A low-calorie gum is preferred as a bulking agent, especially for health-conscious and diabetic people. Examples of low-caloric bulking agents are guar gum hydrolysates, indigestible dextrin, polydextrose, inulin, oligofructose and fructooligosaccharides, which also provide a sweet taste.
Softening agents: Softening agents are included to provide enormous softness during chewing of the medicated gum for better mouth feel. Commonly used softeners are glycerin, lecithin and fatty acids such as stearic acid, palmitic acid, oleic acid and linoleic acid.

Sweetening agents: Sweetening agents are classified into two categories, aqueous and bulk[23]. Aqueous sweeteners are utilized to retain moisture within the formulation for freshness, and include sorbitol, corn syrups and hydrogenated starch hydrolysates. These may also be used as a softening agent or binding agent in MCG. Bulk sweeteners are further classified into nutritive and non-nutritive sweeteners. The amount of bulk sweetener used in chewing gum composition is from 30 to 75%. Sugar and sugar alcohols are each considered nutritive sweeteners. Sugars are mainly sucrose, dextrose, maltose, maltodextrin, fructose and galactose and are used at between 2 and 15%. Sugar alcohols are low-intensity natural sweeteners such as mannitol, sorbitol and xylitol. Sugar alcohols or polyols contain fewer calories (average of 2 kcal/g) than sugar (4 kcal/g) because they are not completely absorbed from the intestine. They also provide a cooling sensation in the mouth. The sweetness of sugar alcohols varies from 25 to 100% as sweet as table sugar (sucrose). The high-intensity artificial sweeteners such as saccharin, aspartame, neotame, acesulfame potassium and sucralose are considered as non-nutritive sweeteners. These sweeteners are evaluated based on their safety, sensory qualities (e.g., clean sweet taste, no bitterness, odorless) and stability in various pH environments. These are compounds with sweetness that is many times that of sucrose, common table sugar. As a result, much less sweetener is required and energy contribution is often negligible. The amount of high-intensity sweetener used in chewing gum composition is between 0.001 and 5.0%, most preferably in amounts from 0.05 to 1.00% of the final weight of chewing gum composition. FDA approved high-intensity artificial sweeteners with sweetness as compared with table sugar (sucrose) and special indications are listed in Table 2.

Table 2: FDA approved high-intensity artificial sweeteners.

<table>
<thead>
<tr>
<th>Approved sweeteners</th>
<th>artificial Times sweeter than sucrose</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccharin</td>
<td>200 -- 700</td>
<td>Sweet bitter profile is concentration dependent; it is sweet at very low concentrations, but bitter at higher concentrations. Approximately 20% of the populations are ‘saccharin sensitive’, that is, they perceive saccharin to be bitter even at low concentrations. On repeated tasting, saccharin becomes less sweet and increasingly bitter</td>
</tr>
<tr>
<td>Aspartame</td>
<td>160 -- 220</td>
<td>Chemically aspartyl-phenylalanine methyl ester. No bitter aftertaste. Very stable in dry solid-state, but unstable in liquid-state and hydrolyzed into aspartylphenylalanine and diketopiperazine, with loss in sweetness. In liquid-state it shows greatest stability between pH 3.4 and 5.0 at refrigerated temperatures. In the body, it is metabolized to phenylalanine, so it is not recommended for phenylketonurics (PKU)</td>
</tr>
<tr>
<td>Neotame (a new version of aspartame)</td>
<td>7000 -- 13,000</td>
<td>Chemically dimethylbutyl-aspartyl-phenylalanine methyl ester, related to aspartame. Resistant to hydrolytic degradation; not metabolized into phenylalanine so no danger for individuals with PKU</td>
</tr>
<tr>
<td>Acesulfame K</td>
<td>200</td>
<td>Heat-stable synergistic sweetening enhancement with aspartame</td>
</tr>
</tbody>
</table>
**Flavoring agents:** Flavoring agents are added to improve the flavor in chewing gum, which can overcome the bitter taste of the drug. There are several natural and artificial flavors that can be generally described to possess similar taste-masking effects, of which some popular flavorants used in pharmaceuticals are listed in Table 3. The amount of flavoring agent used in chewing gum composition is normally a matter of preference subject to the set range and such factors as the individual flavor, the type of bulking agent or carriers used, and the strength of flavor desired.

