

MEDICATED CHEWING GUMS: HIDDEN GEM FOR ORAL DRUG DELIVERY SYSTEM

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Abstract: - Recent years have seen advances in science and technology related to the study and development of drug delivery systems. One potential reason for the oral route's widespread acceptance is its relative ease in administration. One of the most widely used oral confections is chewing gum. It is now thought to be a potentially useful and practical modified-release drug delivery system that can be utilised for a variety of purposes, including pain treatment, avoiding tobacco use, treating travel-related illnesses, improving breath, preventing dental cavities, easing the need for vitamin or mineral supplements, and more. Gum base, often referred to as insoluble gum base resin, is a type of chewing gum that includes elastomers, emulsifiers, fillers, waxes, antioxidants, softeners, sweeteners, food colouring, flavourings, and, in the case of medical gum, active ingredients. It has several benefits over conventional drug delivery systems. Medicated gums, compared to chewable tablets, are meant to be removed from the application site without invasive methods. A specialised in vitro device has been developed to test the release of medication-containing chewing gum. Gums containing medication are ideal mobile drug delivery systems for self-medication because they're discreet and easy to use without water.

Keywords: - Oral drug delivery, Medicated Chewing gum, Patient compliance, Elastomers.

1. Introduction

One of the most popular candies worldwide, especially among teenagers, is chewing gum. An estimated 374 billion sticks of chewing gum are sold annually worldwide, and the chewing gum market is estimated to be worth 5 billion US dollars, or approximately 560,000 tons, yearly. Chewing gum is an insoluble plastic material that has been sweetened and flavoured for chewing. Chewing gum is one of the drug delivery systems with limited treatment cycles and minimum adverse effects that has shown effectiveness in administering medications for oral and dental hygiene. Its advantage over other oral medications is a high level of individual compliance [1].

Chewing Gum can be utilized to prevent dental cavities, which will assist the healthcare industry economically. Despite having a long history dating back thousands of years, modern chewing gum was initially developed and first marketed in 1848 [2]. The Committee for Medicinal Products for Human Use defined medicated chewing gums as "solid single-time-use preparations with a base including primarily of gum that are used to be chewed but not to be swallowed, delivering a slow steady release of the medicine contained." The European Pharmacopoeia also provides information on medicated chewing gums. As it is chewed, the medication in the gum is released into the saliva. There are two ways that the released drug could be absorbed: either through the oral mucosa or into the stomach through gastrointestinal absorption [3]. chewing gum has a long history that dates back to antiquity. Chewing on a variety of gum-like materials, including leaves, waxy substances, skin from animals, and artificially sweetened paraffin, became a habit because chewing was enjoyable and helped to clean the mouth and freshen the breath. In 1848, Chicle was the first chewing gum to be sold commercially. In 1869, the first chewing gum patent was submitted [4]. Since humans first discovered how enjoyable it was to chew a variety of substances in ancient times, chewing gum has been used all across the world [5]. Clinical data indicate that gum without sugar substitutes does not cause caries because polyols do not cause tooth plaque to produce metabolic acids at a clinically significant level. Medicated chewing gum has applications in nutraceuticals, over-the-counter medications, and pharmaceuticals [6]. Chewing gum offers novel advantages over traditional medicine administration methods in the marketplace. Medicated chewing gum contains several substances, such as fluoride to prevent dental cavities, chlorhexidine to sanitise the area, nicotine to help people stop smoking, aspirin to relieve pain, and caffeine to help people remain awake. The US market accounts for approx. .50% of the worldwide market for medicated chewing gums. The active ingredient in chewing gum is either on the outside or the inside of the gum [7]. This systematic literature review's goal is to evaluate the currently available data about the potential therapeutic or anticarcinogenic effects of patients' sugar-free chewing gum.

2. Historical background

Chewing gum has a long history. In 50 AD, the Greeks used mastiche, a resin derived from the mastic tree bark, to clean their teeth and sweeten their breath. The chewing gum has become much more acceptable in society over time. With the increasing acceptance and use of chewing gum, authors, filmmakers, and artists have included themes linked to chewing gum in their works [8]. Chewing gum was not accepted as a drug delivery method until nicotine chewing gum was introduced to the market. The first Medicated chewing gum, known as Aspergum®, was released

in the United States in 1924 [9]. The Commission of European Communities accepted chewing gum as a term for a medicinal dosage form in 1991. The first monograph on chewing gum with medication was published in 1998. Several active components are commercially available as medicated chewing gum, such as fluoride, urea (carbamide), and chlorhexidine for local delivery, and nicotine, aspirin, ascorbic acid (vitamin C), and dimenhydrinate for systemic delivery. Medicated chewing gum has gained acceptance as a drug delivery system in the modern era [10].

