AN UPDATED REVIEW ON MEDICATED GUM AS A POTENTIAL TOOL FOR NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT
In the modern years scientific and technological advancements have been made in the research and development of oral drug delivery system. Such researches show significance of oral route amongst patients. We have reviewed all the features related with medicated chewing gum as a recent drug delivery by introducing the advantages and disadvantages, methods of manufacturing, composition differences, evaluation tests, factors affecting release of active ingredient and pharmaceutical significance of medicated chewing gums. Acceptance of medicated chewing gum has been augmented through years. Medicated chewing gum delivery system is suitable, easy to administer - everyplace, anytime and is pleasantly tasting making it patient acceptable. The advantages and therapeutic benefits of chewing gum support its development as we can see new formulations with new drugs contained have been produced from past and are going to find a place in market by formulation of novel medicated chewing gums.

KEYWORDS: Medicated chewing gum, oral drug delivery, patient compliance.

INTRODUCTION[1,2,3,4,10,24,37,55,56,57]
Chewing Gum (CG) also has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients.[24,37] 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 favored route amongst the patient and clinicians due to various advantages it offers.[37] Chewing gum is a pleasure that almost everyone enjoys.[57] Chewing gums are mobile drug delivery systems.[6] MCG represents the newest system with potential uses in pharmaceuticals, over the counter medicines and nutraceutical. Medicated chewing gum (MCG) is the gum base incorporating drug(s).[56] 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.[1]

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 gum offers advantages in comparison to conventional oral mucosal and oral dosage forms both for local effect, systemic effect and after absorption through the buccal and sublingual mucosal and from the gastrointestinal tract. Chewing gum can be retained in the oral cavity for a long period and, if the drug is readily absorbed across oral mucosa, chewing gum can provide a fast onset time for a systemic effect and the potential for prevention of gastrointestinal and hepatic first pass metabolism of susceptible drugs. Generally, medicated chewing gum has a good stability, the medicine can be taken easily and directly without the prerequisite of water, and if required, prompt discontinuation of medication is possible.[3,1]

In Children particularly may consider chewing gum as a more preferred method of drug administration compared with oral liquids and tablets. Medicated gum is a chewing gum with a reason to introduce medicated substances into blood stream faster than pills. A piece of chewing gum usually consists of gum core, which may or may not be coated. The core is composed of an insoluble gum base resin, elastomers, emulsifiers, fillers, waxes, antioxidants and softeners, sweeteners, flavoring agents, and in case of medical chewing gum, active substances. The water content of chewing gum is very low and no preservative is needed. The gum base determines the basic characteristics of the product; e.g. whether the texture is soft or hard to chew, whether it crumble, whether it stick to the teeth. It also determines the release profile of active substances and changing the
Chewing gum provides new competitive advantages over conventional drug delivery systems. 

**DEFINITION OF MEDICATED CHEWING GUM**

1. **Medicated Chewing Gum (MCG)** is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and intentional to use for local treatment of mouth diseases or systemic absorption through oral mucosa. MCG is considered as vehicle or a drug delivery system to administer active principles that can recover health and nutrition.

2. **Medicated Chewing Gum** which is 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. The drug product is intended to be chewed in the oral cavity for a specific period of time, after which the insoluble gum base is discarded.’

**NEED OF CHEWING GUM AS A DRUG DELIVERY SYSTEM**

Chewing gum provides new competitive advantages over conventional drug delivery systems:

- Highly suitable by children.
- Avoids first pass metabolism and thus increases the bioavailability of drugs.
- Fast onset due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation.
- Gum does not reach the stomach, hence G.I.T. suffers less from the effects of excipients.
- Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa.
- Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased.
- It may prove to be particularly suitable for the systemic delivery of drugs, which are susceptible to metabolism in the gut wall or liver.
- The treatment can be completed at any time. It may give pleasant taste.
- Increased rate of effectiveness rather than other oral delivery systems.
- Reduced risk of overdosing while it's whole swallowed.
- Reduced hypoglycemic shocks in people taking anti-diabetic drugs.
- Stimulating alertness through increased blood flow to brain.
- Help reduce food cravings.
- Easy to carry and transport.
- People find relaxation and comfort in the simple act of chewing gum.

