



Recent Trends in Medicated Chewing Gum Technology: A Review on History, Formulation Strategies and Characterization

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ABSTRACT

In the research and development sector, scientific and technical developments are ready for the expansion of oral drug delivery systems. The medicated chewing gum receives accumulative permission in both pharmaceutical and clinical areas as a drug delivery system. It provides benefits for both local therapy and systemic impact after absorption through the buccal, sublingual mucosa and gastrointestinal tract compared to traditional oral and oral dosage forms. It mainly consists of active substances and a gum core, which is mainly composed of an insoluble gum base, sweetener, antioxidants, softeners, and flavoring agents. Today improved technologies have made it possible to develop and manufacture medicated chewing gum with predefined properties. There is the number of formulations available in the market is for the prevention of caries, lowering of xerostomia and supplementation for vitamin or mineral, etc. In this review article, we focused on the general introduction, unique characteristics, composition, manufacturing, characterization, applications, future trends and safety aspects of the medicated chewing gum formulation in different fields to control and treat the disease by sustained release of the active component. Finally, in upcoming years, we may realize that the medicated chewing gum formulation places preference on other delivery systems to distribute the drugs locally.

Keywords: Chewing Gum technology; Composition; Formulation strategies; Characterization; Applications; Recent Trends.

INTRODUCTION

There are several dosage forms available for drug delivery like tablets, capsules, gels, injectable, inhalers, pastes, creams, ointments, etc. In addition to these dosages form chewing gums are also used for drug delivery. ³Chewing gum is one of the popular confectionery products used worldwide. ² Some chewing gum products used for medicinal products delivery known as 'medicated chewing gum (MCG)'. Medicated chewing gum considered as a novel drug delivery system with solid and single-dose preparation containing a masticatory gum base ^{3, 4, 5} which is fulfilled with the pharmacologically active ingredient. ^{4, 5} It is generally used to treat local mouth infections or for other use by systemic absorption through the oral mucosa. ^{3, 4, 5} Medicated chewing gum must be allowed to chew only not to be swallowed. Nowadays, medicated chewing gum is widely used as a drug delivery system in smoking cessation and dental care in which nicotine products and fluoride or carbamide containing products respectively available for the same. ⁷

Medicated chewing gum is the newest delivery system that has different potential uses in pharmaceutical over the counter medicines and nutraceuticals. Nearly about £ 80 to 100 million medicated chewing gum sold per year. Out of that 55% sold with sugar-free gum. Out of all consumers, 70% are teenagers. A survey conducted showed that the greater quantity of medicated chewing gums chewed by girls than boys. About 79% of sugar-free medicated chewing gum sold in Switzerland. ⁵

Generally, chewing gums are composed of two phases that are a water-soluble continuous phase and a

discontinuous phase of gum base (core) which is mixed in a 1:3 ratio. ² Medicated chewing gum has low water content and no traces of preservatives. Gum core may be or may not be coated with sugar or polyol compounds. ⁸ Flavoring compounds can be incorporated into the chewing gum formulations to increase patient compliance in pediatric dosage forms. ²

As a pharmaceutical dosage form medicated chewing gum was approved by the commission of the European Council in its guidelines for the pharmaceutical dosage form. As per these guidelines medicated chewing gum can be defined as, "solid preparation with a basis consisting of gum which should be chewed and not to be swallowed, providing a slow steady release of the medicine contained". ^{1, 2}

History

Chewing gums has been used for cleaning and freshening purpose since ancient times. About 1000 years ago Mayan Indians used to chew sapodilla tree resin for cleaning their teeth and freshening of their breath. ^{5, 6} There are less history of the development of chewing gum than other dosage forms. The first commercially available chewing gum was marketed in 1948 in the U.S.A. named as, "STATE OF MAINE PURE SPRUCE GUM". In 1869, the first patent of chewing gum was filed ^{3, 5, 6, 8} by a dentist Dr. William F. Semple from Mount Vernon, Ohio under U.S. patent no. 98,304 for the fabrication of chewing gums. This chewing gum consists of liquorice and rubber dissolved in alcohol and naphtha which was used as a dentifrice. He regarded chewing gum not only as a



confectionery but also had an application as a dentifrice.^{1,3-5}

In 1924, the first medicated chewing gum that is 'Aspergum' was sold by Frank M. Dillard and William C. Nalle in the US. They formed the Dillard-Nalle company in December 1927 and sought US trademark protection for Aspergum. Then they began to sell their product in the US in 1928.⁹ Aspergum consists of acetylsalicylic acid, an analgesic, as an active pharmaceutical ingredient.⁵ Chewing gum not accepted as a drug delivery system until 1978. It was accepted after the development of nicotine-containing chewing gum.^{1, 5, 6}