Table 1. Benefits and Challenges of Medicated Chewing Gum

Benefits of medicated chewing gum	Challenges of Medicated Chewing Gum
Chewing gum can be used anywhere, anytime, without the use of water [11]	The sorbitol in the medicated chewing gums formulation may bring on flatulence and diarrhoea
For people of all ages, including the younger generation, as well as particular age groups with difficulty in swallowing, such as children and elderly people, medicated chewing gum (MCG) provides an extremely convenient way of patient compliance for administering medication [12]	Compared to chewable tablets or lozenges, which can be taken in larger quantities and over a shorter amount of time, there is a risk of overdosing with medicated chewing gums [18]
It has a pleasant taste	Investigation has demonstrated that chewing gum exhibits varying degrees of adhesion to enamel dentures and fillings [19]
After a short time of mastication, the product is quickly released from the gum; depending on the active component, some absorption occurs directly through the oral mucosa. Significantly, the gum does not enter the stomach because it is not swallowed. Additionally, the stomach is not in direct contact with large concentrations of the active principle, which lowers the possibility of the gastric mucosa producing an intolerance [13]	Prolonged chewing on the gum can cause facial muscle aches
Counteracts dry mouth prevents candidiasis and caries	Gum additives like cinnamon and flavouring agents can lead to mouth ulcers, and liquorice can raise blood pressure [20]
Highly acceptable by children	Children who chew gum for extended periods may have earache and ocular muscle pain [21]

Reduces and prevents stains on teeth, and helps in tooth whitening by neutralizing plaque acids that accumulate in the mouth after consuming fermentable carbohydrates [8]	Drug Stability: Certain drugs may degrade when exposed to the chewing gum formulation, affecting their efficacy.
Less first-pass metabolism and improved bioavailability	Dosage Control: It can be challenging to ensure precise dosage delivery compared to conventional forms like tablets or capsules
Assist in improving mood by relieving tension and stress [14]	Taste and Flavor: Some medications may have unpleasant tastes or interact with the gum's flavour, making it less appealing to users
Beneficial for xerostomia (dry mouth) [15]	Chewing Behavior: Individual chewing habits vary, potentially impacting drug release and absorption consistency
Excellent for administering acute medications, Maintain good stability [16]	Storage and Shelf Life: Gum's shelf life may be shorter than other dosage forms, and storage conditions must be carefully controlled to maintain drug stability
Many medications, such as aspirin, dimenhydrinate, and caffeine, are absorbed more quickly through medicated chewing gum than through tablets [17]	Accessibility: Not all medications are suitable for delivery via chewing gum, limiting its application across different drugs and therapeutic areas.

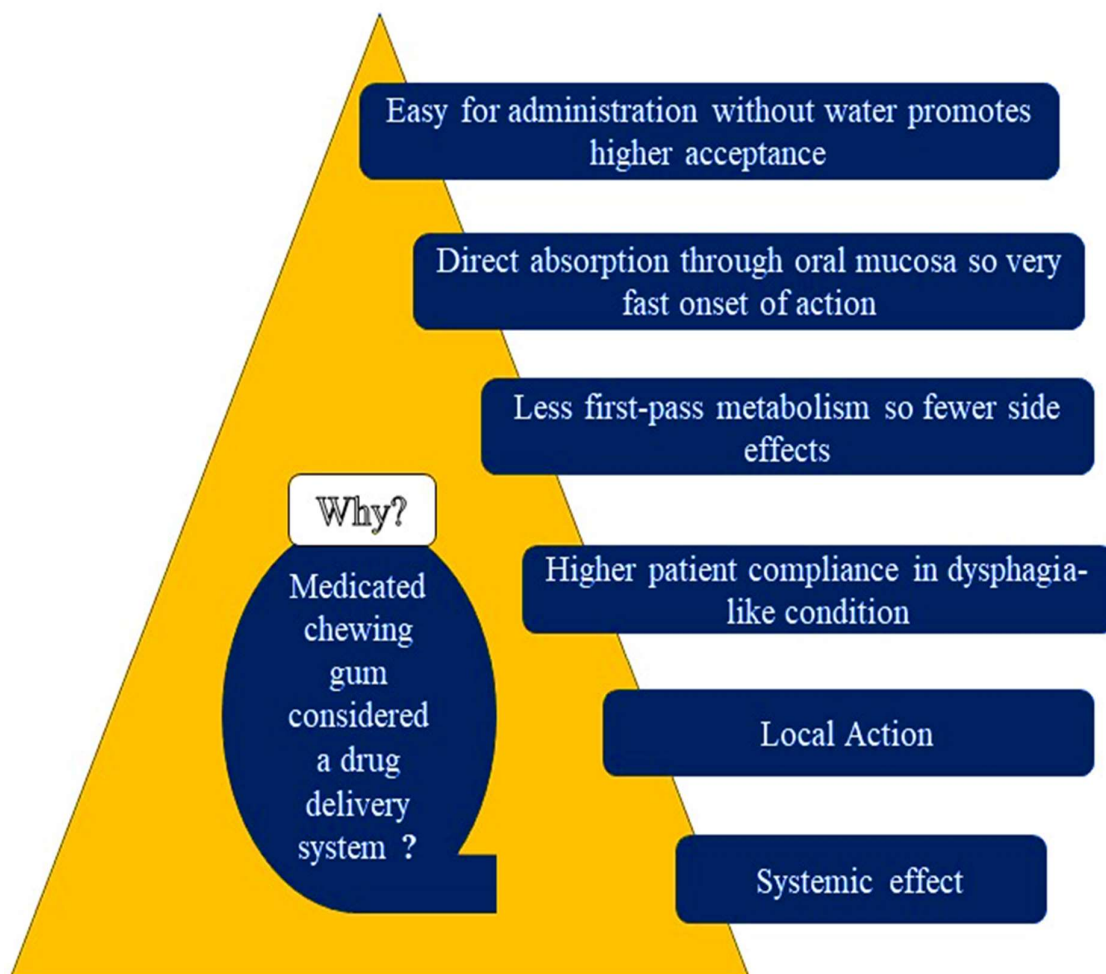


Figure 1. The Rationale Behind Considering Medicated Chewing Gum as a Medication Delivery Method [22]

Further, some patents on chewing gum are summarized in Table 2.

