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Review Article

MEDICATED CHEWING GUM: AS A NEW GENERATION DRUG CARRIER/DOSAGE FORM

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Abstract
The study and development of oral medication delivery systems has seen advancements in both medicine and technology in recent years. Due to greater patient compliance, not only in geriatric and paediatric patients but also in the general population, medicated chewing gum has attracted attention on a global scale throughout the year. This distribution mechanism for drugs since it is easy to use and works without water, self-medication. The invention of medicated chewing gums (MCGs) heralds a revolutionary new era in oral transportable medication. It is described as a solid single-dose formulation with a base of gum that must be effortlessly chewed for a set amount of time. It may also have more than one active component. Additionally, because the official Pharmacopoeias only suggest a small number of tests, there aren't many assessment parameters available

INTRODUCTION

Chewing gum administration systems are patient acceptable as a result they are practical, simple to use anywhere, anytime, and have a nice flavour. This is a brand-new technique of medication delivery that treats mouth conditions locally or allows for systemic absorption via the oral mucus. The gum base contains pharmacologically active ingredients [1]. It has been grown in popularity as an oral drug transport system [2]. And has shown a benefit as a drug delivery technique for medicinal and nutraceutical compounds in addition to its confectionery function [3]. It is well known that the effective medication delivery mechanism is crucial to a pharmaceutical product's successful outcome. A distinctive drug administration method improves patient welfare, resulting new ambitious benefits for a drug and thus higher sales [4]. It is a unique technique for patient comfort and administering it without water encourages greater amenability and also an ideal formulation because it may be taken anywhere without water [5]. This type of dosage form have various benefits over conventional dosage form, including a quicker onset of action, ability to stop therapy if necessary, reduction in issues with first-pass metabolism and drug degradation in gastrointestinal environments [6]. The intended quality of this type of dosage form is significantly influenced by the component makeup and production processes. Chewing gum decreases gingivitis and periodontal disorders while increasing salivation and plaque and produce additional beneficial effects like increased alertness, heightened awareness and memory, a change in mood, and the law of strain. In 1948, "State of Maine pure spruce gum"—chewing gum first sold commercially—was in the U. S. in 1869, a patent application was made. Although it wasn't marketed, the gum was used as dentifrices. The first medicinal chewing gum was produced in 1928 under the "Aspergum" brand. This dosage form with acetylsalicylic acid is still accessible. Another drug that is available over the counter is dimenhydrinate-containing medicinal chewing gum is for motion sickness. It wasn't until 1978 that nicotine chewing gum, which was acknowledged as a powerful drug delivery mechanism, became commercially accessible. In 1991, the European Council's commission permitted the expression "chewing gum" to refer to a medication dose type [7].

MCG, the most recent technique used in pharmaceuticals, over-the-counter medicines, and nutraceuticals. Due to the active pharmaceutical composition often low solubility in saliva or water, chewing gum is used to treat oral conditions [8]. The remaining mass of gum should be discarded once the necessary length of time has passed for it to transport the dosage. The medicine, which has been blended into the base of the gum, is released into the saliva, absorbed through the oral mucosa, or eaten, and finally enters the stomach for gastrointestinal absorption. According to numerous research, this type of dosage form makes people more alert, relaxed, and focused [9]. This type of dosage form is a suitable candidate for local treatment of oral diseases. By masking the disagreeable smack of the pharmaceutical component, it offers the benefit of an amazing pharmaceutical flavour. The hydrophobic nature of the gum base in the form of chewing gum can further regulate how fast the loaded medicine releases. It is feasible to tune the drug discharge by using the proper approach since the gum bases may comprise both hydrophilic and hydrophobic components [10]. These are also quite beneficial in the therapy of oral cancer, hypertension, and cardiovascular disorders (CVS). Nowadays, it is becoming more popular relating to the

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administration for active principles, even for over-the-counter medications to improve fitness and nutrition. In the local or systemic region, it is more concentrated, targeted, and controlled-release dose form for a longer length of time [11].

DEFINITION OF MEDICATED CHEWING GUM

In a novel method of drug administration known as medicated chewing gum (MCG), masticatory gum is mixed with pharmacologically active substances to treat oral problems locally or to allow for systemic absorption through the oral mucosa. This type of dosage form is seen as a way to give medication or as a way to supply active principles that aid in regaining health and nutrition [12].

It is defined as solid, single-dose reparations with a base primarily made of gum that are intended to be chewed but not swallowed to provide a slow, steady release of the medication contained by the European Pharmacopoeia and the Committee for Medicinal Products for Human Use guidelines for pharmaceutical dosage forms. The medication product is intended to dissolve for a set period of time in the mouth, following which the insoluble gum base is to be discarded [13].

