MEDICATED CHEWING GUM (MCG) AS NOVEL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
In the last few years scientific and technological advancements have been made in the research and development of oral drug delivery systems. The reasons of popularity of oral route may be primarily due to its ease of administration. Medicated Chewing Gum is a Novel Drug Delivery System (NDDS) containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. It is a potentially useful means of administer of drugs either locally or systematically via oral cavity. It can be employed for treatment of diseases of the oral cavity and throat, e.g. for caries prevention, or it can release drugs that can be absorbed through oral mucosa directly into the systemic circulation. Medicated chewing gums are excellent drug delivery systems for self-medication as it is convenient and can be administered discretely without water.

KEYWORDS: Medicated Chewing Gum, Novel Drug Delivery System (NDDS), Oral route.

INTRODUCTION
Medicated Chewing Gum is a Novel Drug Delivery System (NDDS) containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. Medicated Chewing Gum is a “Delivery system” are intended to introduce medicated substances into the saliva and thus into the blood stream faster than pills.
Medicated Chewing Gum is considered as Vehicle or a Drug delivery system to administer active principles that can improve health and nutrition. It can be taken discreetly without water and allows for local and systemic delivery.[1]

**Merits of MCG**[^1,6,7,7]

1. Dose not requires 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.
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.

**Demerits of MCG**[^8]

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 flavouring agent, Cinnamon can cause Ulcers in oral cavity and Licorice 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 gums have been shown to adhere to different degrees to enamel dentures and fillers.
6. Prolong chewing on gum may result in pain in facial muscles and earache in children.

**FORMULATION**

Medicated chewing gum is a combination of a water-insoluble phase, known as gum base, and a water-soluble phase of sweeteners, flavoring and sometimes food coloring. is a mixture
of natural or synthetic gums and resins, sweetened with sugar, corn syrup, artificial sweeteners and may also contain colouring agents and flavour. The basic raw material for all MCGs is natural gum Chicle, obtained from the sapodilla tree. Chicle is very expensive 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 chewable gum base portion

Gum base is the non-nutritive, non-digestible, water-insoluble masticatory delivery system used to carry sweeteners, flavors and any other desired substances. It provides all the basic textural and masticatory properties of gum. Generally comprises Elastomers, Resins, Fats and Oils, and Inorganic fillers. Old gum bases were based on either natural elastomers such as latexes, vegetable gums like chicle, spruce gum and mastic gum, or alternatively on waxes, e.g. paraffin wax and beeswax, but today synthetic rubbers are preferred. Gum bases for are different than those for bubble gum. A bubble gum base is formulated with the ability to blow bubbles. contains 20-25% gum base and sugar-free chewing gum contains 25-30% gum base.

a) Elastomers

Elastomers provides elasticity or bounce, controls gummy texture and can be:
1) Natural Elastomer: Natural rubbers like Latexes (e.g. couma macrocarpa (also called leche caspi or sorva), loquat (also called nispero), tunu, Natural gums such as jelutong, Caspi, Perillo or chicle which is still commercially produced)
2) Synthetic Elastomer: Rubbers (e.g. styrene-butadiene rubber, butyl rubber, polyisobutylene).

b) Plasticizers: These are used to regulate cohesiveness of product. These are again divided into Natural and Synthetic.

1) Natural Plasticizers: Include 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.
2) Synthetic Plasticizers: Include Terpene Resins derived from a-pinene and/or d-limonene.
3) **c) Fillers or Texturizers:** Provide texture, improve chew ability, and provide reasonable size of the gum lump with low dose drug.

Commonly used fillers are Magnesium and Calcium Carbonate, Ground Limestone, Magnesium and Aluminium Silicate, Clay, Alumina, Talc, Titanium Oxide & Mono/ di/ tri Calcium Phosphate.

d) **Resins:** Provide a cohesive body or strength. They are most often glycerol esters of gum resin, terpene resins, and polyvinyl acetate.

e) **Waxes:** Act as softening agents. They are most usually paraffin or microcrystalline wax.

f) **Fats:** Behave as plasticizers.

2. **Water-soluble bulk portion**

a) **Softners and Emulsifiers:** These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. Softners include Glycerin, Lecithin, Tallow, Hydrogenated Tallow, Mono/ di/ tri-Glycerides, Fatty acids like Stearic acid, Palmitic acid, Oleic acid and Linoleic acid.

b) **Colourants and Whiteners:** A food coloring is any substance that is added to change its color.

1) **Natural food dyes**
   - Caramel coloring, it is made from caramelized sugar.
   - Annatto is a reddish-orange dye made from the seed of a tropical tree.
   - Beet juice, turmeric, saffron, paprika are also used as colorants.
   - Titanium dioxide occurs naturally in minerals.