Sr.No.	Patent Number	Patent title	Assignee	Description	References
1	US11679081B2	Chewing Gum Comprising Nicotine	McNeil AB, Helsingborg (SE)	The invention relates to chewing gum with atleast one gum core made of nicotine polacrilex, atleast one outer coating covering the core made of atleast one sugar alcohol or mixtures of sugar alcohols, or atleast one buffer present in the coating and/or	[23]

				in a portion fused to the coating, and at least one nicotine bitartrate or nicotine ditartrate dihydrate.	
2	US20230148623A1	Coated chewing gum compositions	Aizant Drug Research Solutions Private Limited Hyderabad (IN)	The invention pertains to chewing gum compositions with coating formulations that contain high-viscosity grade polymers, namely high-viscosity grade cellulose ethers, to improve crunchiness during the first few minutes of mastication. The chewing gum products of the present invention are stable and consist of a gum core and a coating layer around the core. The coating layer is made of high-viscosity grade polymers.	[24]
3	US20230172226A1	Enhanced flavour release chewing gum composition	Roquette Freres, Lestrem (FR)	The chewing gum composition with an improved flavour release method are the subjects of the current invention. The current invention, more precisely, pertains to a formulation for flavour release that includes a polyol powder with a certain surface area that brings a prolonged flavour release.	[25]
4	US20230083049A1	Porous starch as a bulking agent in chewing gums	Roquette Freres, Lestrem (FR)	The purpose of the current innovation is to create chewing gum with porous starch as a bulking agent. The	[26]

				chewing gum manufacturing technique and the chewing gum composition that uses porous starch as a bulking agent are likewise covered by the current invention.	
5	US20230023342A1	Chewing gum containing synergistic medicinal compounds	London Pharmaceuticals and Research Corporation, London, ON(CA)	The goal of the present invention is to treat medical conditions with chewing gum compositions that contain cannabinoids or their derivatives along with other synergistic compounds. These compositions can be used to treat or manage conditions like pain, inflammation, swelling, gout, lupus, anxiety, sleep disorders, premenstrual syndrome, asthma, respiratory and oral conditions, and infectious diseases (viral, bacterial, and fungal).	[27]
6	US20230056600A1	Gum Composition for Removing and Preventing Stains on Teeth	Rena Jhuty, Kent, WA(US)	The chewing gum designed to prevent and remove stains from red wine and other foods and beverages is the subject of the current invention, which is typically related to oral hygiene.	[28]
7	US11445736B2	Chewing gums and methods for their preparation	SUDZUCKER AKTIENGESELLSCHAFT MANNHEIM / OCHSENFURT, Mannheim (DE)	The invention offers a coated chewing gum that is free of sugar and glycerol. Its core is distinguished by the presence of a specific sweetener	[29]

				system, which is made up of, among other things, (1) hydrogenated starch hydrolysate; (2) isomalt particles; (3) sorbitol particles; and (4) at least one of a sweetener enhancer and a high intensity sweetener.	
8	USOO7351438B2	Method of preparing chewing gum powder	Gum Base Co. S.p.A., Milan (IT)	The chewing gum used in this invention is a novel tablet form that can be made by directly compressing a gum formulation in powder form. This chewing gum has a pleasant chewability that doesn't harden as most conventional chewing gums do, and it stays that way throughout the chewing period.	
9	USOO849691 3B2	Compressed chewing gum tablet	Gumlink A/S, Vejle (DK)	A compressed chewing gum tablet with toothbrush-like properties is the subject of the current invention. It is made up of at least gum base and one or more of the following: a) at least one whitening agent; b) at least one fresh-breath agent; c) at least one anti-plaque agent; d) at least one anti-gingivitis agent; e) at least one re-mineralization agent; and f) optionally at least one anti-calculus agent. The compressed chewing gum	

