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AN EMERGING TECHNIQUE OF MEDICATED CHEWING GUM IN DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
Many advances in research and technology have been made in the oral route of drug delivery system in recent years. Because of increased patient compliance not only in geriatric and paediatric patients, but also in the general population, the oral channel of drug delivery system- medicated chewing gum has received worldwide recognition throughout the year. Chewing gum can be used as a mobile medication delivery device for both local and systemic drug administration via the oral route. Because of its ease and ability to be administered without water, it is an exceptional drug delivery device for self-medication. The production technique, advantages, disadvantages, factors impacting the release of medicament, assessment parameter, difficulty related with chewing gum manufacture, and future trends have all been examined in this review paper

INTRODUCTION

Drugs can be delivered in a variety of ways to provide a systemic pharmacological impact. The oral route is the most convenient and widely used way of medication administration. There are a variety of dose forms that can be taken orally, the most common of which is medicated chewing gum [1].The European Pharmacopoeia and the Committee for Medicinal Products for Human Use (CPMP) issued guidelines for pharmaceutical dosage forms in 1991, defining medicated chewing gum as "solid single dose preparations with a base consisting primarily of gum that are intended to be chewed but not swallowed, providing a slow steady release of the medicine contained"[2].

Mobile drug delivery system is another term for medicated chewing gum. As proven by nicotine gum, the correct delivery system can have a substantial impact on success by giving product differentiation in the market. A new drug delivery system is likely to provide additional patient benefits such as discrete and convenient administration, as well as the potential for buccal absorption, resulting in a quick commencement of action [3].

The residual mass of a pharmaceutical chewing gum must be thrown after it has been chewed for the required time period to deliver the dose. The medicine, which is mixed into the gum

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base, is released into the saliva and absorbed through the oral mucosa, or ingested and subsequently enters the stomach for gastrointestinal absorption, during the chewing process. Chewing gum causes people to be more attentive, awake, and at ease, according to empirical evidence collected in multiple studies [4].The first medicated gum to hit the market was Aspergum (acetylsalisylic acid). Following the introduction of nicotine chewing gum in the 1980s, MCGs have become the preferred choice for nicotine replacement treatment[5][6].MCGs are currently recognized as official drug delivery systems by the European (Ph. Eur) and United States Pharmacopoeias (USP)[7].MCGs have been used to administer anti-allergic, nicotine, anti-emetics, aspirin, caffeine, and nystatin to prevent oral cavity, motion sickness, aid with cigarette cessation, analgesic, and to treat oral fungal infections, according to numerous scientific studies [8].

Advantages of Medicated Chewing Gum:

i. By avoiding hepatic first-pass metabolism, medicines' bioavailability is increased [9].
ii. The controlled release of active ingredients lowers the side effects, as high plasma peak concentrations are avoided [10].
iii. The rapid commencement of systemic impact can be attributed to the rapid release of active components into the buccal cavity, their absorption through the buccal mucosa, and subsequent absorption in the systemic circulation [11].
iv. Dry mouth is a possible side effect of certain medications, such as antidepressants, and to combat the dryness in the mouth, a medicated chewing gum has been developed that increases salivary secretion [12].
v. Chewing gum has been widely utilized for the treatment of oral disorders such as mouth ulcers, poor breath, dental plaques, fungal infections, and in the throat because of the prolonged exposure of the drug into the diseased area due to the sustained release of active components from the formulation [13].
vi. Because it is simple to administer and does not require water for swallowing, patient compliance is higher [12].
vii. Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa [13].

Disadvantages of Medicated chewing gum:

i. Sorbitol, which is included in MCG formulations, might induce gas and diarrhea [14].
ii. Flavoring agents (cinnamon) have been shown to cause mouth ulcers, and Liquorice has been shown to promote hypertension in mice [15].
iii. The intraoral use of chlorhexidine has been limited for a short duration due to the unpleasant taste and staining qualities [16].
iv. Gum chewing can cause enamel dentures and fillings to stick together [17].
v. Chewing gum for an extended period of time might cause ocular muscle pain and earache in children [18].