WHY USE MCG AS A MECHANISM FOR DRUG DELIVERY [7]

Gum chewing has special benefits over traditional medicine administration methods:

- Fast onset of movement and excessive bioavailability
- Pleasant taste
- Higher compliance (easy and discreet administration without water)
- Ready to use
- High acceptability among kids.

MERITS

1. Greater efficiency in contrast to alternative oral administration techniques [14].
2. Increasing general and cognitive performance [15].
3. Assistance with swallowing and tasting for persons with dry mouths and the eradication of xerostomia [16].
4. Encourage saliva production in the mouth[17].
5. The treatment may be stopped at any moment, if necessary[18].
6. Reduced discomfort and swallowing issues after tonsillectomy [19].
7. It is used anywhere; administration without water [20].
8. Skips the First Pass Metabolic process increases medication bioavailability as a result. [21]
9. Reduces dental cavities, candidiasis, and dry mouth [3].
10. The stomach is no longer affected by direct contact with large concentrations of active principles, lowering the possibility of gastric mucosa intolerance. [22].
11. Acid plaque that develops in mouth after consuming fermentable carbs is neutralised [23].
12. Tablets of Aspirin and Caffeine demonstrate faster absorption via MCG [24].
13. Highly used by young generations.
14. A percentage of the raw material that makes it to the stomach is transferred with the aid of saliva that is continually and regularly given. As a result, action duration is extended [25].
15. Minute pains, headaches, and muscle discomfort can be treated by gum chewing [26].

DEMERITS

1. It has been demonstrated that chewing gums stick to certain tiers of dental fillings and dentures [27].
2. Merely controlling drug dosage is inadequate. Compared to chewable tablets or lozenges, which might be consumed in higher quantities over a shorter time period, MCGs have a higher risk of overdose [28].
3. CHX oromucosal administration is only allowed for short periods of time as for its unpleasant smack and blemish properties to enamel and the tongue [29].
4. Regular gum chewing can also make kids' ears hurt and their face muscles hurt. [30]
5. Salivary dilution reduces the amount at one location, causing fluctuation [11].
6. The chemicals sorbitol and mannitol practised in the manufacturing of chewing gum may cause flatulence and diarrhoea [31].
7. Dose Dumping.

Table No.1 Marketed Medicated Chewing Gum for Pharmaceuticals and Nutraceuticals

Marketed MCG	Active Ingredients	Indication
Aspergum	Aspirin (acetyl salicylic acid)	Pain relief
Orbit white Happydent white Trident white	Calcium as a tricalcium phosphate	Dental hygiene & for tooth whitening
Fluogum Fluorette	Fluoride as a sodium fluoride	Prevention of dental caries
Niquitincq Nicorette	Nicotine	Smoking cessation
Travvel gum	Dimenhydrinate	Motion sickness
Hexit Vitaflochx	Chlorhexidine	Antibacterial

COMPOSITIONS OF MEDICATED CHEWING GUMS

The main component of chewing gum is a water-insoluble gum base, that is coupled with other ingredients including sweeteners, softeners, food colouring, preservatives, antioxidants, flavouring agents, etc. to create an unflavoured, neutral masticatory gum base [32]. The water-insoluble gum segment and the water-soluble phase are the two components that make up chewing gum (the sugar or sugar alcohol phase) [21]. Chewing gums coatings may contain the third phase. The third stage is taking into account composite materials [32].

Water-insoluble gum phase:

This chewing gum category consists of gum base, fillers, elastomers and plasticizers. Gum base (20–30%), elastomer (10–30%), plasticizer (20–35%), and fillers (0–0.5%) make up the bulk of this part. Normal chewing gum typically has a 20 to 30% gum area, while sugar-free gum typically has a 50 to 60% gum part. The gum section's composition has an impact on the chewing gums' best qualities, including stickiness, chewiness, binding of flavouring ingredients, chewing gum aroma release, etc [33][34].

Gum base

The crucial basic material practised in the manufacture of chewing gum. It may start out naturally or artificially. Natural gum is produced from the chicles of the sapodilla tree. It belongs to the Sapotaceae family and is known by its botanical name, Manilkara zapota. From July through February, during the wet season, Mexico and Guatemala both harvest it [33] The polyterpene units that make up the chicle. This chicle gum isn't usually so inexpensive and difficult to get. It is thus gradually replaced with the aid of synthetic gums such polyvinyl acetate, isobutylene-isoprene copolymer, and basic co-polymer of butadiene and styrene. To assist the transport of medications by chewing gum, gum base is an inert, insoluble, non-nutritive material. [4].