				tablet is created, atleast in part, from a compressed mixture of granules and agents.	
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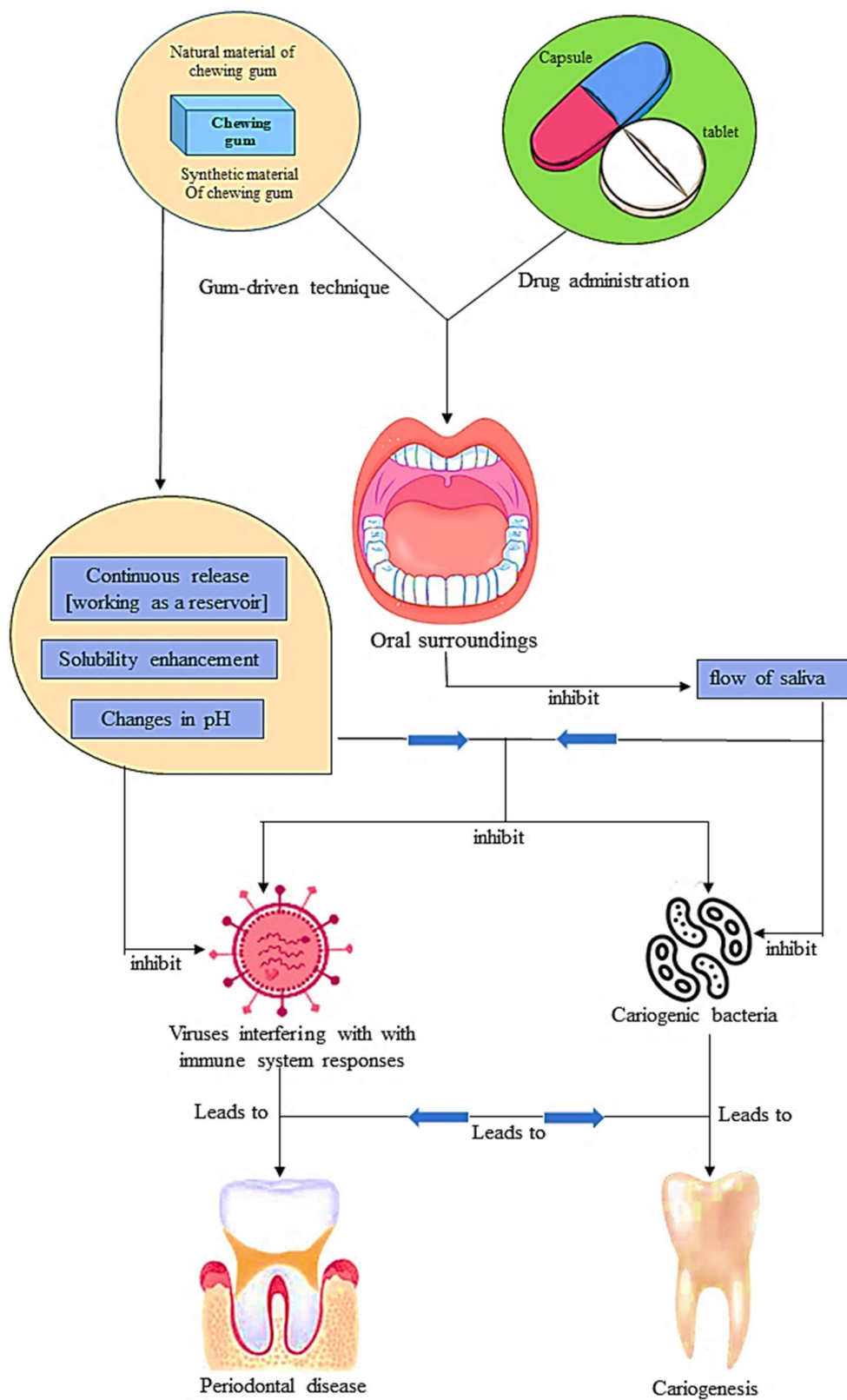


Figure 2. Diagram of The Gum Drug Delivery Approach and Factors Affecting it [30]

3. Medicated Chewing Gum and Interaction with Saliva

Chewing is a complicated motor activity that the central nervous system generates and regulates. More specifically, a group of neurons termed central pattern generators (CPGs) located in the pons and medulla produce the intrinsic, rhythmic jaw patterns of movement that occur during chewing [31]. The central pattern generators (CPGs) can also be triggered or regulated by the brain's higher centres, specifically the inferior-lateral portion of the sensorimotor cortex. Moreover, mechanoreceptors in the muscles, periodontal ligaments, lips, and oral mucosa can affect and control the action of the masticatory muscles during biting and chewing. Therefore, to properly manage and break down the food item, chewing entails the coordinated interaction of several orofacial structures, including the jaw, masticatory muscles, and tongue [31].

Chewing gum produces saliva, one of the body's most potent defence systems. Humans need saliva to maintain healthy teeth. Three major preventative (anticaries) roles of saliva are as follows [32]:

- i. Food debris is diluted and washed away
- ii. Plaque acids are neutralized and buffered by the bicarbonate
- iii. Early dental caries lesions are helped to remineralize by the calcium and phosphate ions and Saliva also has antimicrobial properties.

Medicated Chewing gum is a simple, effective, and pleasurable technique for stimulating saliva production without the need for drugs. The stimulation of flavours and the gustatory action of chewing work together to increase saliva production in the mouth.

Table 3. Medicated Chewing Gum Available All Over the World

Marketed Chewing Gum	Indication	Active Ingredient	Manufacturer	References
Nicorette®	Smoking Cessation	Nicotine	GlaxoSmithKline	[33]
Chooz®	Stomach acid neutralization	Calcium Carbonate	Lessons Overseas Corporation, USA	[34]
Stay Alert®	Alertness	Caffeine	Stay Alert Safety Services, Inc	[13]
Fluorette®	Cariostatic	Fluoride	Fertin Pharma A/S	[35]

Vitaflo CHX®	Preventing tooth decay	Chlorhexidine	Fertin Pharma A/S	[36]
Nicotinelle®	Smoking Cessation	Nicotine	Novartis Consumer Health	[37]
Travvel®	Motion sickness	Dimenhydrinate	Asta Medica	[38]

4. Composition of Medicated Chewing Gum:

Chewing gum is typically made up of two phases [14]:

(1) a continuous, water-soluble phase that includes non-masticatory ingredients like flavourings, plasticizers, and API;

(2) an insoluble, discontinuous phase called the tasteless masticatory gum base. The gum base is the main ingredient that gives the chewing gums their rubbery structure. A gum base is also utilized in chewing gum to hold Flavors, sweeteners, and other ingredients.