**DEMERITS OF MCG**

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. Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers.
4. Extended chewing of gum may result in pain in facial muscles and ear ache in children.
5. Short time of administration due to eating, speaking, and drinking.
6. Additives in gum like flavoring agent, Cinnamon can cause Ulcers in oral cavity and Liquorice cause Hypertension.
7. Allergic reaction to synthetic sweeteners.

**COMPONENTS OF THE MCG**

Chewing gum is a mixture of natural or synthetic gums and resins sweetened with sugar, corn syrup, artificial sweeteners and may also include coloring agents and flavor. The basic raw material for all CG is natural gum Chicle, obtained from the sapodilla tree. Chicle is very costly and difficult to procure therefore other natural gum or synthetic materials like polyvinyl acetate and similar polymers can be used as gum base. Typically Chewing Gum comprises two parts.
1. Water insoluble chewable gum base portion
2. Water-soluble bulk portion

1. Water insoluble gum base generally comprises of
   - Elastomers (40-70% by wt. of gum base)
     Elastomers provide elasticity and control gummy texture. Natural Elastomer: Natural rubbers like Latex or Natural gums such as Chicle gum, nispero, rosadinha, jelutong, LechiCasp, Perillo, and Chicle and Synthetic elastomers like poly-isobutylene and butyl rubber are generally used.
   - Plasticizers (3-20% by wt. of gum base)
     These are used to control cohesiveness of the product. These are again divided into Natural and Synthetic.

Natural Plasticizers contain Natural rosin esters like Glycerol Esters of Partially dimerized Esters, Glycerol Esters of Pentaerythritol Esters of Rosin.

Synthetic Plasticizers include Terpene Resins derived from α-pinene and/or d-limonene.

- Fillers or Texturizers (2-60% by wt. of gum base)
  Provide texture; improve chewability, and provide reasonable size of the gum lump with low dose drug. Commonly used fillers are Magnesium and Calcium Carbonate, Ground Silicate, Clay, Alumina, Talc, Titanium Oxide & Mono/ Di/ Tri Calcium Phosphate.

2. Water soluble portions comprises of
   - Softeners and Emulsifiers
     These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. Softeners include Glycerin, Lecithin, Tallow, Hydrogenated Tallow, Mono/ Di/ Tri- Glycerites, Fatty acids like Stearic acid, Palmitic acid, Oleic acid and Linoleic acid.
   - Colorants’ and Whiteners
     It may consist of FD & C type dyes and lakes, fruit and vegetable extracts, Titanium Dioxide.

- Sweeteners (50-65% of gum base composition)
  Aqueous Sweeteners can be used as softeners to merge the ingredients and retain moisture. These include Sorbitol, hydrogenated Starch hydrolysates and Corn Syrups. Corn syrup keeps gum fresh and flexible.
  Bulk Sweeteners include Sugar and Sugarless components. Sugar Components include Saccharides like Sucrose, Dextrose, Maltose, Dextrin, Fructose, Galactose and Corn Syrup. Sugarless Components include sugar alcohols such as Sorbitol, Mannitol, Xylitol, Hydrogenated Starch hydrolysate. High intensity artificial Sweeteners can also be included to provide longer lasting sweetness and flavor perception e.g. Sucralose, Aspartame, salt of Acesulfame, Alitame, Saccharin, Glycyrrhizin, Dihydrochalcones

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

- Flavoring Agents
  A variety of flavoring agents are used to improve flavor in chewing gum includes essential oils, citrus, fruit essences, peppermint oil, spearmint oil, mint oil, clove oil, and oil of wintergreen. Artificial flavoring agents can also be used.