2) **Artificial food dyes**

In the USA, the following artificial colorings are permitted:
   - FD&C Blue No.1 - Brilliant Blue FCF, E133 (Blue shade)
   - FD&C Green No.3 - Fast Green FCF, E143 (Bluish green shade)
   - FD&C Red No.3 - Erythrosine, E127 (Pink shade)
   - D&C Yellow No.6 - Sunset Yellow FCF, E1 10 (Orange shade)
c) **Sweetners**: These are of three types:
   1) Aqueous Sweetners.
   2) Bulk Sweetners.
   3) Sugar Substitutes.

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

e) **Flavouring Agents**
Essential oils, such as Citrus oil, fruit essences, Peppermint oil, Spearmint oil, Mint oil, Clove oil & Oil of Wintergreen. Artificial flavouring agents can also be used.

f) **Antioxidant**: Protect from oxidation and extend shelf-life. The most common type is BHT. Antioxidants are molecules that slow or prevent the oxidation of other molecules.

Antioxidants are classified into two broad divisions:
1. **Hydrophilic**: They are soluble in water.
2. **Hydrophobic**: They are soluble in lipids.

g) **Emulsifiers**: Help to hydrate. The most common is lecithin or glycerol monostearate.

h) **Active Component**: In 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.

**MANUFACTURING PROCESS**
Different methods employed for the manufacturing of MCG can be broadly classified into three main classes namely.
1. Conventional/ Traditional Method (Melting).
2. Freezing, Grinding and Tabletting Method.
3. Direct Compression Method.

1. **Conventional/ Traditional Method**
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 up to 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**

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.

**2. Freezing, Grinding and Tabletting Method**

This method has been developed with an attempt to lower the moisture content and alleviate the problems mentioned in conventional method.

**Freezing and Grinding**

The MCG 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 MCG and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally, the temperature of the refrigerated mixture is around \(-15^\circ\)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 \(-78.5^\circ\)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. 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 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 therapeutics 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.

**Tabletting**

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 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 tableting equipment and requires careful monitoring of humidity during the tableting process.

### 3. Direct Compression Method

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 PDA, 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.

Releases of Drug from directly compressible formulations and from MCG 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. s formed using compressible formulation are 10 times harder and crumble when pressure is applied resulting in faster release than conventional methods.

**In-vitro Drug Release Testing**

**A. FACTORS AFFECTING RELEASE OF ACTIVE INGREDIENTS**[^8,10]

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[^6].

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[^2].

**In-vitro Release Of Drug From Mcg’s**[^10,11,12]

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 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 temperature of the chamber can be maintained at $37\pm0.5^\circ\text{C}$ 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.

**THERAPEUTIC USES**

1. 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.
2. It has been proved that chewing non-s increases plaque pH, stimulates saliva flow and decrease decay.\[^{14}\]
3. MCGs containing Chlorhexidine for treatment of gingivitis and plaque has been available.
4. The use of MCG in the treatment of oral infections has also been reported.
5. 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.
6. MCGs are also useful delivery system for agents intended for systemic delivery.
7. Drug that is released from MCGs within oral cavity can be absorbed via buccal mucosa.
8. 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 diseases.
9. Oral diseases are prevented or cured with MCG.

Medicated Chewing Gum provides a vast number of competitive advantages:

1. **Well-being**
   - Beneficial to patients who have difficulty in swallowing tablets.
   - Improved oral hygiene and a fresh feeling in the mouth.

2. **Convenience and lifestyle**
   - A perfect fit with a busy and socially oriented lifestyle.
   - Administration without water; can be taken everywhere.
CONCLUSION
Medicated chewing gum is a Novel Drug Delivery System (NDDS). The Medicated chewing gum compositions includes: A Gum base component; Water soluble sweetener component such as sucrose, sorbitol, xylitol, alone or in combination with intense sweeteners such as saccharin or aspartame, Emulsifier such as lecithin, Plasticizer such as corn syrup, hydrogenated corn syrup, Coloring agents, Antioxidants, Softeners, Waxes; for example, natural and synthetic waxes, Mineral adjuvants such as calcium carbonate, magnesium carbonate, Preservatives: For example, titanium dioxide and other dyes, High intensity sweetener, Flavorant.

The gum base will be present in amounts from about 5% to about 94%, by weight of the final chewing gum composition.

The development costs of new active pharmaceutical ingredients have increased dramatically and pharmaceutical companies are currently intensifying their focus on new initiatives to achieve maximum profit from their products and brands.

A cost effective way to generate increased revenue is line extensions based on new pharmaceutical formulations.

REFERENCES
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