Review Article

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MEDICATED CHEWING GUMS: A REVOLUTION IN SELF-MEDICATION AND DRUG DELIVERY

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Abstract :

Medicated chewing gums (MCGs) are characterized as 'solid single-dose preparations with a base consisting mainly of gum that is intended to be chewed but not to be swallowed, providing a slow steady release of the medicine contained'. The European Pharmacopoeias (Ph. Eur) along with the U.S. Pharmacopoeias (USP) formally acknowledged medicated chewing gums as an acceptable method for medication administration. MCGs have become a new and exciting method in the realm of oral drug delivery. The potential benefits of chewing gums over conventional drug delivery method are examined in this review paper. Notable benefits include the circumvention of hepatic first-pass effect, patient compliance, local and systemic action, and various other advantages that make them an exciting alternative in pharmaceutical research. This comprehensive review paper covers all essential aspects related to medicated chewing gums, including their composition, advantages, disadvantages, methods of preparation, and future trends. It also underscores the potential of medicated chewing gums as a useful substitute to buccal medication delivery and emphasizes the need for further exploration and research in this field.

Key Words: Medicated Chewing Gums, Buccal Administration

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. Introduction

Oral drug delivery is convenience, so patients favour this mode of administration. Nevertheless, it has intrinsic disadvantages, such as hepatic first-pass metabolism and GI tract enzymatic degradation, which restrict its use for specific drug classes. Bio-adhesive buccal drug delivery offers an alternative route for drugs susceptible to first-pass effects. This approach capitalizes on the sublingual and buccal routes within the oral mucosal cavity, addressing many challenges associated with oral administration. The sublingual and buccal routes offer several advantages, including ease of access, the resilience of the epithelium, the ability to use the dosage form as needed, reduced susceptibility to

enzymatic degradation, rapid recovery from stress or mucous membrane damage, and the capability to discontinue drug absorption in the event of toxic effects by removal from the buccal cavity. The administration of medication through the cheek mucosa, or mucosal membranes, is known as buccal delivery 1. The buccal mucosa is highly vascularized, and blood flows directly into the jugular vein. Oral mucosal routes are better for drugs that are hydrolysed in the stomach or heavily metabolized in the liver because they avoid the GI tract and the hepatic first-pass effect. These routes also have the advantage of having a heavy blood supply, greater bioavailability, lymphatic drainage, and direct access to the systemic circulation. If a drug delivery system is made to be mucoadhesive, the thin mucous film that covers the oral mucosa's surface can offer a way to keep the drug delivery system in touch with the mucosa for an extended amount of time. Nonetheless, the mouth cavity presents several difficulties for systemic medication distribution. Various reasons such as a moist environment, oral cavity covered with mucus, and constant bathing in saliva, etc make it critical to formulate and hence there are not many sublingual/buccal delivery products available in the market 1–3.

Table 1. Advantages and disadvantages of buccal/sublingual delivery systems.

ADVANTAGES	DISADVANTAGES
1)Moderate permeability and accessibility.	1)Mucus in the oral cavity can be a barrier.
2)Less enzymatic activity	2)The surface area of the sublingual region is 26.5cm2 and that of the buccal region is about 50.2cm2 which is less for absorption.
3)Releases drugs in a controlled manner	3)The continuous secretion of saliva dilutes the drug and potentially leads to loss of dissolved drug.
4)Provide the drug in a unidirectional way	4)Choking or swallowing the drug can be a concern.
5)The formulation and drug remain in oral cavity for an extended period.	5) Patients generally do not prefer this route of administration because to its unpleasant taste and odour.
6) Food or the rate at which the stomach empties have no effect on the rate at which a medication absorbs.	6) Long-term utilisation of this technique with acidic or generally burning medications and fillers can cause tooth staining.
7)Dosage form localization is easy and facilitates ease of removal without significant associated pain and discomfort. Dosage form localization is simple and makes removal easier without causing a lot of pain or suffering.	
8) Drugs can have their systemic availability increased by adding permeability enhancers to their formulation.	