**Table 3:** Flavorants used in pharmaceuticals

<table>
<thead>
<tr>
<th>Taste of drug</th>
<th>Flavors used for taste-masking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweet</td>
<td>Fruit and berry, honey, vanilla, bubble gum</td>
</tr>
<tr>
<td>Bitter</td>
<td>Wild cherry, raspberry, coffee, chocolate, mint, grapefruit, passion fruit, peach, orange, lemon, lime, anise</td>
</tr>
<tr>
<td>Acidic sour</td>
<td>Lemon, lime, orange, cherry, grapefruit, liquorice</td>
</tr>
<tr>
<td>Alkaline</td>
<td>Mint, chocolate, cream, vanilla</td>
</tr>
<tr>
<td>Metallic</td>
<td>Burgundy, berries, grape, marshmallow, Guyana</td>
</tr>
<tr>
<td>Salty</td>
<td>Butterscotch, maple, apricot, peach, melon</td>
</tr>
</tbody>
</table>

**Coloring agents:** In the US, FD & C numbers (which generally indicate that the FDA has approved the artificial coal tar dye colorant for use in foods, drugs and cosmetics) are given to approved synthetic food dyes that do not exist in nature, whereas in the European Union, E numbers are used for all additives, both synthetic and natural, that are approved in food applications. In the US, the following seven coal tar dyes are permitted as of 2007:

- FD&C Blue No. 1 -- Brilliant Blue FCF, E133 (blue)
- FD&C Blue No. 2 -- Indigotine, E132 (dark blue shade)
- FD&C Green No. 3 -- Fast Green FCF, E143 (bluish green)
- FD&C Red No. 40-- Allura Red AC, E129 (red)
- FD&C Red No. 3 -- Erythrosine, E127 (pink)
- FD&C Yellow No. 5-- Tartrazine, E102 (yellow)
- FD&C Yellow No. 6-- Sunset Yellow FCF, E110 (orange).

But, as FD&C Yellow No. 5 (Tartrazine) causes hives in < 0.0001% of those exposed to it and provokes asthma attacks in aspirin-intolerant individuals, most pharmaceutical companies have eliminated the use of this colorant in their products. Owing to safety concerns of artificial dyes, natural colorants obtained from plant and animal sources have become more popular. Plant extracts such as chlorophyll-green, annatto-yellow, curcumin-yellow, saffron yellow and animal extracts such as cochineal red are incorporated to enhance a pleasing appearance or hide the colors of drugs or excipient in the final product. Opacifiers such as titanium dioxide and magnesium oxide are also included to provide whiteness to the final product.

**Glidants:** Improve the flow property of material from hopper to the die cavity by reducing interparticulate friction. Colloidal silica, that is, syloid, pyrogenic silica (0.25%), hydrated sodium silicoaluminate (0.75%) and corn starch (3 -- 10%) are used successfully as glidant to induce flow. Anti-adherants avoid sticking of material to die walls and picking of material by punches. These materials themselves undergo deformation easily on
compression. Talc (1 -- 5%) and corn starch (3 -- 10%) are very good examples of anti-adherants. Lubricants are added to reduce the friction between the cylindrical surface of the compressed dosage form and the die wall during compression and ejection. Metallic stearates (0.25 -- 1%) (magnesium and calcium stearate) and high-molecular-mass polyethylene glycol (PEG 4000 and PEG 6000) are commonly used as water-insoluble lubricants. Boric acid (1%), DL-leucine (3 -- 10%), sodium benzoate (5%), sodium acetate (5%) and sodium lauryl sulphate (1 -- 5%) are successful examples of water-soluble lubricants.