- Active Component
  In medicated chewing gum active pharmacological agent may be present in core or coat or in both. The proportion of which may vary from 0.5-30% of final gum weight. A small, unionized, lipophilic and enzymatically stable active agent is likely to be absorbed more readily. A saliva soluble ingredient will be completely released within 10-15 minutes of chewing whereas lipid soluble ingredient will dissolve in the gum base and thereafter be slowly and completely absorbed. MCG consists of masticatory gum core that may be coated. The core is composed of an aqueous insoluble gum base which can be mixed with Sweeteners and Flavors. The coating can be applied as a film of polymers, waxes, sweeteners, flavors and colour or a thick layer of sugar or sugar alcohol.

Table No. 1: Components required for MCG formulation^{[2,48,49,50,51]}

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water insoluble gum base</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elastomers</td>
<td>Provides elasticity and controls gummy texture</td>
<td>Natural (chicle gum, nispero, rosadinha, jelutong, perillo, lechi-capri, sorva etc.) and synthetic rubbers (butadiene, styrene, polymers, poly-isobutylene, polyethylene mixtures, polyvinyl alcohol etc.)</td>
</tr>
<tr>
<td>Elastomer solvents</td>
<td>Softening the Elastomer base component</td>
<td>Terpinene resins (polymers of alpha-pinene or beta-pinene), modified resins or gums (hydrogenated, dimerized or polymerized resins)</td>
</tr>
<tr>
<td>Plasticizers</td>
<td>To obtain a variety of desirable textures and consistency proper-ties</td>
<td>Lanolin, palmitic acid, oleic acid, stearic acid, glyceryl triacetate, propylene glycol monostearate, glycerin, natural and synthetic waxes, hydrogenated vegetable</td>
</tr>
</tbody>
</table>
### MANUFACTURING PROCESSES

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

1. **Conventional/ Traditional method (Melting or Fusion method)**

   - The first step of a typical process for manufacturing chewing gum is to melt and soften the gum base at about 60°C and place it in a kettle mixer, in which blades soften the base, then extra ingredients such as sugar, glycerin, sweeteners, taste-masking agent are added to the softened base, latterly the flavoring agent is added in the mixing procedure at 40°C, then cooling and rolling steps would be done, and the rolled chewing gum would then be cut into pieces of desired shapes and sizes. To make a coated gum tablet, a coating agent should be sprayed to form a uniform surface.

   - Second type of this method is somehow different: The major step of preparation is to set up a mixer (the mixer could be sigma blade or other types of mixers), if a sugar-containing gum is needed, the first step is to add corn syrup to the mixer, and then finely powdered sugar is added gradually. Sugar, used in this step, could be powdered sucrose, dextrose, fructose, corn syrup solids or combination of them.

   - After adding these sweeteners, plasticizers are added to modify the texture and regulate the cohesiveness. Glycerin is the most preferably plasticizer used. Other components specified in Table 1 could be added to the matrix according to required characteristics, such as fillers, colorants and flavorings. But it is suggested that flavorants being added to the matrix at the end of procedures when base gum is totally and completely homogenized because most flavorants are moderately volatile.

   - The mechanical forces of mixer, that is, compressive and shear and heat can ease the softening process. When no heat is applied, a higher power is demanded. The mixing process continues until a homogenous mass is formed. The mixing process should last about 8 min.

   - Another way of mixing ingredients is to add sugar gradually till the end of adding other components.

   - After matrix preparation and completely mixing it, the commercially prepared particles of gum base are added to the chamber all at once. But it is alleged that these particles should have been heated and mixed before adding all other ingredients to the matrix preparation chamber.