Innovative formulations and technologies have emerged as significant contributions in the realm of pharmaceutical research, offering multifaceted benefits to patients. A distinguishing trait of these formulations is their user-friendliness, rendering them particularly appealing. Oral-based chewy delivery is emphasized as a viable choice because of its unique qualities, which include quick onset of action, convenience of administration, fewer side effects, and better local impact on oral disorders. Despite several advantages, medicated chewing gum (MCG) is not gaining popularity due to the difficulty of its formulation, the lack of standardized testing methodologies, and the intricacy of its manufacturing. Chewing gum is increasingly becoming recognised as a medication delivery strategy that is seeing significant advancements in contemporary times.

The Committee for Medicinal Products for Human Use (CPMP) published guidelines for pharmaceutical dosage forms in 1991, which define MCGs as "solid single-dose preparations with a base consisting mainly of gum that is intended to be chewed but not swallowed, providing a slow steady release of the medicine contained." The European Pharmacopoeia (Ph. Eur) and the U.S. Pharmacopoeia (USP) have formally acknowledged medicated chewing gums as an acceptable method of medication administration. .

Medicated chewing gums offers a promising solution to these challenges by capitalising on the strengths of both traditional drug delivery methods. Both sublingual/buccal tablets and chewing gum share the advantage of bypassing the first-pass effect, enabling drugs to enter the bloodstream directly. While buccal and sublingual tablets have a surface area of approximately 50cm2 and 30cm2, which limits absorption, the entire buccal cavity offers an extensive surface area of around 170cm2, facilitating enhanced absorption and thereby mitigating the first-pass effect limitation. Moreover, chewing gum's size reduces the risk of unintentional swallowing, and the act of chewing provides an additional driving force for absorption, further improving drug delivery. Furthermore, sublingual and buccal tablets typically contain lower doses of drugs, whereas chewing gum formulations can accommodate higher doses, addressing the issue of drug dissolution loss. Even if some drug is lost due to saliva, a higher dose can still be maintained to achieve the desired therapeutic effect. There are various methods like ion- exchange resin complexation, weak cation and anion exchange, and cyclodextrin complexes used to not only conceal taste but also increase solubility . Another notable advantage of medicated chewing gums is their simple gum/polymer base, which minimises irritation associated with long-term use. In summary, medicated chewing gum appears to be a versatile and effective approach to overcoming these drug delivery challenges. This review paper explores the diverse applications of medicated chewing gum, with a particular emphasis on its potential utilization as an alternative to buccal tablets in drug delivery strategies.

2. Composition of MCGs

The composition of MCG encompasses a blend of natural and synthetic, comprising a water-soluble components and water-insoluble gum bases. They primarily consist of a tasteless masticatory gum base as the core with small amounts of non-masticatory additives like flavours and sweeteners. In this composition sweeteners play a pivotal role in incorporating bitter drugs. Sugar sweeteners such as sucrose, dried inverted sugar, sorbitol, saccharin, and other components are added up to 30-60% combined with high-intensity

artificial sweeteners, and flavouring ingredients to accomplish taste masking. Use of aqueous sweeteners such as sorbitol, corn syrup and hydrogenated starch also help the product retain moisture, freshness and plasticity. The gum base itself is constructed from a combination of natural gums, latex, plastics, solid kinds of paraffin, and beeswax as a non-nutritive part of MCG. Elastomers, which are polymers chosen for their capacity to confer elasticity, are introduced in varying proportions depending on the specific formulation, enhancing the flexibility of the gum. Natural and synthetic elastomers both are added in appropriate proportions depending on the formulation. Emulsifiers, included in the formulation, facilitate the dispersion of two immiscible phases, enhancing the softness of the gum and its ability to form bubbles during chewing. It contributes to maintaining consistency and softness throughout the product's shelf life and the hydration effect while chewing. To render the gum user-friendly and pliable, plasticizers are utilized, thereby enhancing the texture, reducing brittleness, and softening the elastomers. Rubber is incorporated in the formulation to bind elastomers and texturizers together effectively. Other ingredients used are flavouring agents, colourants, antioxidants, anti-caking agents, and anti-tack agents to enhance the properties .