Table 4. Components Essential for The Production of Medicated Chewing Gum [39]

Sr.No	Composition of Medicated Chewing Gum	Objective	Examples
1	Elastomers	Gives the chewing gum its, gummy texture, and cohesiveness.	Elastomers include gums like Jelutong, Lechi Caspi, Perillo, and Chicle, as well as natural rubbers like Latex. synthetic elastomers such as butyl rubber and polyisobutylene are also used.
2	Plasticizers	To control the product's cohesion	Pentaerythritol esters of resin, glycerol esters of polymerized esters, glycerol esters of partially dimerized rosin, and natural rosin esters such as

			glycerol esters or partially hydrogenated rosin are natural plasticizers. A-pinene and/or d-limonene-derived terpene resins are synthetic plasticizers.
3	Resins	Elasticity and plasticity are balanced by resins use as a mastication agent and binding agent between elastomers and fillers.	natural resins made from pine resins, glycerol esters Synthetic polyvinyl acetate resin
4	Emulsifiers and fats	soften the mixture and provide the necessary mouthfeel and chewing consistency. During mastication, emulsifiers facilitate the absorption of saliva into the chewing gum.	Emulsifiers: Tallow, glycerin, and lecithin are softeners. Monoglycerides, diglycerides, and partially solidified vegetable and animal fat are also included. Mono, di, and triglycerides; hydrogenated tallow; and fatty acids, such as palmitic, oleic, linoleic, and stearic acids.
5	Fillers or Texturizers	Give the appropriate texture. enhance chewability and offer a suitable size	Magnesium and Calcium Carbonate, Titanium Oxide, Clay, Alumina, Talc, Magnesium and Aluminum Silicate, and Mono, Di, and Tri-Calcium Phosphate
6	Antioxidants	To prevent oxidation of the gum base and flavors	Ascorbic acid, tocopherol, and butylhydroxytoluene have been used.
7	Sweeteners	Provide a more sustained sense of sweetness and flavor To combine the ingredients and hold onto the moisture, aqueous sweeteners can be utilized as softeners.	Aqueous sweeteners include hydrogenated starch hydrolysates, corn syrups, and sorbitol.

			<p>Bulk Sweeteners: Saccharides such as sucrose, maltose, dextrin, fructose, galactose, and corn syrup are examples of sugar components. Sugar alcohols like sorbitol, mannitol, xylitol, and hydrogenated starch are examples of sugarless components.</p> <p>High-intensity artificial sweeteners made from hydrolysate:</p> <p>Acesulfame salt, sucrose, aspartame, glycyrrhizin, alitame, saccharin, and dihydrochalcones</p>
8	Colourants and whiteners	gives the mixture a soothing tone and enhances the formulation's acceptability	Titanium dioxide, fruit and vegetable extracts, FD and C type dyes, and lakes.
9	Flavouring agents	To increase consumer acceptability	Essential oils include peppermint, spearmint, mint, clove, oil of wintergreen, citrus, and fruit essences.
10	Anti-caking agent	Avoid the subsequent grinding of the chewing gum particles clumping together.	Precipitated silicon dioxide, solid carbon dioxide
11	Grinding agent	Preventing the gum from adhering to the grinding tool.	Maltodextrin, an alkaline earth metal phosphate, or an alkaline metal phosphate
12	Compression adjuvant	To simplify the process of compression easier	Talc, silicon dioxide, calcium stearate, and magnesium stearate

5. Methods of Preparation of Chewing Gum: -

Three general categories can be used to categorize the different processes utilized in the production of chewing gum:

1. Conventional Method.
2. Freezing, grinding and tableting Method
3. Direct Compression Method.

5.1 Conventional Method

Production of medicated chewing gum involves melting or softening the gum base and then mixing it with sweeteners, syrups, active ingredients, and other substances. The mixture is rolled into a thin sheet, and powdered sugar is added to improve flavour and prevent sticking. The gum is cooled in a controlled environment for up to 48 hours, after that cut into pieces, and allowed to cool under specific conditions [40].

Limitations:

- a) The use of this method for thermolabile drugs is restricted due to the elevated temperature utilized in melting.
- b) Melting and blending extremely thick gum mass facilitates precise control, and drug dosage consistency is challenging.
- c) Absence of exact form, weight, or shape of dosage design.
- d) It can be difficult to change technology to accommodate the strict manufacturing conditions required for the production of prescription medications.
- e) The composition of chewing gum like this is tough to shape into tablets for chewing gum due to their 28% moisture content. If tried to pulverize and tablet such a material, it would cause the grinding machine to jam. screen adhesive, blades attached to. strikes and would be challenging to condense [41].

5.2 Latest technology

As technology develops, advanced automatic instruments can overcome several limitations of the conventional method, including the inaccuracy of content uniformity and the lack of excellent texture, shape, or weight [12].