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### Table 1

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fillers or texturizers or mineral adjuvant</td>
<td>Provide texture, improve chewability, provide reasonable size of the gum lump with low dose drug</td>
</tr>
<tr>
<td>Calcium carbonate, magnesium carbonate, Aluminum hydroxide, talc, aluminum silicate</td>
<td></td>
</tr>
<tr>
<td>Water soluble portions</td>
<td>These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum</td>
</tr>
<tr>
<td>Glycerin, lecithin, tallow, hydrogenated tallow, mono/di/tri glycerides</td>
<td></td>
</tr>
<tr>
<td>Colorants and whiteners</td>
<td>Gives the formulation soothing color and improves acceptability of the formulation</td>
</tr>
<tr>
<td>Titanium dioxide, natural food colors and dyes suit-able for food, drug and cosmetic applications</td>
<td></td>
</tr>
<tr>
<td>Sweeteners</td>
<td>To provide the desired sweetness of the product</td>
</tr>
<tr>
<td>Water soluble sweetening agents (xylose, ribulose, glucose, mannose, galactose, sucrose, fructose, maltose, melonlin, sugar alcohols like sorbitol, mannitol etc.), water soluble artificial sweeteners (sodium or calcium saccharin salts, cyclamate salts etc.), di-peptide based sweeteners (aspartame, alitame etc.), naturally occurring water soluble sweeteners, chlo-rinated derivatives of ordinary sugar (sucralose), protein based sweeteners (thaumatin I and II)</td>
<td></td>
</tr>
<tr>
<td>Antioxidants</td>
<td>Prevents any possible microbial growth</td>
</tr>
<tr>
<td>Butylatedhydroxytoluene, butylatedhydroxyanisole, propyl gallate</td>
<td></td>
</tr>
<tr>
<td>Flavoring agents</td>
<td>To enhance consumer acceptability</td>
</tr>
<tr>
<td>Essential oils (citrus oil, fruit essences, peppermint oil, spearmint oil, mint oil, clove oil and oil of win-tergreen) and synthetic or artificial flavors</td>
<td></td>
</tr>
<tr>
<td>Bulking agents</td>
<td>Used if low calorie gum is desired</td>
</tr>
<tr>
<td>Polydextrose, fructo oligosaccharides, oligo-fructose, inulin, gum hydrolysate, indigestible dextrin</td>
<td></td>
</tr>
<tr>
<td>Compression adjuvant</td>
<td>To ease the compression process</td>
</tr>
<tr>
<td>Silicon dioxide, magnesium stearate, calcium stearate, talc</td>
<td></td>
</tr>
</tbody>
</table>
mass of gum base. In this stage, mixing will continue for 10-20 min.\textsuperscript{13,14}

- The difference between these almost new methods from the conventional (fusion) method in mixing techniques is wherein the sweetener matrix is first formed then gum base particles as pellets are added, but in conventional (fusion) method, the sweeteners and other ingredients are added to the molten gum base.

- This new processing method has advantages over the previous way of processing, that is, the probability of producing sugar lumps is less than before.\textsuperscript{14,33}

**Limitations**

- Elevated temperature used in melting restricts the use of this method for thermo liable drugs.
- 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.

2. Cooling, Grinding and Tableting Method (Thermolabile)\textsuperscript{5,8,10,29}

**Cooling and Grinding**

- One another method to provide a chewing gum with desired taste, color and flavor is to mix gum base with favorable and suitable sweeteners, corn syrups, starches, flavoring agents, and colorants and then refrigerate and cool it by a freezer apparatus or by contacting with a coolant like carbon dioxide to a temperature below \(-15^\circ\text{C}\) which is therefore crushed and broken up with a cutter or grinding apparatus to obtain minute particles then these finely ground particles are heated to a temperature which makes them adhere to each other and form a slick and uniform bulk with consistent texture and low specific gravity. If the fragments are such that they do not self-adhere, low pressure would be applied manually or mechanically before they are warmed to the normal room temperature to thereby endorse self-adhesion.