3. Advantages of MCGs

The major advantage is in protecting the medications that are sensitive to enzymatic or chemical attacks within the gastrointestinal tract (GI). Chewing gum has a low first-pass impact, hence a lower dosage is formulated, which sets it unique from other oral administration methods. Increased rate of effectiveness and utilization for systemic and local drug delivery. Gum may be easily removed at any moment to provide a lower possibility of overdose, and MCGs also lessen the chance of the gastrointestinal mucosa becoming intolerant. It is sufficiently robust against oxygen, light, and moisture. Treatment for xerostomia and assistance with swallowing and taste for those with dry mouths. Minimizes discomfort and swallowing issues after tonsillectomy. Enhancing blood flow to the brain to stimulate attentiveness. Also, product distinctiveness from a marketing perspective.

Table 2. Applications in local and systemic therapy

Applications in local therapy	Applications in systemic therapy
To practice good oral hygiene	For treating mild headaches, pains, and aches in the Muscles
For the treatment and control of oral illnesses	Nicotine-containing chewing gum formulations for smoking cessation
Prolong effect as the rate of release can be controlled	As chewing gum reduces food cravings, it can be used in treating obesity. Due to their shown potency, active substances including guarana, caffeine, and chromium and therefore generally used in the formulation.

Gums containing fluoride have been shown to be beneficial for adults and children with xerostomia avoid dental cavities.	Medicated chewing gum can be used to treat a variety of conditions, including xerostomia, allergies, nausea from motion, acidity, cold and cough, diabetes, depression, and others.
Chewing gum containing chlorhexidine has benefits in treating oral, pharyngeal, and gingivitis.	
In chewing gum formulation, the unpleasant taste of chlorhexidine can be adequately encapsulated	
It can also be used to prevent the formation of plaque.	

4. Techniques of manufacturing MCGs

The following different methods are used for manufacturing of chewing gums:

1. **Fusion method**: First the gums are melted to 60°C and then transferred to the high-shear mixer. To this softened base, other ingredients are added along with slow cooling. The final step after cooling is rolling and cutting gums in the desired shape and size. This process can be modified for sugar-containing gums. Here the first step is the addition of corn syrup to gum bases in sigma blade mixers and then fine powder of sugar is mixed followed by plasticizer ad other ingredients 5.

2. **Cooling, grinding and tableting method:** One of the common methods is, mixing all the components and then cooling them by freezer apparatus or carbon dioxide as coolant of temperature -15°C. They are then crushed and ground using a grinding equipment to produce smaller particles. As the temperature rises and coolant is removed these fine particles adhere and form chewing gums . Additionally, it is described as a cooling, milling, and tableting procedure in certain literature .

3. **Direct compression**: The first step is to add dry gum base and granulating agent (most preferably sorbitol) together in a mixer. Then all the other ingredients are added to the formulation in powder form and further directly compressed. Lubricants and anti-adherents are used to avoid sticking to die and punches.

Many recent manufacturing processes are patented based on the one-pot process, the addition of sugar in different steps, etc. Recent advancement in technology allows us to manufacture medicated chewing gums by the innovative technique of 3D printing .

Ion exchange complexation, cyclodextrin complexation, and microencapsulation are also being used for MCG manufacturing .

5. Evaluation studies for MCGs

Oral mucosal administration of drugs is often exposed to systemic circulation with a fast onset of action. This expectation coincides with the observation that drugs are usually absorbed rapidly into the oral mucosal membranes, given the brief period they spend in the oral cavity, which typically lasts only around 5 to 10 minutes. However, there is a difference in rapid clearance of the drug from the oral cavity and rapid systemic exposure. After the solid product enters the oral

cavity, it's preferable for it to rapidly disintegrate within the mouth, leading to the formation of a solution that can be absorbed by the mucosal membranes. This allows the drug to eventually enter the systemic circulation. However, it's important to note that some of the drugs may be lost from the oral cavity due to swallowing. This potential loss can happen at any stage, starting from when the formulation enters the oral cavity which subsequently disintegrates into a solution. The process is also influenced by saliva excretion, which plays a significant role in these drug-delivery systems .