**Active Component:** In medicated chewing gum active pharmacological agent may be present in core or coat or in matrix. The proportion of which may vary from 0.5-30% of final gum weight. A small, unionized, lipophilic and enzymatically stable active agent is likely to be absorbed more readily. A saliva soluble ingredient will be completely released within 10-15 minutes of chewing whereas lipid soluble ingredient will dissolve in the gum base and thereafter be slowly and completely absorbed[ 24]. Methods to increase the rate and extent of release of APIs include the addition of buffering agents or solubilizing agents and coating/encapsulating the API.

**Manufacturing Processes:**
Different methods employed for the manufacturing of CG can be broadly classified into three main classes namely.
2. Freezing, grinding and tabletting Method.
3. Direct Compression Method

1. **Conventional/ traditional Method[25]:** Components of gumbase are softened or melted and placed in a kettle mixer to which sweetners, syrups, active ingredients and other excipients are added at a definite time. The gum is then sent through a series of rollers that form into a thin, wide ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavour. In a carefully controlled room, the gum is cooled for 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: [26]**
1.) Elevated temperature used in melting restricts the use of this method for thermo labile drugs.
2.) Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult.
3 ) Lack of precise form, shape or weight of dosage form.
4.) Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.
5.) Such a chewing gum composition is difficult to form into chewing gum tablets because of their moisture content (2-8%). If attempted to grind and tablet such a composition would jam the grinding machine, stick to blades, screens adhere to punches and would be difficult to compress.

2. **Cooling, Grinding and Tableting Method:**
This method has been developed with an attempt to lower the moisture content and alleviate the problems mentioned in conventional method.

**Cooling and Grinding[27]:** The CG composition (base) is cooled to a temperature at which the composition is sufficiently brittle and would remain brittle during the subsequent grinding step without adhesion to the
grinding apparatus. The temperature required for cooling is determined in part by the composition of the CG and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperatures of the refrigerated mixture are around -15°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 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, 2-8% by weight of grinding aid such as alkaline metal phosphate, an alkaline earth metal phosphate or malto dextrin can be incorporated. However practical use of these substances is limited because these substances are highly alkaline and hence would be incompatible with acidic ionisable therapeutic agents. They also tend to remain in the composition and final chewing gum tablet and thus may be problematic for therapeutic and safety point of view. After the composition is ground to a powder, the coolant can be removed by allowing the coolant to evaporate. Alternatively it has been found that such a powdered mass when warmed to room temperature from the refrigerated state, they become cross linked or self adhere together to form an integrated body which incorporates minute air bubbles in the texture between the particles. This provides a chewing gum product that is light and gives a soft chewing impression when chewed.

Tableting:
Once the coolant has been removed from the powder, the powder can be mixed with other ingredients such as binders, lubricants, coating agents, sweeteners etc, all of which are compatible with the components of the chewing gum base in a suitable blender such as sigma mill or a high shear mixer. Alternatively a Fluidized Bed Reactor (FBR) can be used. The use of FBR is advantageous as it partially rebuilds the powder into granules, as well as coats the powder particles or granules with a coating agent thereby minimizing undesirable particle
agglomeration. The granules so obtained can be mixed with antiadherents like talc. The mixture can be blended in a V type blender, screened & staged for compression. Compression can be carried out by any conventional process like punching.

Limitation:
It requires equipment other than conventional tabletting equipment and requires careful monitoring of humidity during the tabletting process

3. Use of directly compressible chewing gum excipients[28]:
The manufacturing process can be accelerated if a directly compressible chewing gum excipient is available. The limitations of melting & freezing can be overcome by the use of these. PHARMAGUM®, 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 gumbase and sorbitol. Pharmagum®M contains gumbase, mannitol & Isomalt. Release of nicotine from directly compressible nicotine gum formulations and from Nicorette® prepared by conventional methods have shown that use of Pharmagum in formulation showed a faster release rate. Formulations made with Pharmagum® M & S are similar to tablet in appearance. Gums formed using compressible formulation are 10 times harder and crumble when pressure is applied resulting in faster release than conventional methods. Use of Pharmagum S, M and C enables formulators to utilize a gum delivery system quickly & more cost effectively than by traditional methods.