- Amongst the various coolants like liquid nitrogen, hydrocarbon slush use of solid carbon dioxide is preferred as it can give temperatures as low as \(-78.5^\circ\text{C}\), it 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.\textsuperscript{8}

- Alternatively, the steps of cooling the chewing gum composition can be combined into a single step. As an example, cooling the grinding apparatus itself which can be done by contacting the grinding apparatus with a coolant or by placing the grinding apparatus in a cooling jacket of liquid nitrogen or other cold liquid. For more efficient cooling, the chewing gum composition can be pre cooled prior to cooling to the refrigeration temperature.

- Sometimes a mixture of chewing gum composition, solid carbon dioxide and precipitated silica is ground in a mill grinder in the first step. Additional solid carbon dioxide and silica are added to the ground composition, and the composition is further ground in the second step. This two step grinding process advantageously keeps the chewing gum composition at a very low temperature.

- 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. Anti-caking agent like precipitated silicon dioxide helps to prevent agglomeration of the subsequently ground chewing gum particles. 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 integrated.

**Tableting**

- Once the coolant has been removed from the powder, the powder can be mixed with other ingredients such as binders, lubricants, coating agents, and sweeteners etc., all of which are compatible with the components of the chewing 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 Fluidized Bed Reactor 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 anti adherents 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. It requires equipment other than conventional tableting equipment and also requires careful monitoring of humidity during the tableting process which is the major limitation.

3. Direct compression method\textsuperscript{5,6,8,54}

- A new technology to make a chewing gum tablet is direct compression and tableting at high-speed standard machine, but as explained in a patent, this way of forming chewing gum tablets provides a quickly dissociable chewing gum, but after a few
seconds of chewing, particles adhere together to form a uniform and homogenous mass.

- In this method; we need a granulating agent, most preferably that is sorbitol which can also act as a sweetener. A lubricant such as magnesium stearate, talc, stearic acid, hydrogenated vegetable oils and sodium stearyl fumarate is added to formulation before tableting.
- First step of this method is dry mixing of gum base, granulating agent and at least one processing material then adding active ingredient, sweeteners, and other needed ingredients to the formulation in free flowing form of materials then directly compressing the chewing gum into tablets.
- In the first step, the temperature should not elevate higher than the melting point of the gum base. After obtaining a uniform and slick mass, the temperature would lower to add other ingredients. [8]
- The manufacturing process can be accelerated if directly compressible chewing gum excipients are available. The limitations of melting & freezing can be conquer by the use of these.
- Pharmagumis 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 chewing gum tablet using conventional tablet press thus enabling rapid and low cost development of a chewing gum delivery system. It is manufactured under CGMP conditions and complies with Food Chemicals Codex specifications as well as with FDA, so they can be considered as "Generally regarded as safe" (GRAS).
- Pharmagum is available in three forms namely S, M and C. Pharmagum M has 50% greater gum base compared to Pharmagum S. Pharmagum S consists primarily of gum base and sorbitol. Pharmagum M contains gum base, mannitol. 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.[5]

**PROBLEMS ASSOCIATED WITH MANUFACTURING OF MCG**

1. Capping, lamination, picking and sticking are the most common processing problems. [9]
2. 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. [10]
3. Heating and melting can make controlling the accuracy and uniformity of the drug difficult. [10]
4. It is tough to provide sanitary conditions to make MCGs. [10]
5. Moisture content of chewing gum may cause the gum jam to the blades and punches of apparatus, screens, surfaces and chamber's wall. [9]
6. Caking and balling of the gum prevent formation of gum fragments. [10]
7. Ejection of final compressed mass from the mixer is difficult and may stick up into the tubes and stick to punches. [8]
8. Forming a low calorie chewing gum has resulted in a gum with hard chew, poor texture, and bad taste or off-taste. [11]
9. Bad smell and undesired taste of ingredients applied in the compound. [12]
10. Sugar spots or lumps may appear in the final texture and cause undesired feeling. [13]
11. Some ingredients and active agents can irritate mucosa. [12]
12. High temperature to facilitate the mixture of gum base, leads to spoil other ingredients. [12]