COMPOSITION OF MEDICATED CHEWING GUM

Medicated chewing gum is a mixture of natural or synthetic gum, resins, coloring agent, sweetening agents and flavors.

Basically, chewing gum has two parts

i. Water insoluble gum base part
ii. Water soluble bulk portion

i) Water insoluble gum base consists of :

a) **Elastomers** (40-70% by weight of gum base): It is a polymer with a high elongation property that is used in the preparation to provide the chewing gum flexibility and manage the gluey texture [19] [20].
b) **Plasticizers** (3-20% by weight of gum base): It's a substance used in chewing gum formulations to give it softness and make it more user-friendly. It improves gum quality by adding plasticity, reducing brittleness, and softening elastomers [21] [22].
c) **Fillers or texturizers** (2-60% by weight of gum base): It adds texture to the overall look and makes blending and other operations easier [10].

ii) Water soluble part consists of :

a) **Softeners and Emulsifiers**: Emulsifiers are used to help two immiscible phases mix, and softeners are used to improve the softness and ability to create bubbles[23].It aids in mixing and softening during shelf life, as well as providing moisture while eating medicated gum for a better mouth feel. Glycerin, lecithin, and fatty acids like stearic acid, palmitic acid, oleic acid, and linoleic acid are often used softeners [24].
b) **Bulking agents:** When a powerful or low-dose medicine needs to be integrated into the formulation, bulking agents are used to achieve the desired bulk of chewing gum. As a bulking agent, low-calorie gum is favoured, especially among health-conscious and diabetic individuals. Guar gum

hydrolysates, indigestible dextrin, polydextrose, inulin, oligofructose, and fructooligo saccharides are examples of low-calorie bulking agents [25].

c) **Coloring agents:** Colors approved by the United States, FD&C, are utilized. Pigments are added to the chewing gum composition at a rate of about 6% by weight, and titanium dioxide is added at a rate of about 2% by weight. In addition, natural culinary colors and pigments are used in the chewing gum composition [26].

d) **Sweetening agents (50-65% of gum base):** These ingredients are used in prescription formulations to improve taste and disguise the bitterness of some medications [27].

e) **Flavoring agents** e.g., synthetic oils and essential oils like peppermint oil, citrus oil, clove oil, anise oil, spearmint oil [28].

MANUFACTURING PROCESS OF MCGS

Medicated chewing gums are manufactured under GMP guidance. There are three main methods for the manufacture of MCGs. They are;

1. Traditional or conventional method
2. Cooling, grinding and tableting method
3. Direct compression method

1. Traditional or Conventional Method (Melting/ Fusion method):

Sweetening agents, syrups, active pharmaceutical substances, and excipients are added to a mixer after the components of the gum base are softened or melted at around 60°C. The gum is then pushed through a succession of rollers to create thin, wide sheets that resemble ribbons. During the manufacturing process, the gum is covered with finely powdered sugar or sugar alternatives to improve the flavour and prevent the gum from sticking. The gum is then maintained in a controlled environment for 48 hours to allow it to set correctly. The gum is then sliced to the correct size and allowed to cool at a controlled temperature and humidity at the end of the manufacturing process [29][30].This technique can also be carried out in the following manner: If a sugar-containing gum is required, the first stage in the preparation is to set up a mixer (the mixer might be a sigma blade or other types of mixers). If a sugar-containing gum is required, the first step is to add corn syrup to the mixer, followed by the addition of finely powdered sugar. Powdered sucrose, dextrose, fructose, corn syrup solids, or a combination of these sugars can be employed. Modification of texture and management of cohesiveness can be accomplished with the addition of sweetening and plasticizing chemicals. The most common plasticizer is glycerin. Other ingredients, such as bulking agents, colouring agents, and flavouring agents, can be added to the formulation as needed. Because most flavouring agents are highly volatile, it's best to use them only after the gum base has been completely homogenised at the end of the formulation process [31][32].The softening process may be aided by the mixer's force, such as compressive, shear rate, and heat provided. When there is no need for heat, a higher power is required. Continuous mixing of the gum base and other ingredients should be done until a homogeneous mass is formed, and the procedure should be sustained for at least 8 minutes [33].After forming the matrix and thoroughly mixing it, commercially prepared gum base particles are immediately added into the chamber, and mixing is continued for around 10-20 minutes [34].This method differs from the traditional method due to the mixing technique. In this method, the sweetener matrix is generated first during the mixing process, and then pellets of gum base are added, whereas in traditional methods, the sweeteners, along with other components, are added to the molten gum base. The advantage of this new method over the old method is that it has a decreased tendency to form sugar lumps. Particles must be heated and blended before adding other ingredients to the formulation [35].