By 1892, William Wringley Jr. firstly marketed his chewing gum product as 'LOTTA AND VASSAR'. Thereafter he again launched his second chewing gum product as 'WRINGLEY'S SPEARMINT GUM'. In 1975, William Wringley's company newly launched a chewing gum known as FREEDENT which was specially designed for denture wearers.⁵

Advantages

1. It is useful due to the convenient route of administration.^{3, 6, 8}
2. It is advantageous for patients with dysphagia because there are no requirements for the swallowing of chewing gum.^{4, 5, 6, 8}
3. There is no requirement of water to take this medicament. Therefore, it can be administered anywhere.^{3, 4, 5, 6}
4. It has higher patient compliance.^{3, 4}
5. It helps in counteracting dry mouth (xerostomia) through the stimulation of salivary secretion. It also prevents caries and candidiasis.^{3, 4, 5, 6, 8}
6. It is highly accepted by children because of its confectionery like appearance and taste.^{3, 4, 5, 6}
7. It is one of the best options for acute medication.^{4, 5, 6}
8. It is not allowed to be swallowed. Thus, it increases the bioavailability of the drug by avoiding first-pass metabolism.^{3, 4, 5, 6, 8}
9. There is a rapid release of active ingredients in the buccal cavity. Hence, the fast onset of action can be achieved with greater availability.^{3, 4, 5, 6, 8}
10. It reduces the risk of intolerance of the gastric mucosa because the stomach does not get in direct contact with a higher concentration of active pharmaceutical ingredients.^{4, 5, 6, 8}
11. The saliva which is delivered continuously and regularly to the stomach delivers some amount of drug which is helpful in the enhancement of the duration of action.^{4, 5, 6, 8}
12. It provides both local and systemic effects.^{3, 4, 8}
13. It has fewer side effects^{3, 8} with less risk of overdose.³
14. It retains good stability in the oral cavity for a longer duration of time.³
15. Some drugs show faster absorption through medicated chewing gum than that of tablets. For example Aspirin, dimenhydrinate, and caffeine.^{4, 5}
16. It helps to neutralize plaque acids that are formed in mouth after eating fermentable carbohydrates.⁵
17. It can increase salivation.^{4, 5} The stimulated saliva has a buffering capacity which may help in reducing the acidity of gastric fluid.^{4, 8}
18. The amount of gum remained after chewing does not reach the stomach that's why there will be fewer side effects of excipients on GIT.^{4, 8}
19. It improves focus and concentration by providing relief from stress.⁸
20. It may help in whitening of teeth by reducing and preventing stains.⁵

Disadvantages

1. Medicated chewing gums may show side effects due to the presence of different excipients in it. For example, Sorbitol – Flatulence and diarrhea^{3, 4, 5, 8}; Flavoring agents – Ulcer formation in the oral cavity^{3, 4, 5}; Liquorice – Hypertension.^{3, 4}
2. The unpleasant taste of chlorohexidine and its staining ability to the teeth and tongue limits its use in oromucosal application.^{3, 4, 5}
3. This delivery system may adhere to the enamel dentures and fillers.^{3, 4, 8}
4. It may result in pain in facial muscles and earache in children because of prolonging chewing of gums.³⁻⁵
5. There may be a risk of overdosing in medicated chewing gums than that of chewable tablets or lozenges.^{3, 4, 5}
6. It causes side effects if administered in more quantity within a short period.^{3, 4}



CLASSIFICATION²

Chewing gums are classified as follows:

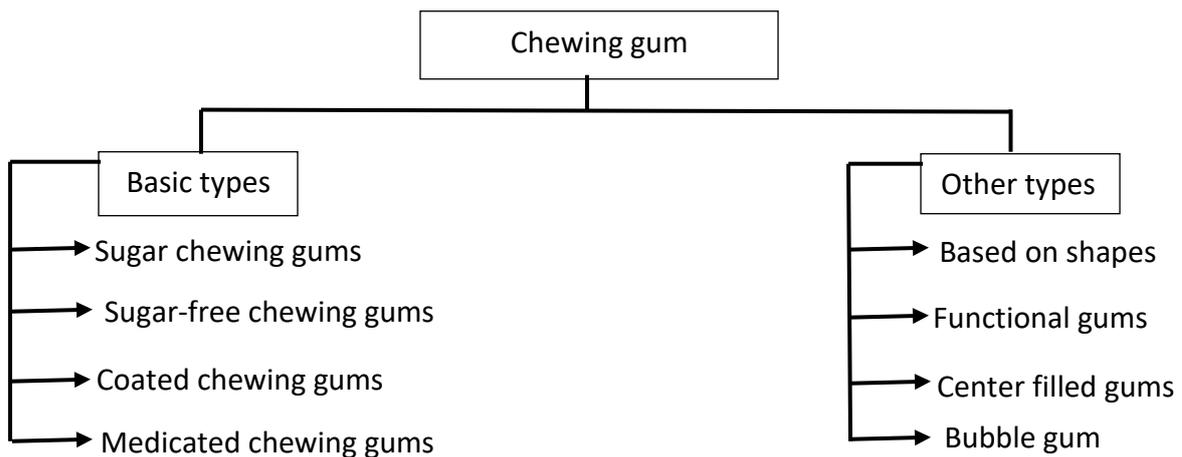


Figure 1: Classification of Chewing Gums

Basic types of chewing gums

Sugar chewing gums

It consists of 80% sugar and glucose syrup mixed with the gum base.

Sugar-free chewing gums

In this type of gum, sugar substituted with polyol compounds and high-intensity sweeteners for sugar and glucose syrup.

Coated chewing gums

Coatings present on this chewing gums increase the visual impact of the product, thereby it also increases patient compliance. The coating helps to control the water activity and shelf life of the product.

Medicated chewing gums

This type of chewing gums contains pharmaceutical or nutraceutical compounds that are released in a controlled manner during mastication. So, these gums are accepted as drug delivery systems. It has many potential applications like smoking cessation, treatment of motion sickness, anti-oxidant, oral antifungal, alertness, anti-nausea, anti-emetic, antiseptic, freshening of the oral cavity, healing, etc.

Other types of chewing gums

Bubble gums

Some chewing gums have a film-forming property. Because of this property they can blow a bubble. Therefore, they are known as bubble gums.

Center filled gums

Some chewing gums have flavored liquid in the form of soft mass in its center, named as center filled gums.

Functional gums

Some chewing gums are formulated as per the needs of human resources to fulfill the special function. These are known as functional gums. For example, the addition of vitamins or minerals in the gum to provide a practical function to it.

Based on shape

There are different types of chewing gums depending on the shapes like ball gum, stick gum, tube gum, wrap gum, ribbon gum, tab gum, dragee gum.

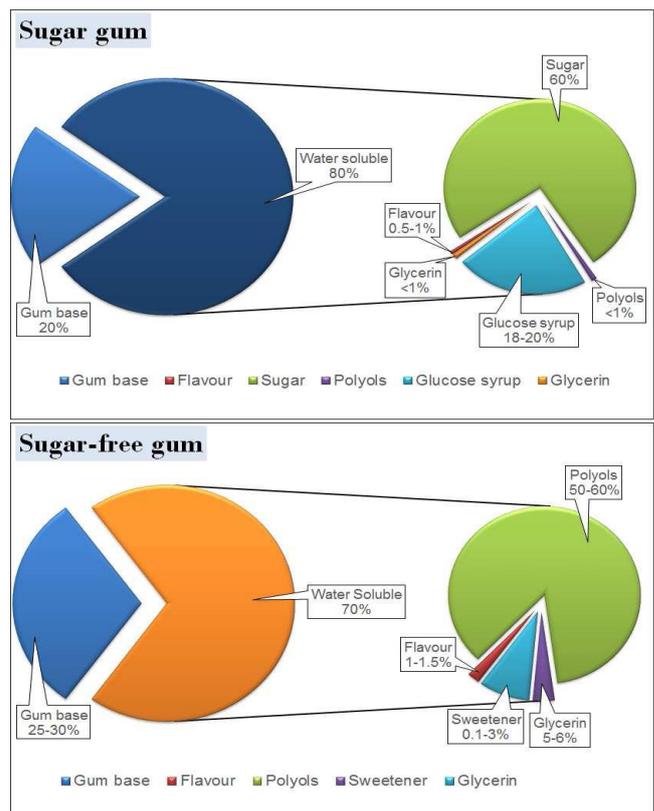


Figure 2: Average quantitative formulation of sugar and sugar-free chewing gum components. ²

COMPOSITION

Chewing gums are basically composed of neutral and tasteless masticatory gum base ^[1] which is formulated by using water-insoluble gum base and different additives like sweeteners, softeners, food colorings, preservatives, antioxidants, flavoring agents, etc. ^{2, 3, 5} Chewing gums consists of two phases, viz. water-insoluble gum phase and water-soluble phase (sugar or sugar alcohol phase).²⁻⁵ There will be a presentation of the third phase in the coated chewing gums. Compound material considered as a third phase in it.² The coating may be composed of active substance, colorants, flavoring agents, sweetening agents. All the ingredients must be of bio-compatible and biodegradable property. Because it must show clinical efficacy and potential safety if some amount of dose may be swollen from medicated chewing gums. ³