**STABILITY** [11,40]

Chewing gum is a very stable product due to its low moisture content and less reactive nature than that of other oral ingredients. Chewing gum normally contains little water (2.5%). If the water content is very critical for the stability of drug, the chewing gum can be manufactured without water (less 0.2%). This will however, often make the product hygroscopic and will affect the texture. The low water content also inhibits microbial growth in the chewing gum during storage. Furthermore, the product can be protected against oxidation by a sealed coat and by an appropriate packing. [1]

In general, the stability of the active substance is good because chewing gum holding drug protects it from oxygen, light, and humidity. High temperature for some heat-sensitive components to facilitate mixing can be avoided by increasing other powers, instead. Undesired interactions between different components can be prevented by encapsulation or coating of some ingredients by suitable substances so that less contact between compounds occurs. [40] For every temperature labile component, e.g. enzymes, the process temperature of 50-60°C during mixing may create a stability problem. It is however possible to operate the process at a lower temperature to avoid this issue.

**EVALUATION PARAMETERS** [2,22,29,30,41,52,58]

1. **Content uniformity**
   Ten MCGs 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. [41]

2. **Mass uniformity**
   Twenty MCGs are selected arbitrarily and weighed, not more than two single mass should vary the average mass. [41]
3. Dissolution test

Mastication devices are designed to simulate human chewing behavior. To mimic a drug release in these devices or machines, the following test is specified. This test determines the dissolution rate of active ingredients in MCG, a part of MCG is placed in the chamber of an apparatus which contains:

- Chewing chamber
- A vertical piston and
- Horizontal pistons with sealed rings. MCG is chewed by horizontal pistons and is fixed by vertical piston.

During each chewing cycle, apparatus speed and pistons’ movements should be controlled not to interfere with each other’s work. Actually, horizontal and vertical pistons are, respectively, instead of teeth and tongue.

In the first apparatus adopted by European pharmacopoeia (EP), a defined volume of dissolution medium is shed into mastication chamber, the acidity of medium reaches to pH 6.0 by phosphate buffer and the temperature should be 37°C ± 0.5°C and the piston speed is 60 rpm.

The usual number of chews per minute of a normal person is 60 strokes /min, then a part of MCG or the whole gum is placed into the chamber and the apparatus is set and the procedure is started. The machine is stopped at determined time, the remaining part of the gum is then removed and a sample of dissolution medium is prepared, the content of active agent(s) is determined by a suitable method, after each sampling, dissolution medium could have been replaced by a new and fresh medium so that the dilution factor should be calculated. The content of active agent(s) in the gum residue could be determined too. This test is carried out on three MCGs for three times.

4. 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.

5. Evaluation of mechanical properties of chewing gums

Tensile test

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:

\[
\text{Stress} = \frac{\text{Load}}{\text{Initial cross-sectional area}}, \quad \text{Strain} = \frac{\Delta l}{l_0} \quad (\text{Elongation/Initial gage length}).
\]

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 non uniformity 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.

FACTORS AFFECTING RELEASE OF ACTIVE INGREDIENT

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

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

  - Salivary glands
    - Drug delivery system should be placed either over a duct or adjacent to the salivary duct because it may result in excessive washout of drug or rapid dissolution of the system making it difficult to achieve high local drug concentration.

- Chewing time and chewing rate
  - Time should be around 20 to 30 min. the rate of chewing also affects the drug release. The average chewing rate is about 60 chews /min.

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

- **Contact Time**
The local or systemic effect is dependent on time of contact of MCG in oral cavity. In clinical trial chewing time of 30 minutes was considered close to ordinary use.

- **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.

- **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.

- **Formulation factor**
Composition and amount of gum base influence rate of release of active ingredient. If lipophilic fraction of gum is increased, the release rate is decreased.