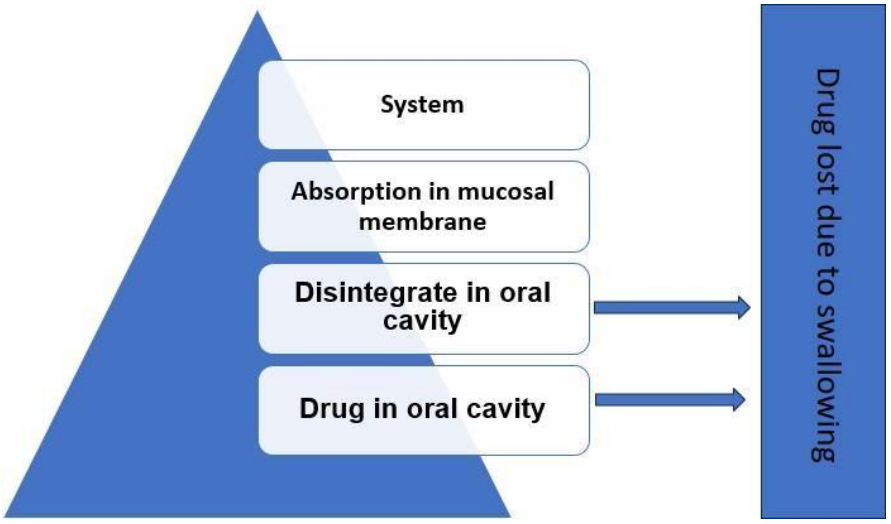

Figure 1. A typical drug concentration profile in the blood

5.1 Weight uniformity

The weight variation test is carried out by selecting twenty MCGs randomly. They are weighed individually. No more than two single masses should fluctuate the average mass [5].

$$\frac{Individual\ weight\ of\ gum}{Average\ weight\ of\ 20\ gums} \times 100 \quad \ldots (1)$$

5.2 Content uniformity

Ten MCGs are selected randomly to evaluate content uniformity. In order to ensure the uniformity of dosage units in a single-dose formulation, their contents are measured using appropriate analytical techniques. The average medication concentration for each piece of gum should be between 85 and 115%. [5].

5.2 Friability test

To assure the friability of medicated gums, ten samples are randomly selected. De-dusted carefully before a test, then loaded to the tester to rotate at 25 rpm for 100 times. Then finally weighed by de-dusting again. The difference in weight must be less than 1%.

$$F\% = \frac{W_{intial} - W_{final}}{W_{intial}} \times 100 \quad \ldots (2)$$

Where F% is the friability percentage

W_{intial} is the weight before testing

W_{final} weight after testing

5.2 Plasticity and elastic recovery

Chewability is a crucial MCG characteristic. To measure applied forces and distance, strain gauges and displacement transducers are fitted. Elastic recovery is driven by bonding forces and elastic

energy stored in particles during densification. Plasticity evaluates deformability under compression, and the least elastic recovery value is preferred. These characteristics may be computed using the force-displacement curve. The measuring of the force-displacement curve using a direct compression approach is one of the widely used techniques.

$$E_1 = \frac{max}{2} - (E_2 + E_3) \quad F \quad C \quad \ldots (3)$$
$$B$$

$$E_2 = \int_A F_{upper}\, ds - E_3 \quad \ldots (4)$$

$$E_3 = \int_B^D F_{upper}\, ds \quad \ldots (5)$$

$$Plasticity = \frac{E_2}{E_2+E_3} \times 100 \quad \ldots (6)$$

Where F_{upper} is maximum force measured on upper punch

F_{max} is maximum force during compression

C is displacement

E_2 is effective work done

E_3 is elastic recovery

And A, B, D are positions of upper punch.

5.1 Tensile test

This test determines the load necessary for elongation prior to the detection of fracture. Tensile strength, yield strength, and fracture strength are the metrics that were measured in this test using stress-strain curve. The stress and strain are obtained by the following formulas which are further used to obtain the other parameters -

$$Tensile\ strength = \frac{Load\ taken\ to\ break\ (in\ N)}{Cross\text{-}sectional\ area\ (in\ mm^2)} \quad \ldots (7)$$

5.1 Stability

Chewing gums are stable and less reactive. It also protects the active ingredients from oxygen, light, and humidity. However, the major challenge in manufacturing is its storage conditions, shelf life, and impact of some compounds that affect the stability. To limit light exposure, water and moisture infiltration, proper packing and storage are required.