Water-insoluble gum phase

This phase of chewing gum consists of gum base, elastomers, plasticizer, and fillers. ^{2, 3, 5, 6, 8} The main composition of this phase includes gum base (20-30%), elastomer (10-30%), plasticizer (20-35%) and fillers (0-0.5%). ² Generally, regular chewing gums have 20-30% of gum phase while sugar-free chewing gums has that amount up to 50% on an average. ² Composition of gum phase affects the optimal properties of chewing gums like stickiness, chewiness, binding of flavoring compounds, aroma release of chewing gum, etc.²

Gum base

It is the fundamental raw material to fabricate chewing gums. It may be of natural or synthetic origin. Natural gum that is chicle isolated from the sapodilla tree ^{5, 8, 7}. It belongs to the Sapotaceae family with botanical name *Manilkara zapota* (L.) Van Royen. It is harvested during the rainy season from July to February in Mexico, Belize, and Guatemala. ⁸ The chicle composed of polyterpene units. ^{7, 8} This chicle gum is not so cheap and difficult to obtain. ^{5, 8} Therefore, as time passes it was substituted by synthetic gums such as polyvinyl acetate, isobutylene-isoprene copolymer and butadiene-styrene like basic copolymer. ^{5, 8} Gum base is an inert, non-edible, insoluble, non-nutritive material used to support chewing gum-based drug delivery.^{2, 6}

Elastomers

These are used to provide elastic property to the chewing gums. It also controls the gummy texture of chewing gum.^{3, 5} Elastomers used in the fabrication of chewing gums may be of natural elastomers are Latex, Jelutong, Lechi, Caspi, Puerile, Chicle.^{3, 5, 8} Synthetic elastomers are butadiene, styrene copolymers, polyisobutylene, isobutylene-isoprene copolymers, polyethylene mixtures and non-toxic vinyl polymers like polyvinyl alcohols.^{6, 8} Conventional elastomer solvents may also be used in the softening of elastomers.⁶ Elastomer solvents consist of terpinene resins such as polymers of α -pinene, methyl, glycerol or pentaerythritol esters of resins or modified

resins and gums, like hydrogenated, dimerized or polymerized resins or mixtures. The elastomer solvents may be used in concentrations of 5-75% by weight of gum base.⁶ The choice of an elastomer in chewing gum formulation plays an important role for aroma release of chewing gum. For any chewing gum formulation, it is important to stay flavor of chewing gum for a longer time. If there is a high-affinity present between elastomer and flavoring agent, then the flavor will be perceived for a longer duration of time during the mastication of chewing gum. If the concentration of elastomer solvent increased, then the resulted chewing gum show stickiness to the tooth surface and if the concentration decreased, then mastication parameters affected negatively. ²

Plasticizer

These are used to regulate the cohesiveness of the product. ^{3, 5} It provides enormous softness during mastication for better mouthfeel. ⁸ There are two types of plasticizers used in the formulation of chewing gum, viz. natural and synthetic. Natural plasticizers are glycerol esters, partially hydrogenated resins, ^{3, 5} polymerized glycerol esters, glycerol esters of partially dimerized resins, pentaerythritol esters of resins, ⁵ glycerin, lecithin, fatty acids like stearic acid, palmitic acid, oleic acid, and linoleic acid. Synthetic plasticizers are sodium stearate, glyceryl triacetate, glyceryl lecithin, glyceryl monostearate, acetylated monoglyceride. ⁶

Fillers

These are used to modify the texture of gum. It is one of the low-cost ingredients which helps in processing. ² It also improves chewing ability to chew gums. It provides the required size to gum lump with a low dose of the drug. ^{3, 5} For example, talc, alumina, titanium oxide, ground limestone, magnesium carbonate, clay, magnesium and aluminium silicate, ³ di-calcium phosphate, calcium carbonate, ⁶ bentonite, tri-calcium phosphate. ⁸

Water-soluble gum phase

This phase of chewing gum contains bulk as well as high-intensity sweeteners, softeners, emulsifiers, flavors, colors, anti-oxidants. ^{2, 3, 5}

Sweeteners

There are two types of sweeteners used in the fabrication of chewing gum, viz. aqueous and bulk. ^[5, 8] The sensory properties of the final product may get affected due to the particle size of sweeteners. The large particle of sweeteners may give a gritty texture to the final product.²

Aqueous sweeteners

These are used to retain the moisture of formulation for freshening purpose and also to soften the blend of gum.^{5, 8} These consist of sugars like sorbitol, hydrogenated starch hydrolysates, and corn syrups. ^{3, 5, 8} Corn syrup helps to keep gum fresh and flexible.⁵ These sweeteners can also



be used as binding agents or softening agents in the fabrication of medicated chewing gums.⁸