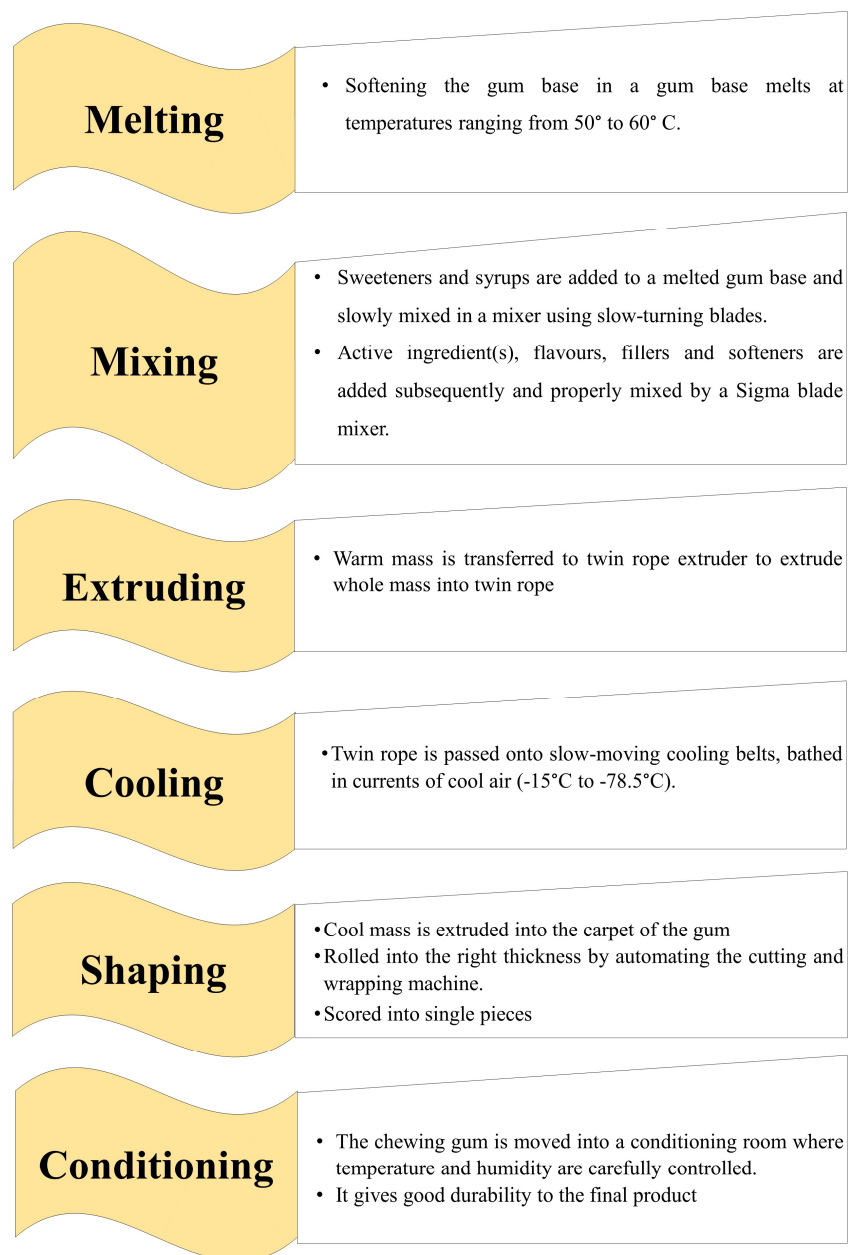


Figure 3. Schematic Representation of The Various Processing Steps Involved in Manufacturing Medicated Chewing Gums with The Latest Technology

5.3 Tableting

Another method to manufacturing chewing gum with the desired flavour, colour, and texture is to combine the gum base with appropriate and suitable sweeteners, corn syrups, starches, flavouring agents, and colourants. Then, contact the gum with a coolant, such as carbon dioxide, to cool it down to a temperature below -15°C . The gum is then ground into tiny particles using a cutter or grinding device, and heated to a temperature that causes the particles to stick together to form a slick, homogeneous bulk with a consistent texture and low specific gravity. If the fragments are not self-adhering, mild pressure would be applied manually or mechanically and then warmed to room temperature. Edible ingredients can be blended with powdered components or coated with tiny particles. Punches may need to be compressed to be tabletized, however, to prevent sticking to the punch surfaces, an anti-adherent agent should be added.