5.2 Dissolution test

The degree and rate at which a dosage form dissolves are determined by dissolution testing. Traditional dissolution testing equipment designed for regular tablets or capsules is inadequate for testing Modified-Release Chewing Gums (MCGs) due to their unique characteristics, specifically the need for a specialized device replicating human chewing behaviour. Unlike conventional dosage forms that are swallowed, MCGs are masticated. The MCG is introduced into the chamber, with the apparatus calibrated to simulate the average person's chewing rate of 60 strokes per minute. Once the machine ceases operation, the gum is transferred to a prepared sample of dissolving liquid, and the quantity of the Active Pharmaceutical Ingredient (API) is quantified using a suitable method. After three iterations, the concentration of the active agent is determined, enabling the assessment of the dissolution rate.

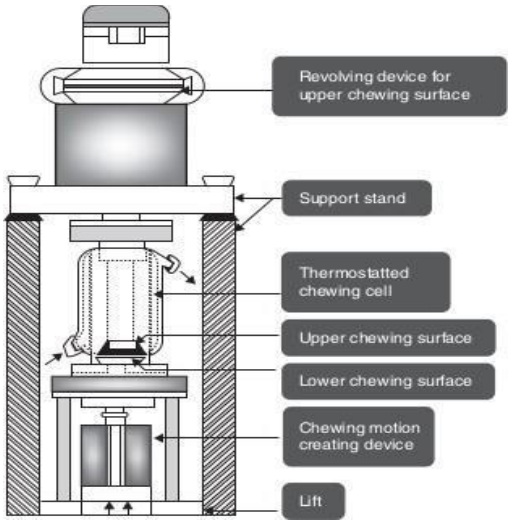

Figure 2. Schematic representation of single module chewing apparatus (unofficial).

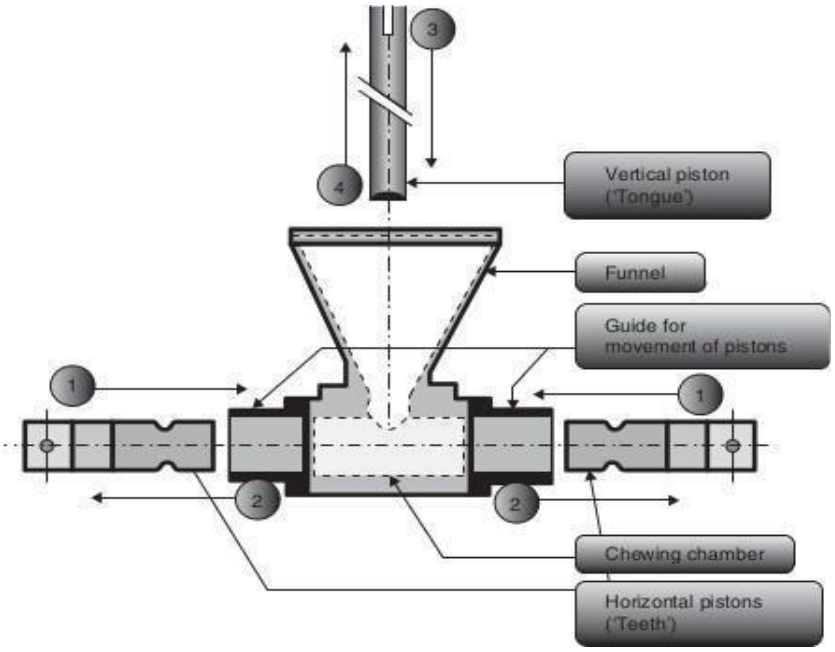

Figure 3. Schematic representation of modified dissolution apparatus as per European Pharmacopoeia, where numbered arrows indicate sequence of motion.