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

1. Sugar free chewing gum is known to be beneficial to dental health. It has been shown that use of sugar free chewing gum after meals re-elevates plaque. pH plays an important role in the development of dental caries. Therefore, in caries prevent ion programs, sugar-free chewing gum is recommended after meals and snacks as a supplement to tooth brushing.

2. Chewing gum as a drug delivery system also provides benefits to systemic drug delivery, especially if the active substance is absorbed through the buccal mucosa, fast and acute treatment, convenience, no need for water and thereby easy administration – any time anywhere – reduced risk of gastro intestinal side effects. These benefits apply not only to the treatment of adults, but also to the treatment of children and adolescents.

3. Absorption from the chewing gum formulation was shown to be faster than absorption from the tablet, and consequently, a chewing gum formulation may provide faster pain relief.

4. Allergy, nausea, motion sickness, diabetes, anxiety, dyspepsia, osteoporosis and cough and cold are all indications for which chewing gum as a drug delivery system could be beneficial.

5. Chewing gum containing antacids or mucolytics also presents advantages for patients.

6. Chewing gum as a drug delivery system offers convenience in the treatment/prevention of motion sickness and nausea.

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**CHEWING GUM PACKAGING**

The advantages of chewing gum packaging are clear to the world since it extends shelf-life of the product by preventing aroma and flavor to disappear. It also provides moisture retention and gum stability. There are too many packaging methods with a broad range of options. In almost all of packaging types, we require a wrapping machine that receives and wraps the sticks of gums; in some cases, the wrapper machine seals the end of the package. The manufacturing and packing steps should be performed at about 20-25°C and relative humidity of 57%. Packaging has an important portion in the whole process both in terms of cost and time.  

Undoubtedly, packaging influences attraction of product among consumers, thus a well-favored and stylish design can attract more consumers to buy the specific product. Therefore, besides protecting the content, avoiding
impurity, expediting transport and improving storage. packaging can influence consumers’ willingness to buy the product and capture his attention during purchase competition. [43]

FUTURE TRENDS[1,8]
Future of chewing gum will reveal all of the scientists’ efforts for the development of chewing gum as a modern drug delivery system and progress of chewing gum production technology in preference to other delivery systems to deliver drugs locally to the oral cavity. The reason is simple that the chewing gum delivery system is not only offers clinical benefits but also convenient, easy to administer, anywhere, anytime and is pleasantly tasting making it patient acceptable.

In the future, other attempts will be seen to formulate more drugs using chewing gum as a drug delivery system. Treatment of fungal diseases, prevention of caries and other dental health issues, smoking cessation, etc., are common health work of MCGs. But remineralization of teeth, cold relief, energy enhancing, anti-nausea and so many new advantages of this novel drug delivery system are going to play an important role through future studies. MCGs are admissible alternatives of chewable or standard tablets and oral disintegrated dosage forms.

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 product line extension makes it an attractive delivery form. Reformulation of an existing product is required for patient protection, additional patient benefits and preservation of revenues. We predict a brighter future for MCG as a novel drug delivery system than previous oral systems.

SUMMARY AND CONCLUSION[1,8]
According to the benefits of chewing gum as a novel drug delivery, like concurrently supporting both local and systemic delivery, protection against acids and enzymes, low first pass metabolism, elevating alertness and cognitive function, good stability, taste masking of certain drugs and a lot more; we can conclude that chewing gum will be much more familiar to patients and market in the next few years. However, their new and old applications prove our statement as it can be seen that there are treatments for motion sickness, pain, smoking, dental caries, tooth decay, otitis media, GI problems, oral fungi, inflammatory problems etc., by formulating efficient chewing gums that contain at least one drug as active agent.

The technology to bring chewing gum to market and health system as a reliable alternative for different kinds of tablets has not been ready and fully understood yet because there are much more information and knowledge to be explored for manufacturing chewing gums.

Scientists and researchers should also consider new formulations for chewing gums for increasing variations of chewing gum due to patients’ different styles and providing appropriate release pattern for chewing gums containing drugs.

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