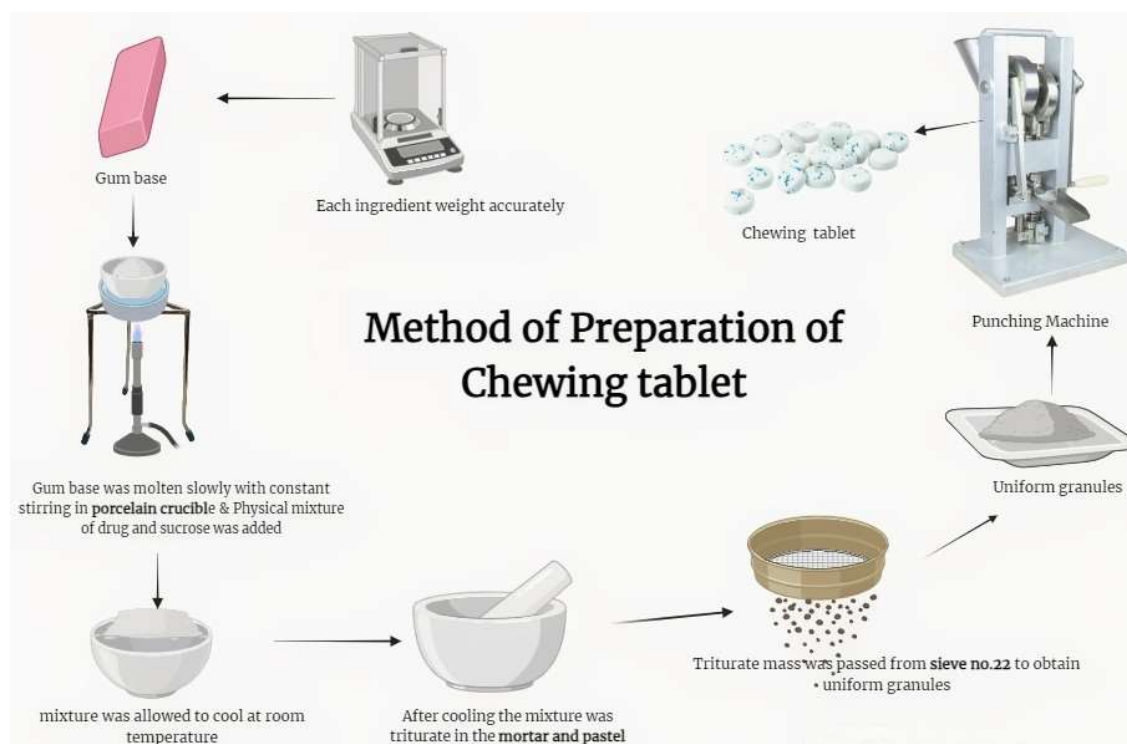


Figure 4. Method of Preparation of Chewing Gum Tablet

5.4 Direct Compression Method

The potential of chewing gums has not yet been completely realized, despite the advantages previously indicated. This is because the technology needed to manufacture chewing gum differs from that needed to produce pharmaceuticals. Conventional chewing gum production requires

infrastructure and specialized machinery for hot-melt procedures, which are uncommon in the pharmaceutical sector.

Free-flowing, immediately compressible co-processed gum materials are now available in the market. Examples include Pharma gum and Health in Gum (created by CAFOSA, Chemically, it is a blend of sugar, gum, plasticizers, and anti-caking agents with polyols (sorbitol, xylitol, and mannitol). Manufactured by cGMP guidelines, these gums satisfy food chemical standards and are classified as "generally regarded as safe" (GRAS) under FDA title 21 C.F.R. Section 172.615. This gum material may be used to make chewing gum that is immediately compressed on an in-house tablet compression machine used by pharmaceutical companies, allowing for the quick and affordable manufacturing of Medicated chewing gums. processing of thermosensitive APIs is also feasible as doesn't require a high temperature. This method also works well with APIs that are sensitive to water.

Table 5. Limitations of Various Methods of Manufacturing of Chewing Gum [39]

Sr.no	Manufacturing method	Limitations
1	Conventional/ traditional method	The production of thermolabile materials may provide difficulties due to high melting points. It is impossible to dose gum accurately if it is extremely viscous; Absence of exact dosage form, shape, and weight: Compression and grinding: Because of its high moisture content, chewing gum is challenging to manufacture as tablets.
2	Freezing, grinding and tableting method	Expensive, high-tech equipment is needed; it becomes difficult to carefully regulate humidity levels during the manufacturing process.

6. Factors Influencing Active Ingredient Release

6.1 Contact Time

Whether an effect is localized or systemic depends on when medicated chewing gum interacts with the mouth cavity. In a clinical trial, a 30-minute chewing period was found to be similar to normal usage.

6.2 Physicochemical Properties of Active Ingredients

The physicochemical characteristics of the active component have an essential role in drug release from MCG. While fat-soluble drugs are absorbed slowly into the gum base, saliva-soluble components are released quickly.

6.3 Inter-Individual Variability

Chewing intensity and frequency can vary from person to person and influence the release of Medicated chewing gums medication. An *in vitro* study by European Pharmacopoeia suggests chewing at a rate of 60 cycles per minute to ensure optimal release of active ingredients [42].

6.4 Formulation Factors

The gum base's composition and quantity have an impact on how quickly the active component is released. As the gum's lipophilic content increases, the release rate decreases.

Some Important Formulation Aspects:

- Increased softeners and emulsifiers in the gum base speed up release, whereas rigid gum may slow it down [43,44].
- Pharmaceuticals that are insoluble in water are made more soluble in water through cyclodextrin complexation [45,46].
- A solid system containing lipophilic active substances bonded to cation exchange resin allows for long-term medication delivery [47,48].

7. The Scientific Justification for Determining Drug Release *in Vitro*

For nicotine polacrilex gums, the USP monograph does not yet include a drug release test. Recently, a great deal of effort has been put into determining the *in vitro* release kinetics of certain dosage forms, such as medicated chewing gum [49,50]. Researchers suggested minimal parameters for experimental conditions regarding the site of release and absorption because of the complexity of the release processes involved. In addition to testing for product quality, drug release studies can offer valuable insights into the features of the product, making them an essential tool for product development and screening, and to a lesser extent, for assessing the product's performance *in vivo* [51].

8. Approaches of Drug Release Testing

The fundamental idea is to resemble the chewing motion of a piece of gum on a tiny chewing chamber filled with a specified volume of buffer solution at a specific temperature by using a basic masticatory

movement [38]. The chewing pace and angle have an impact on the drug release rate because they supply the shear force required to expose new gum surfaces and are prerequisites for more drug release. The following factors affect the changeover from the inactive gum to the active dose form:

- Mechanical forces
- Temperature
- Water permeability and wettability

The frequency of chewing and the drug's water solubility are typically directly correlated with the rate of drug release under sink conditions, while the mass of the gum base is indirectly correlated with this rate of release.

9. Evaluation parameter of Chewing Gum:

9.1 Physical Evaluation

Every formulation of medicated chewing gum is examined visually, and based on solubility tests, relative humidity, colour, and moisture absorption, the physical characteristics of the gum base are examined [52]. The following characteristics are examined:

9.1.1 Weight Variation

The method described in the experimental work is used to vary the weight of each formulation. Ten chewing gums weigh in a single batch and the average weighted, standard deviation is calculated from there.

9.1.2 Hardness/Plasticity

The Monsanto-type hardness tester chose to determine the hardness of all Medicated chewing gum formulations because there is no documented way to do so.