6. Future trends

Medicated chewing gums, while already offering significant benefits due to attractiveness, patient compliance, and effective drug delivery technique, present a field of research that warrants comprehensive exploration. The manufacturing of optimal drug administration through chewing gum can greatly benefit patients and influence both buccal absorption and the business landscape. Medicated chewing gums have evolved beyond their initial application for smoking cessation and are now marketed for a variety of biological action. Nicotine chewing gum is the best example for right formulation can significantly influence market. Medicated chewing gums have evolved into versatile means of delivering various substances, including caffeine for increased alertness, fluorides for dental health, chlorhexidine for addressing tooth decay, dimenhydrinate for combating motion sickness, and Calcium carbonate for neutralizing stomach acid .

Recent research has ameliorated this area which results in several patents for products, manufacturing processes of medicated chewing gums. Future developments may lead to the formulation of numerous other drugs through this route of administration, with biodegradable chewing gums representing a trendy product on the horizon. The studies have proved that Chromium picolinate supplements helps to reduce high insulin levels by acting on insulin receptors. There are already products available in the market for managing minor heachaches, pains and muscle aches. Additionally, medicated chewing gums, in addition to their anti-fungal and anti-microbial properties, medicated chewing gums have also demonstrated effectiveness as an anti-plague solution. With recent technological advances in technology, chewing gums are developed containing probiotics. Nausea and vomiting are symptoms of pathophysiological diseases such as mobility, cancer, and pregnancy which can be treated by this delivery effectively. Nanotechnology can enhance bioavailability due to their uptake through buccal cavity. Medicated chewing gums have wide range of applications in orthodontic process, anaesthetics, and teeth whitening agent.

Chewing gums are not only used for therapeutic purposes but are also employed in the realm of psycho- spirituality. Many botanical plant extracts are used to enhance mindfulness and provide nourishment. In a testament to the versatility and innovative potential of this field, medicated chewing gums can now be manufactured using three-dimensional (3D) printing technology through semisolid extrusion. Further research can also be done in using medicated chewing gums for treatment of cancer like diseases. As new innovative techniques and applications are emerging, the realm of medicated chewing gums will maintain its appeal to consumers.

Table 1. List of drugs given by buccal cavity and their applications

Drugs	Application
Esomeprazole, omeprazole	Gastroesophageal reflux and pump inhibitor
Norethindrone and ethinyl oestradiol	Birth control
Indomethacin	Acid secretion, cramps, diarrhea, water retention
Ranitidine, cimetidine, famotidine	Non-steroid anti-inflammatory drugs
Cetirizine cyclotrimer complex	Anti-histaminic, mouth dryness
Chromium picolinate	Insulin levels
Chromium guaran, caffeine	Obesity
Pilocarpine, cevimeline	Xerostomia
Chlorhexidine, Xylitol	Gingivitis, periodontitis, and pharyngeal infections
Sulfonylurea, Metformin, Insulin spray	Diabetes
benzodiazepines	Anxiety, depression
Miconazole	Anti-fungal
	Anti-bacterial, anti-microbial
Chlorine dioxide	Teeth whitening
Lactobacillus acidophilus etc	Probiotics
Lidocaine, prilocaine hydrochloride	Anaesthetics
Cannabinoid based	Nausea, vomiting with chemotherapy
Calcium carbonate	Acid neutralization
Fluoride	Cariostatic
Chlorhexidine	Tooth decay
Dimenhydrinate	Motion sickness
Aspirin, Ranolazine	Angina

Conclusions

Simplicity of administration without the need for water, and improved patient suitability make medicated chewing gums an exceptional choice for self-medication. The application of MCGs is anticipated to increase to encompass a wider variety of therapeutic categories with the development and adoption of new assurance and inspection methods by pharmacopoeias. With their nicotine gums,

antihistamine gums, motion-sickness gums, nutraceutical and multivitamin gums, and weight management gums, MCGs have already begun to effectively capture market share. Clinical studies have shown the advantages of chewing gum as a medication administration method, highlighting its practicality, convenience, potential for buccal absorption, and local therapeutic effects. In summary, this review underscores the transformative potential of medicated chewing gums as drug delivery and paving the way for a brighter and more informed future in this field of study.

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