Bulk sweeteners

These contain sugar and sugarless components.⁵ 30-75% of these sweeteners used in the fabrication of the chewing gum.⁸ These bulk sweeteners are further classified into two types, viz. nutritive sweetener and non-nutritive sweeteners.⁸

Nutritive sweeteners

These contain sugar and sugar alcohol compounds. 2-15% of these ingredients used to formulate chewing gum.⁸ Sugars mainly involves components like sucrose, dextrose, maltose, fructose, galactose, maltodextrin,^{5, 8} dextrin.⁵ Sugar alcohols used in chewing gums are mannitol, sorbitol, xylitol,^{3, 8} hydrogenated starch hydrolysate.⁵ These are also known as polyols.^{2, 8} Sugar alcohols or polyols are low-intensity natural sweeteners.⁸ These are generally used in the formulation of sugar-free chewing gum.² Polyols does not get completely absorbed from the intestines. Thus, they provide lower calories (2 Kcal/g) than that of the sugar (4 Kcal/g).⁸ This property of polyols provides non-calorigenic characteristics to the chewing gum formulation. These polyols also not responsible for the development of dental caries, so accepted as non-cariogenic substances.² These can provide a cooling sensation in the mouth during mastication.⁸ Polyols cannot be served as an energy source for bacteria to regulate their growth and reproductive function. Xylitol has a relatively higher cost than other polyols. Therefore, it is used in combination with mannitol, sorbitol or lactitol.²

Non-nutritive sweeteners

The high-intensity artificial sweeteners are known as non-nutritive sweeteners. These sweeteners are generally evaluated for their safety, sensory qualities and ability to stand various pH environments. The examples of these sweeteners used in the chewing gum formulation are saccharin, aspartame, neotame, acesulfame potassium, sucralose,^{2, 8} thaumatin.² As these sweeteners have a high intensity of sweetness, they required in the lowest concentration between 0.05-1 percent of the final weight of chewing gum.⁸

Softeners and emulsifiers

These agents used in the fabrication of chewing gum to provide chewability and better mouth feel of the gum.^{3, 5, 8} Generally used in the range of 0.5-15% concentration.⁸ For example Glycerin, lecithin, stearic acid, palmitic acid, oleic acid, linoleic acid,^{3, 5, 8} tallow, hydrogenated tallow, mono or di or tri-glycerides.⁵

Flavoring agents

These agents are used to improve the flavor in chewing gum.^{3, 5, 6, 8} Generally, they mask the bitter taste of the drug by incorporating flavor in it.⁸ Several flavoring agent presents are used such as citrus oil, fruit essence,

essential oils, peppermint oil, spearmint oil, mint oil, clove oil and oil of wintergreen.^{3, 5, 6}

Table 1: FDA approved high-intensity artificial sweeteners⁷

Approved artificial sweeteners	Times sweeter than sucrose	Description
Saccharin	200-700	Sweet at very low concentration and bitter at high concentration. Bitter after taste.
Aspartame	160-220	No bitter after taste. Stable in the dry solid-state but unstable in a liquid state. Sensitive to hydrolysis.
Neotame (advanced aspartame)	7000-13,000	Resistant to hydrolytic degradation.
Acesulfame K	200	Heat stable Shows synergistic action with aspartame.
Sucralose	600	Heat stable. Stable over a broad pH range.

Table 2: Flavoring agents for specific taste-masking⁸

Taste of drug	Flavors used for taste-masking
Sweet	Fruit and berry, honey, vanilla, bubble gum
Bitter	Wild cherry, raspberry, coffee, chocolate, mint, grapefruit, passion fruit, peach, orange, lemon, lime, anise
Acidic sour	Lemon, lime, orange, cherry, grapefruit, liquorice
Alkaline	Mint, chocolate, cream, vanilla
Metallic	Burgundy, berries, grape, marshmallow, Guyana
Salty	Butterscotch, maple, apricot, peach, melon

Bulking agents

This type of ingredient used in case of potent drug or low dose drugs to produce the required bulk of chewing gum.^{3, 5, 8} For health conscious and diabetic peoples, a low-calorie gum used as a bulking agent in chewing gum.⁸ For example, polydextrose, oligofructose, inulin, guar gum hydrolysate, indigestible dextrin^{3, 5, 8}, fructo-oligosaccharide.⁸

Coloring agents

These are used to provide a better look at the formulation. It increases patient compliance. Different food colors, natural dyes, pigments used for coloring purposes. It may be used in the concentration of 0.1% of the final product. Various FD and C approved colors used for it.^{3, 6, 8}