9.1.3 Stickiness

After placing Medicated chewing gum on a level surface, a 250-gm cylindrical hammer is struck by it for 10 minutes. There are roughly 30 hammerings every minute. After ten minutes, noted that a mass had stuck to the hammered surface.

9.2 Chew Out Study

The formulation of the chew-out research protocol is authorized by Fertin Pharma Pvt. Ltd., Denmark, a leading global manufacturer of medicated chewing gum. Several characteristics are examined in the

chew-out study's initial phase, including texture, elasticity, smoothness, cheesiness, sweetness, softness, juiciness, cooling effect, and lubricating sensation [53].

9.3 The *in vitro* drug release studies based on: -

- A modification in the upper masticatory jaw's twisting angle from ($5^{\circ} - 30^{\circ}$).
- A modification of 12 mm in the space between the lower and upper masticating jaws.
- An increase in the lower masticating jaw's chewing frequency from 20 to 120 strokes per minute.
- A temperature change of 30° – 40° degrees Celsius.

The chewing gum is set up between the pistons on the chewing surface's bottom. The gums swell and stir the test medium during the chewing process, which involves rotating the upper masticating surface and simultaneously applying ascending and downhill to the lower masticating surface. An ideal chewing frequency for the study is 60 ± 2 strokes per minute. At predefined intervals, an aliquot of the artificial saliva obtained, and its drug content evaluated by UV spectrophotometric analysis [54,55].

9.4 Analysis of Synthetic Gum Base Stability

10 grams of synthesized gum base should be stored in a container at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$ for six months (WHO stability guideline). After six months, check for any physical changes and signs of gum ageing [56].

10. Therapeutic Uses of Medicated chewing gum

Sugar-free gum stimulates saliva production, it can help prevent dental cavities, which is why gums are becoming more and more popular and acceptable. It has been demonstrated that chewing gum without medication increases saliva production, elevates the pH of the plaque, and decreases decay [57,58]. To treat gingivitis and plaque, medicated chewing gum containing chlorhexidine has been made available [59]. The oral cavity reaches a high concentration of Medicated chewing gum when its active component is released, it can be used to treat or prevent certain oral cavity disorders. medicated chewing gum is an additional useful delivery route for drugs intended for systemic dispersion. The buccal mucosa allows for the absorption of medications that are released from the gums inside the mouth. Medicated chewing gums can also be used as an alternative to buccal and sublingual tablets, which are intended to function systemically because of the active ingredient's more uniform release and greater area of absorption in the oral cavity. There are medicated chewing gums available for both systemic conditions such as vitamin C deficiency [60], pain and fever [60], alertness [62], motion sickness [63],

smoking cessation [64], and local conditions such as plaque acid neutralization [65], fresh breath, disinfection [66], anticaries [67], antiplaque [68], antifungal [69] and antibacterial [70].

Safety Considerations

It has been established that the degree to which commercial chewing gums adhere to dentures, fillers, and crowns varies. Excessive chewing results in sore jaw muscles. Chewing gum seems to provide a lower chance of accidental or inappropriate overdosing than flavoured chewable tablets. Like other medications, medicated chewing gums should be kept out of children's reach. People who are prone to allergic reactions should also be advised to check the flavouring and sweetening agents contained in the chewing gum formulations [71].

Future trends

In addition to its therapeutic advantages, chewing gum is a visually appealing, discrete, and effective drug delivery method. A few decades ago, surgery was the only option for treating some diseases, but nowadays, there are some innovative drug delivery techniques available to address an increasing number of disorders.

11. Applications: The following are Some of The Applications of Medicated Chewing Gum

11.1 Dental caries [8]

- Chewing gum formulations aim to prevent and cure oral diseases.
- It can regulate how quickly active ingredients are released, giving a longer local effect.
- Additionally, it raises the pH of the plaque again, which lessens the severity and frequency of dental caries.
- Gums containing fluoride have been shown to help adults and children with xerostomia avoid dental cavities.
- Chewing gum containing chlorhexidine is useful in treating oral and pharyngeal infections, gingivitis, and periodontitis.
- It can also be applied to stop the growth of plaque.
- Chewing gum containing chlorhexidine has a very flexible composition since it disperses evenly throughout the oral cavity and leaves teeth less stained.
- In a chewing gum formulation, the harsh taste of chlorhexidine can be effectively covered up.

11.2 Systemic Therapy [72]

There are various indications that chewing gum can be beneficial as an oral drug delivery system; a few of these are included below:

Smoking Cessation, Obesity, Additional signs Chewing gum as a medicine delivery device may be helpful for conditions including xerostomia, allergies, motion sickness, acidity, cold and cough, diabetes, anxiety, etc.

Conclusion

In addition to its therapeutic advantages, chewing gum is a discreet, effective, and appealing drug administration method. Many diseases could only be treated surgically a few decades ago, but new medication delivery technologies are now being used to treat an increasing number of disorders. A new medicine delivery system often needs some time to become well-known in the industry and attract patients. Chewing gum, on the other hand, is thought to demonstrate its status as a practical and beneficial drug delivery system because it satisfies the stringent quality standards of the pharmaceutical industry and can be designed to produce various active ingredient release profiles. Medicated chewing gum is a desirable delivery form due to its quick action, buccal administration capacity, and possibility for product line extension. It is necessary to reformulate a current product to maintain revenue, protect patents, and provide additional patient advantages.

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