Factors affecting release of active ingredients:
1) Contact Time: The local or systemic effect is dependent on time of contact of MCG in oral cavity. In clinical trial chewing time of 30 minutes was considered close to ordinary use.

2) Physicochemical properties of active ingredient: Physicochemical properties of active ingredient plays very important role in release of drug from MCG. The saliva soluble ingredients will be immediately released within few minutes whereas lipid soluble drugs are released first into the gum base and then released slowly.

3) 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 suggest 60 cycles per minute chewing rate for proper release of active ingredient[29].

4) Formulation factor: Composition and amount of gum base affect rate of release of active ingredient. If lipophilic fraction of gum is increased, the release rate is decreased[30].

Applications:
1. Dental caries[31,32]- Prevention and cure of oral disease are obvious targets for chewing gum formulations. It can control the release rate of active substances providing a prolonged local effect. It also reelevates plaque pH which lowers intensity and frequency of dental caries. Fluoride containing gums have been useful in preventing dental caries in children and in adults with xerostomia. Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oral and pharyngeal infections. It can also be used for inhibition of plaque growth Chlorhexidine chewing gum offers numerous flexibility in its formulation as it gives less staining of the teeth.
and is distributed evenly in the oral cavity. The bitter taste of chlorhexidine can be masked quite well in a chewing gum formulation.

2. Systemic therapy- chewing gum as a drug delivery system is beneficial to a number of indications, some of which are discussed below:

(a) Pain- Treatment of minor pains, headache, muscular aches can be successfully accomplished
(b) Smoking cessation- Chewing gum formulation containing nicotine, lobeline and silver acetate have been clinically tested as aids to smoking cessation. Nicotine33 is a natural alkaloid occurring in the leaves of tobacco plant. It is a therapeutic agent intended to help smokers break the psychological habit of smoking by reducing the nicotine withdrawal symptoms normally experienced when smoking is stopped. The formulation nicoretteÒ available as mint and classic with different flavor and dosage, is developed with ion- exchange resin, released 90% of drug after 30 min chewing. The release rate was controlled by the rate and vigour of chewing. Thus the patient can control the drug intake to match his needs. Increasing the pH of the medium in which it is dissolved can enhance nicotine absorption.
(c) Obesity- Active substances like chromium, guaran and caffeine are proved to be efficient in treating obesity. Chromium is claimed to reduce craving for food due to an improved blood-glucose balance. Caffeine and guaran stimulate lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger.
(d) Other indications- xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough[34], Diabetes, Anxiety etc are all indications for which chewing gum as drug delivery system could be beneficial.

Some important formulation aspects:
1.) Increased amount of softners and emulsifiers in gum base fasten release whereas hard gum may retard[35,36].
2.) Cyclodextrin complexation or solubilisation technique increases aqueous solubility of drugs that are poorly water soluble.[37,38]
3.) A solid system of lipophilic active ingredients bound to the cation exchange resin permits a sustained drug delivery system.
4.) Microencapsulation or agglomerations are the methods to modify and control the release of active ingredient.[39,40]