Anti-oxidants

The agents used to protect the formulation from oxidation are known as anti-oxidants.^{2, 3} These are used in the concentration of gum base. For example, propyl gallate, butylated hydroxyl anisole (BHA), butylated hydroxyl toluene (BHT), tocopherol, and ascorbic acid.^{2, 3, 6, 8}

Active component

This may be present in core or coat or maybe in both of chewing gum. It may be added in the proportion of 0.5-30% of the final weight of medicated chewing gum. An active component with small particle size, lipophilic property, an enzymatically stable and unionized form readily becomes bioavailable. An active component having a higher solubility in saliva will be completely released within 10-15 minutes of mastication. But lipid-soluble drugs firstly dissolve in the gum base and it gets slowly and completely absorbed.^{5, 8} The addition of buffering agents or solubilizing agents and coating or encapsulation increases the rate and extent of release of the active component.⁸

Factors Affecting Release of Active Component

Physicochemical properties of drug

The physicochemical properties of the drug like molecular mass, ionized or non-ionized form, lipophilicity or hydrophilicity, stability to salivary enzymes (amylase) and its solubility in salivary fluid plays an important role in the release of drug from medicated chewing gum and absorption of the drug through the oral mucosa.⁸ Hydrophilic drugs get easily soluble in saliva while lipophilic components released slowly in the oral cavity.^{3-5, 8}

Inter person variability

Medicated chewing gum does not have therapeutic certainty related to the drug delivery method because of the mechanical chewing action of the patient. That's why it has not yet been fully exploited. The therapeutic effect of medicated chewing gum depends on chewing.^[8] As a chewing rate, force, frequency and chewing time changes person to person which may lead to variation in results. Approximately, the average chewing rate of medicated chewing gum was found to be 60 chews per minute. European pharmacopeia prescribed an in-vitro study which suggests that 60 strokes per minute are sufficient for a proper release of active ingredients.^{3, 4, 5, 8}

Contact time

Local and systemic effects of medicated chewing gum depend on contact time in the oral cavity.^{3, 4}

Formulation factors

The rate and extent of drug release from medicated chewing gum depend on composition, amount and type of gum base.^{3, 4, 5, 8} Lipophilic fraction of the gum base has

inverse proportion with the release of the active component.^{3, 4, 5}

Manufacturing Process

There are different methods available for manufacturing of chewing gum which can be classified into three main classes namely,

1. Conventional or traditional method
2. Cooling, grinding, and tableting
3. Direct compression method

Conventional or traditional method

This method is also known as the 'fusion or melting' method. Firstly, the gum base softened or melted and placed in a kettle mixer. Then, sweeteners, syrups, active ingredients, and other excipients are added to it at a definite time. Formation of thin, wide ribbon of gum allowed by passing it through a series of rollers. During this process of ribbon formation, a light coating of finely powdered sugar or sugar substitutes is added. This will help to keep the gum away from sticking. It will also help in the enhancement of flavor. The gum is allowed to cool for 48 hrs in a carefully controlled room. This process helps in the proper setting of gum. Finally, the gum is cut in the desired size and cooled carefully at a controlled temperature and humidity.

Limitations

- i. Thermo-labile drugs may get damaged due to the use of elevated temperature in the melting process.
- ii. The highly viscous substance may result in inhomogeneity of bioactive amount.
- iii. Medicated chewing gum has 2-8% of moisture content which may produce difficulties in the production of tablets like jamming the machines, sticking to blades and adhering to punches during compression.
- iv. Lack of precise form, shape or weight of dosage form.

Cooling, grinding and tableting^{2, 3, 5, 8}

This method lowers the moisture content of gum and overcomes the problems mentioned in a conventional or traditional method.

Cooling and grinding

The medicated chewing gum base is cooled to a temperature at which the composition is adequately brittle and would stay brittle throughout the following grinding step without adhesion to the grinding equipment. The temperature needed for cooling is set partially by the composition of the chewing gum and is determined by trial and error by perceptive the properties of the cooling change of state gum composition. Generally, the temperatures of the refrigerated mixture are around -



15°C or lower. Amongst the assorted coolants like Nitrogen, hydrocarbon slush, use of solid carbonic acid gas is most well-liked because it will provide temperatures as low as -78.5°C. It easily sublimates on the warming of the blend, is not consumed by the composition of the medicated chewing gum, does not interfere adversely with the handling apparatus and does not leave any residue that may be unwanted or possibly dangerous. The refrigerated composition is then crushed or ground to obtain minute fragments of finely ground pieces of the composition. Alternatively, the steps of cooling the medicated chewing gum composition will be combined into one step. For example, cooling the grinding equipment itself which may be done by contacting the grinding equipment with coolant or by putting the grinding equipment in cooling jacket of liquid nitrogen or other cold liquid. For more efficient cooling, the chewing gum composition can be pre-cooled before cooling to the refrigeration temperature. Sometimes a mixture of chewing gum composition, solid carbon dioxide and precipitated silica is ground during a first grinding step in a mill grinder.