These days, the gum bases that are used regularly contain elastomers, resins, waxes, lipids, and emulsifiers. Frequently, polyisobutene or styrene-butadiene copolymers are incorporated to the elastomers. Wax and polyvinylacetate additions lessen the gum's propensity to stick to teeth ("detackifier") and break into pieces while being chewed ("bite through"). Hydrogenated soybean oil is an example of a partly hydrogenated fatty acid ester softener. Lecithin and glycerol monostearate are emulsifiers that help chewing gum absorb more saliva during the entire mastication process. Other substances that have been added to the chewing gum bases are included in the patent papers. The chewing gum bases' additives might be hydrophilic or lipophilic in nature. Information and experience are essential components needed while creating a medicated chewing gum to choose the appropriate aggregate of compounds that are suited as the drug's delivery vehicle [35][36][37].

Elastomers [38]**:**

Elasticity and sticky texture are controlled by the elastomer. Natural elastomer: Natural rubbers like latex and natural gums like jelutong, lechicaspi, perillo, and chicle are widely used in addition to synthetic elastomers like poly-isobutylene.

Plasticizers [39]**:**

These are employed to control a product's cohesion. These are again separated into Natural and Synthetic categories. Rosin esters such as glycerol esters, partly hydrogenated rosin, polymerized rosin esters, partially dimerized rosin esters, and rosin esters made from pentaerythritol are examples of natural plasticizers. Terpene Resins made from d-limonene and/or -pinene make up synthetic plasticizers.

Fillers [40]**:**

Low dosage medicine gives the gum a lumpy texture, enhances chewability, and offers a tolerable length. Magnesium and calcium carbonate, ground limestone, magnesium and aluminium silicate, clay, alumina, talc, titanium oxide, and mono/di/tri calcium phosphate are among the fillers that are frequently employed.

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Sweetening agents:[41]

There are two categories of aqueous and bulk sweeteners. Aqueous sweeteners including sorbitol, corn syrups and hydrogenated starch hydrolysates are employed to keep the formulation wet to keep it fresh. For binding or softening agent, they will also be used in MCG. Bulk sweeteners further divide sweeteners into nutritious and non-nutritive categories. Between 30% and 75% of chewing gum's makeup is made up of bulk sugar. A healthy sweetener is one that contains either sugar or sugar alcohols.

Softners and emulsifiers:[42]

They are included to enhance the chewability and texture of the chewing gum. Softeners are composed of glycerine, lecithin, hydrogenated tallow, mono-, di-, and tri-glycerides, as well as fatty acids including stearic, palmitic, oleic, and linoleic acids.

Adjuvants:[42]

Useful charging agents include talc, calcium carbonate, and others. Mineral fillers and textural additions including talc, tricalcium phosphate, dicalcium phosphate, aluminium hydroxide, calcium carbonate, and magnesium carbonate are employed.

MANUFACTURING PROCESSES

Different manufacturing methods of chewing gum is broadly divided into three types, including [43]:-

1. traditional/conventional approach (Melting)
2. Tableting, grinding, and freezing.
3. Direct compression

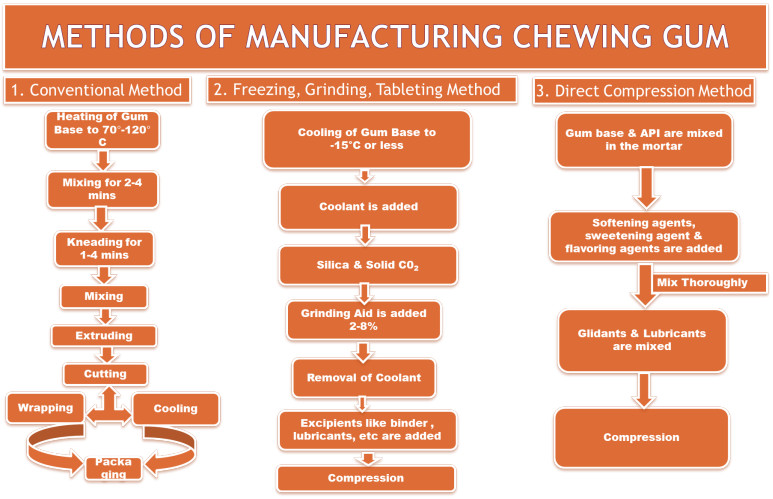

Fig. 1: Flow Chart of Different Methods of Manufacturing Medicated Chewing Gum

Conventional or traditional method: [42]

The components were blended, melted, and pushed through many rollers to produce thin, broad ribbon of gum. During this procedure, a thin coating of finely crushed sugar or sugar alternatives is practised to improve flavour and prevent gum from sticking. The gum is refrigerated in a controlled environment up to 48 hours. As a result, the gum may now fully set. After being sliced into the required lengths, the gum is chilled at a specified humidity and temperature.