Limitation: The melting of thermo-labile pharmaceuticals requires a high temperature, which can be difficult to achieve. If the gum is extremely viscous, precise dosage is impossible. There is a lack of precision in the dosage form, shape, and weight. Chewing gum is difficult to make into tablets due to the higher moisture content [36].

2. Cooling, grinding and tableting method:

Cooling: The gum base is cooled to the point where the composition is suitably brittle and will remain brittle. The temperature of a refrigerated combination is usually approximately -15°C or less. Liquid nitrogen, hydrocarbon slush, and solid carbon dioxide are among the main cooling agents [9].

Grinding: A chewing gum component, solid carbon dioxide, and precipitated silica are pulverised in a mill grinder. To prevent gum from sticking to the grinding apparatus, 2 to 8% by weight of a grinding aid such as alkaline metal phosphate, alkaline earth metal phosphate, or maltodextrin is added [11].

Tableting: After the coolant has been removed from the powder, it can be blended with other substances such as binding agents,

lubricating agents, coating agents, and sweetening agents [12].The granules can then be combined with anti-adhesive substances such as talc. The compression of chewing gum is done using a traditional method such as punching [17].

3. **Direct Compression Method:**

The direct compression method is used to make chewing gum tablets, and it uses specifically engineered compactable gum components in the form of powder. The active medicinal component, sweetening agent, and other essential ingredients are combined into the formulation in free flowing form and then it is directly compacted into chewing gums in the first phase [30] The temperature should not be elevated above the gum base's melting point. After achieving a constant and smooth mass, the temperature can be reduced to allow for the inclusion of further formulation ingredients [11].Directly compressible gums are needed to speed up the production of medicated chewing gum. The use of immediately compressible chewing gum excipients in the formulation may be able to circumvent the gum base's melting and freezing limits. The active ingredient in the compressed chewing gum tablet can be released into the buccal cavity. The rate of dissociation reaches its peak after 2-10 chews [37].

Factors affecting the release of active ingredients: There are different factors which affects the release of drug from the MCGs.

i) The amount of active medicinal substances released by MCG differs between two people. Chewing gum's medicinal effect is determined by how it is chewed. Chewing strength, frequency, and duration vary from person to person, resulting in a wide range of consequences. The average chewing speed is 60 chews per minute [10].
ii) The rate of release of active substances is determined by the content and the gum base. If the lipophilic proportion of gum is raised, the rate of release will be reduced [9].
iii) Physicochemical features of active ingredients: An active ingredient's release rate is determined by the solubility of the active medicinal component in saliva and water. Extremely hydrophilic substances are released entirely in 10-15 minutes, but highly lipid-soluble drugs are released first into the gum base and subsequently into the saliva [37][30].
iv) Water solubility: If the active pharmaceutical ingredient is soluble in water, it will release faster than other active pharmaceutical ingredients that are only slightly soluble in water and lipid because they are bound to lipophilic substances and gum bases, resulting in a slower drug release into the oral cavity [30].