Additional solid carbon dioxide and silica are added to the ground composition and in a second grinding step, the composition is further ground. This two-step grinding method well keeps the medicated chewing gum composition at the lowest temperature. The presence of solid carbon dioxide also serves to enhance the efficiency of the grinding process. The same method will be created multiple by adding/incorporating further carbonic acid gas and/or precipitated oxide at every step. Certain additives will be added to the change of state gum composition to facilitate cooling, grinding and to achieve desired properties of chewing gum. These embrace the use of an anti-caking agent and grinding agent.

Use of anti-caking agent

An anti-caking agent like precipitated silicon dioxide can be mixed with the composition of the chewing gum and solid carbon dioxide added before grinding. This helps to prevent the subsequently grounded chewing gum particles from agglomerating.

Use of grinding agents

To prevent the gum from sticking to the grinding instrument, it is possible to incorporate 2-8 percent by weight of grinding aid such as alkaline metal phosphate, an alkaline earth metal phosphate or maltodextrin. However practical use of these substances is limited because these substances are highly alkaline and hence would be incompatible with acidic ionizable therapeutic agents. They also tend to remain in the composition and final chewing gum tablet and thus may be problematic for

a therapeutic and safety point of view. The coolant can be removed after the composition is ground to a powder by permitting the coolant to evaporate. Alternatively, it has been found that such a powdered mass when warmed to room temperature from the refrigerated state, becomes cross-linked or self-adhere together to form an integrated body incorporating minute air bubbles in the texture between the particles. This provides a lightweight chewing gum product and during chewing gives a soft chewing impression.

Tableting

After removing the coolant from the powder, the powder can be mixed with other ingredients such as binders, lubricants, coating agents, sweeteners, etc. all of which are compatible with the components of the chewing gum base in a suitable blender such as sigma blade mixer or a high shear mixer. Alternatively, a fluidized bed processor used because it partially not only re-construct the powder into granules but also coats the powder particles or granules with a coating agent thereby minimizing undesirable particle agglomeration. The granules so obtained can be mixed with anti-adherents like talc. The mixture blended in a V type blender, screened and staged for compression. Compression can be carried out by any conventional process like punching. Limitation: It requires equipment other than conventional tableting equipment and requires careful monitoring of humidity during the tableting process.

Direct compression method

Recently, free-flowing directly compressible co-processed gum materials such as Pharmagum developed by SPI Pharma 32 and Health in gum developed by CAFOSA 33, have become available in the market. It is a chemical combination of polyols like sorbitol, xylitol, mannitol, and sugar with gum, plasticizers and anti-caking agents. This gum is manufactured under cGMP conditions and comply with food chemical specifications and is 'generally regarded as safe' (GRAS), regulated by FDA title 21 C.F.R Section 172.615. Chewing gum produced from this gum material can be compressed effectively on a pharmaceutical in-house tablet compression machine, allowing the medicated chewing gum to develop quickly and cost-effectively. As it does not require high temperature, the thermo-sensitive active component can also be processed. This method is also ideal for water-sensitive active components. Formulations made with Pharmagum M and Health in gum is similar to the tablet in appearance. Gum formed using a compressible formulation is many times harder and crumbles, and when pressure is applied it gives a faster release of drugs than conventional methods owing to lower bonding of drugs with gum material.