Limitations: [44][45]

• The high melting temperature employed in this approach limits its application to drugs that were thermosensitive.

• Controlling the accuracy and uniformity of the medication dosage is challenging due to the melting and mixing of the very viscous gum substance.
• Gum additives may adhere to tools, blades, and punches if their moisture level is between 2 and 8%, and they may be difficult to compress.

Cooling, grinding and tabletting method:[46][47]
The method's goals are to decrease the material's moisture content and to address problems with the traditional methodology-

Cooling:
The base is chilled until the composition is sufficiently brittle and can maintain this brittleness during the next grinding stage without adhering to the grinding machinery. The chilled aggregate has an average temperature of no more than -15° C. The chewing gum's composition and empirical observation of the cooled chewing gum composition's characteristics are used to establish the temperature needed for cooling. As coolants, we use liquid nitrogen, carbon dioxide, and hydrocarbon slush. Carbon dioxide is preferred because 78.50 °C low temperatures are possible. Warming up the mixture causes the solid carbon dioxide to easily sublime, however it isn't always absorbed by the ingredients of chewing gum. It no longer negatively interacts with the processing equipment and doesn't leave behind any undesirable or perhaps hazardous residue. To create microscopic bits of finely ground composition, the cold composition is then crushed or ground. Alternately, it should be combine the techniques for chilling chewing gum's composition into a single phase.

Grinding:
Grinding machines can be cooled by either keeping them in touch with a coolant or by enclosing them in a liquid nitrogen or other cold liquid cooling jacket. Before chilling to the refrigerator temperature, the chewing gum's ingredients might be pre-cooled for more efficient cooling.

Steps involved:
✓ A blend of chewing gum components, solid carbon dioxide, and precipitated silica is processed in a mill grinder.
✓ The already ground mixture is further ground after the addition of solid carbon dioxide and silica.
✓ By using these two-step grinding procedures, the chewing gum composition is advantageously retained at a low temperature. The presence of solid carbon dioxide improves the efficiency of the grinding process. The same procedure can be repeated multiple times by including additional carbon dioxide and/or precipitated silica at each step. To help freeze, grind, and provide chewing gum the required qualities, certain additives might be added to the composition. These include using anti-caking chemicals and grinding agents.

Tableting:
One of the more traditional ways to compress is through punching. The tabletting step of this strategy, like traditional ones, requires precise humidity control.

Limitations: [4]
It necessitates equipment other than standard tableting equipment and careful humidity monitoring throughout the tableting operation.

Direct compression method:
The direct compression method is used to make chewing gum tablets from powdered materials that have been precisely designed to be compactable. After the active medicinal ingredient, sweetening agent, and other essential ingredients have been introduced into the mixture in free flowing form during the first step, the formulation is immediately compacted into chewing gums [48]. No longer should the temperature increase past the gum base's melting point. After a constant and uniform mass has been achieved, the temperature can be lowered to allow the addition of more formulation ingredients [12]. Directly compressible gums must be used to expedite the process of medicated chewing gum. The use of chewing gum excipients inside the components can get around the gum base's limitations on melting and freezing. The active medication contained in the crushed chewing gum tablet may release into the buccal cavity. The rate of dissociation peaks between 2 and 10 chews. [20].
Limitations:
1) Having trouble getting the finished product out of the mixers.
2) Gum that has stuck on a device.

CONCLUSION
Chewing gum is a popular drug delivery method for self-medication because it is simple to administer without water, has a high patient compliance rate, and is easy to use. It allows for the local and systemic distribution of medication. Chewing gum has the potential to develop into a key treatment delivery method for ailments that require an immediate start of action, such as motion sickness, nausea, allergies, pain, migraines, and infections. We can infer that patients, particularly geriatric, paediatric, and favoured demographics, will accept chewing gum more in the future. The benefits of using medicated chewing gum as an innovative drug delivery method include protection from acids and enzymes, increased alertness and cognitive abilities, low first pass metabolism, flavour protection for many medications, quitting smoking, prevention of dental cavities and mouth ulcers, among others.

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COMPETING INTERESTS
The authors declare that they have no competing interests.

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