EVALUATION PARAMETER OF MEDICATED CHEWING GUM

There are different evaluation parameters for medicated gum

i) **Physical appearance**: We examine several batches of the product and visually inspect it for organoleptic characteristics such as appearance, colour, odour, and taste. The texture research is also done physically, with the gum being pressed between the thumb and finger and graded on its quality [38].
ii) **Determination of content uniformity**: Ten MCGs are chosen at random from the same batch and their contents are measured; if all of the products are within the range of 85 percent to 115 percent of an average content, the test will pass; nevertheless, if one single preparation is outside of this range, the test will fail [30].
iii) **Elasticity study**: Chewing gum's elasticity is one of its most important qualities. Elasticity is important for better patient compliance as well as proper release of the active ingredient from the product [37].
iv) **In-vitro drug release study:** The medicated chewing gum's dissolving research is considerably different from that of other traditional dosage forms. The patient's chewing ability and oral health have an impact on the active component release from the dose form [38].The mechanical chewing device, which is a self-fabricated gadget that mimics human chewing action, is used to release active chemicals from medicated chewing gum. The device is made up of a chamber for the releasing medium and a piston that impacts the chewing gum in a random pattern. Gum is kept inside the compartment, where the horizontal piston retains the medicinal gum in place while the vertical piston chews it. To set the pH, phosphate buffer is employed instead of saliva as the releasing medium. Warm water is circulated around the chamber to keep the temperature consistent. The piston strikes the gum at a rate of 60 beats per minute [39][40].
v) **Stability study:** Chewing gum is thought to be a fairly stable product since it has a low moisture content and is less reactive than other oral ingredients. The product's stability is impacted by its shelf life, storage conditions, and the

presence of certain components in the chewing gum [30].A chewing gum normally contains roughly 2.5 percent water. If the water content is too high for the drug's stability, chewing gum can be made with only 0.2 percent water, resulting in a hygroscopic product with a changed texture. Microbial development was suppressed during chewing gum storage due to the low water content of the product [37]. Antioxidants are used in the chewing gum formulation to prevent the oxidation of active medicinal components. Because the water content of the formulation is low and there will be no microbiological development within the formulation, there is no need to add a preservative. Some of the formulation's elements can be encapsulated or coated with the help of suitable substances to eliminate unwanted interaction between the components, allowing for a larger reduction in interaction within the compounds [41].Xylitol may improve the chewing gum's shelf life stability, which means that the water content of the gum remains consistent regardless of temperature, and the gum's flexibility, elasticity, splitting, and softness do not alter significantly. The process temperature of 50-60°C may cause stability problems for some thermo-labile chemicals, such as enzymes, during mixing. Ingredients can be blended at a lower temperature to avoid such issues [42].

Problem associated with the manufacturing of chewing gum

Capping, lamination, picking, and adhering are the most common processing issues associated with chewing gum formulations. The majority of pharmaceutically active chemicals have an unpleasant taste or odour, resulting in an unpleasant chewing gum product. Several active chemicals irritate the mucosal barrier, while others degrade quickly, making them unsuitable for use in the formulation. The gum base is heated in the techniques mentioned above to make combining the ingredients easier. The active components and tastes, as well as the thermo-labile compounds, degrade at high temperatures. Organic solvents are widely used in medicated gum preparations to solubilize the active components, and removing these organic solvents from the end product is difficult. These chemical solvents, even in tiny amounts, can cause health concerns [43].

Medicated Chewing Gum and its Pharmaceutical Significance: It is an appealing, distinct, and competent medication delivery technology, in addition to its scientific advantages. Because of their local and systemic effects on the oral cavity, medicated chewing gums have been widely used. There are various types of commercialized MCGs that are commonly used for allergies, motion sickness, anti-plaque, anti-fungal, stimulant, and other purposes. Chewing gum releases an active component at a controlled rate for a longer period of time, resulting in a local impact that lasts longer [37].

1. Medicated chewing gum, as an oral drug delivery mechanism, is highly useful in the treatment and prevention of motion sickness and nausea [44].
2. Chewing gums that are sugar-free are good for your teeth. The usage of sugar-free chewing gum after meals re-elevates plaque, according to the study. The pH of the mouth is significant in the development of dental caries. As a result, sugar-free chewing gum has been proposed as a supplement to brushing after meals to prevent dental caries [45].