In-vitro drug release testing apparatus:
Number of apparatus for studying in-vitro drug release from medicated chewing gum has been developed. An apparatus[41] for in vitro drug release testing of medicated chewing gums has been developed by Kvist C et al. They have studied the effect chewing surfaces, twisting movements of surfaces and temperature of test medium on release rate of drug from MCG. Another novel dissolution apparatus has been developed for MCG by Rider JN et al.[42, 43]. The apparatus consist of conical Teflon base and a rotating, ribbed Teflon plunger suspended in a dissolution vessel. The rotation speed, plunger frequency, medium volume, medium type, medium sampling location, number of plunger ribs and number of gum pieces were studied by them. In 2000, European Pharmacopoeia[44, 45] published a monograph describing a suitable apparatus for studying the in-vitro release of drug substances from MCG. The chewing machine consists of a temperature-controlled chewing chamber in which the gum piece is chewed by two electronically-controlled horizontal pistons driven by compressed air. The two pistons transmit twisting and pressing forces to the gum, while a third vertical piston, (“tongue”) operates alternately to the two horizontal pistons to ensure that the gum stays in the appropriate position. The
The temperature of the chamber can be maintained at 37±0.5°C and the chew rate can be varied. Other adjustable settings include the volume of the medium, the distance between the jaws and the twisting movement. The European Pharmacopoeia recommends using 20 ml of unspecified buffer (with a pH close to 6) in a chewing chamber of 40 ml and a chew rate of 60 strokes per minute.[46]

**Therapeutic uses of MCG:**
The use of sugar free gum to counteract dental caries by stimulation of saliva secretion has led to a more widespread use and acceptance of gums. It has been proved that chewing nonmedicated chewing gums increases plaque pH, stimulates saliva flow and decrease decay[47]. MCGs containing Chlorhexidine for treatment of gingivitis and plaque has been available. The use of MCG in the treatment of oral infections has also been reported[48]. The active ingredient is released from the MCG and sufficient concentration is achieved in the oral cavity to prevent or treat local conditions of oral cavity. CG is also useful delivery system for agents intended for systemic delivery. Drug that is released from gum within oral cavity can be absorbed via buccal mucosa. The MCGs can also be used as an alternative tool to buccal and sublingual tablets which are intended to act systemically because active ingredient is released more uniformly and cover greater area of absorption in oral cavity. Oral diseases are prevented or cured with MCG. MCGs for systemic effect in conditions like vitamin C deficiency, pain & fever, alertness, motion sickness, smoking cessation, as well as for local effect in the conditions like plaque acid neutralization, fresh breath, disinfection, anti-caries, antiplaque, antifungal, antibacterial are available[49].

**Safety Aspects:**
Difference commercial chewing gums have been shown to adhere to different degree to dentures, fillers and crowns. Over chewing causes painful jaw muscles. Chewing gum appears to offer a smaller risk of overdosing by mistake or misuse than flavored chewable tablets. Medicated chewing gums should, like other medicaments, be kept out of reach of children and it would be wise to advice people prone to allergic responses to check the flavoring and sweetening agents included in the chewing gum formulations[50].

**Table4: Marketed Product of MCG**

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicorette</td>
<td>Nicotine</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Nicotinell</td>
<td>Nicotine</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Niquitin CQ</td>
<td>Nicotine</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Fluorette</td>
<td>Fluoride</td>
<td>Prevention of dental carries</td>
</tr>
<tr>
<td>Vitaflo CHX</td>
<td>Chlorhexidine</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>Hexit</td>
<td>Chlorhexidine</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>Stay Alert</td>
<td>Caffiene</td>
<td>Motionsickness</td>
</tr>
</tbody>
</table>

**Future Trends:**
Chewing gum not only offers clinical benefits but also is an attractive, discrete and efficient drug delivery system. A few decades ago, the only treatment for some disease was surgical procedure but now more and more disease can be treated with Novel Drug Delivery Systems. Generally, it takes time for a new drug delivery system to establish itself in the market and gain acceptance by patients, however chewing gum is believed to manifest its position as a convenient and advantageous drug delivery system as it meets the high quality standards of pharmaceutical industry and can be formulated to obtain different release profiles of active
substances. The potential of MCG for buccal delivery, fast onset of action and the opportunity for productline extension makes it an attractive delivery form. Reformulation of an existing product is required for patent protection, additional patient benefits and conservation of revenues.
References:


19. Weil AT. Coca leaf as a therapeutic agent, American Journal Drug Alcohol Abuse. 5(1); 1978:75-86