Table 1: Medicated chewing gum and their therapeutic activities

S. No	Therapeutic activity	Example
1.	Smoking Cessation	Silver Acetate, Nicotine [30]
2.	Motion Sickness	Dolasetron, Domeperidone Maleate Chlorpheniramine Maleate [1][2][3][7]
3.	Analgesic	Aspirin(Aspergum)[11]
4.	Acid Neutralization	Antacid [11]
5.	Stimulant	Caffeine(44,45)
6.	Antiplaque & Antibacterial agent	Chlorhexidine gluconate [46] [47]
7.	Anti-oxidant, Antiseptic and healing	Green tea, Aloe-vera [48] [49] [50]
8.	Dental caries	Fluoride [4]
9.	Allergies	Cetrizine [51]
10.	Gingival inflammation	Green tea [48][49]
11.	*Oititis Media*	Xylitol, Chlor-hexidine, Salvadorapersica [52]
12.	Deficiency of vitamin C	Vitamin C [11]

3. Two different formulations of acetylsalicylic acid must be chosen to test bioavailability: a medicated chewing gum and an unbuffered tablet formulation. Chewing gum formulations have been demonstrated to have a higher absorption rate than pill formulations, resulting in faster pain relief [46].

4. A pharmacokinetic study of nicotine gum found that only a small percentage of the released nicotine is absorbed through the buccal mucosa, but instead is ingested and undergoes first-pass metabolism. According to the study, only roughly 80% of the nicotine produced is absorbed by the buccal route [47].
5. Gingivitis, periodontitis, and a variety of oropharyngeal infections may be helped by chewing gum using Chlorhexidine as an active pharmaceutical ingredient. It has been shown to be effective for senior patient dental care and plaque prevention. Furthermore, chlorhexidine in a chewing gum formulation decreases tooth discoloration and is an excellent alternative to chlorhexidine mouthwash. During the chewing process, the released chlorhexidine is equally dispersed into the oral cavity and remains there for a long time. The harshness of the chlorhexidine must be adequately concealed in order to obtain a better gum composition [48].
6. Food cravings are said to be reduced by chromium, which improves blood glucose homeostasis. Chewing gum has been shown to be useful in the treatment of immediate cravings and oral habits. As a result, there is a rationale for including the active moiety in chewing gums that have a tendency to manage weight [49].

FUTURE TRENDS

Chewing gum can contain a variety of medications that might be studied for incorporation. Nicotine chewing gum is an example of a systemic buccal drug delivery device that provides quicker onset of action and bypasses first pass metabolism. Because chewing gum must be kept in the mouth for extended periods of time, flavour retention and taste masking become the most difficult challenges for formulators. Chewing gum's convenience and high adequacy, combined with improved flavour, sweetening, and taste masking, will result in increased patient compliance. New gum base preparations that are compressible, edible, and potentially biodegradable will broaden chewing gum's applications, however the impact of these bases on medication release must be studied carefully. On a product–by–product basis, drug entrapment and release is continuously being developed [50].Chewing gum is a pleasant, distinct, and efficient method of medicine delivery, in addition to being clinically useful. In general, it takes a long time for a new drug delivery system to establish itself in the market and gain patient acceptance; however, chewing gum is expected to assert its position as a suitable and advantageous drug delivery system because it meets the pharmaceutical industry's high standards of quality and can be formulated to achieve distinct drug release profiles[51].MCGs are an appealing delivery strategy because of their ability to be delivered via buccal route, their quick beginning of action, and the potential for product line growth[52].

CONCLUSION

Because of its simplicity, improved patient compliance, and ease of administration without water, chewing gum can be considered an exceptional drug delivery system for self-medication. It can be used for both local and systemic medication delivery. Chewing gum has the potential to become a first-choice medicine delivery method for conditions requiring a quick onset of action, such as motion sickness, nausea, allergy, pain, headache, and infections. In light of the advantages of medicated chewing gum as a novel drug delivery system, such as protection against acids and enzymes, increased alertness and cognitive functions, low first pass metabolism, taste masking of many drugs, smoke cessation, dental caries, mouth ulcer, and so on, we can conclude that chewing gum will gain more acceptance by patients in the future, including geriatric, paediatric, and general populations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Deepika Khatiwara, Priyanka Ranabhat and Moumita Paul designed the work and made necessary corrections and revisions in the manuscript. Arnab Bagchi collected the content and did literature review and also contributed in drafting the manuscript. All the authors framed the final manuscript.

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