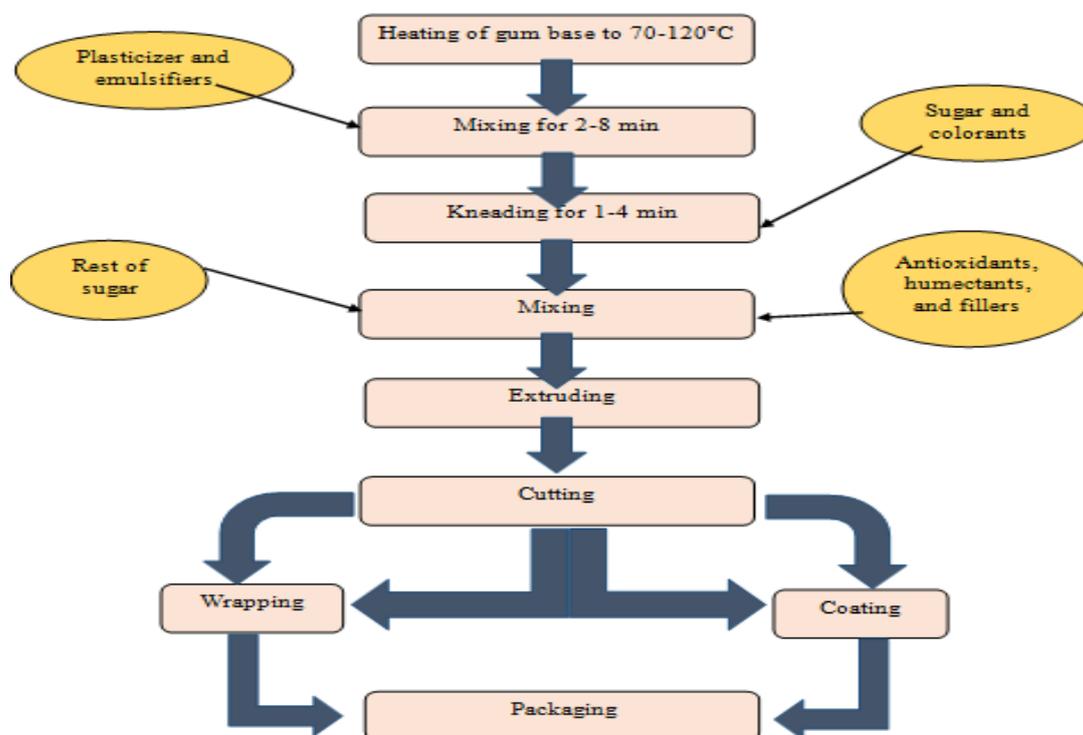


Figure 3: The general production process of chewing gum²

Problems Occurred During Manufacturing^{5,6}

1. During the manufacturing process of medicated chewing gum, gum base heated at elevated temperature to facilitate the mixing of other ingredients. This step may cause degradation of heat-sensitive or thermos-labile compounds. It may be an active component, flavor or any other excipient.
2. Some active components are soluble only in organic solvents. Therefore, during the manufacturing process, organic solvents are used to solubilize the active components. It is quite difficult to eliminate these organic solvents from the end product. If even a trace amount of organic solvent remaining in the final product, it may cause health-related risks.
3. Water can also be used in the manufacturing of medicated chewing gum, but it is difficult to eliminate from the final product. It is not possible to remove water from medicated chewing gum at low-temperature conditions while the elevated temperature may tend to degradation of the product. Heating may generate stickiness in the gum which makes handling difficult. This process may interfere with large scale, semi or automated products. The presence of water in gum increases the moisture content of the end product. An increase in moisture content leads to produce difficulties in the tableting of gum.
4. If the moisture level of gum is not controlled, it will jam the grinding machine, stick to the blades,

screens and other surfaces. If the moisture content is more than 2% by weight, it may produce other problems like adherence of gum to the punch or press and difficulties associated with compressibility.

Formulation Aspects^{5,8}

Ion exchange resin complexation

Lipophilic active ingredients complexed with the ion exchange resin to provide sustained drug delivery. For example, Polacrillin potassium. This approach also helps in masking the bitter taste of drugs. Most of the drugs contain ionic sites in their molecules, but a charge present on resin provides a mean to bind such drugs loosely. This formed complex helps in preventing the release of drug in the saliva, thus masking the taste. Weak cation exchange or weak anion exchange are used to mask the taste, depending on the nature of drugs.

Cyclodextrin complexation

Solubility, stability, and bioavailability of different active components present in the formulation can be enhanced by using cyclodextrin complexes. This approach also helps in masking the taste of certain active components. There are three naturally occurring cyclodextrins, viz. α , β and γ containing 6, 7 and 8 glucopyranose units respectively. Hydroxypropyl derivatives of β -cyclodextrin are water-soluble. For example, randomly methylated β -cyclodextrin (RM β CD) and sulfobutyl ether β -cyclodextrin sodium salt (S β E β CD). Hydrophilic cyclodextrin derivatives are considered as non-toxic derivative at low to moderate oral dosage, thus it is used to increase the aqueous solubility of poorly water-soluble drugs. For example, 2-

hydroxypropyl β -cyclodextrin derivative. Lipophilic cyclodextrin derivatives have limited use in oral administration because it shows potential toxicity. For example, methylated cyclodextrin and sulfobutyl ether cyclodextrin.

Microencapsulation

Microencapsulation is one of the successful approaches for sustaining the release of the active component, sweetener and flavoring agent from medicated chewing gum. It is carried out by using water-soluble or water-insoluble polymer. Rapid exhaustion of flavor and sweetness sensation during mastication occurs within the first 3-5 min of chewing. But the microencapsulation process overcomes these drawbacks. The particle size of any solid substance suspended in the chewing gum is an important factor during microencapsulation. The particle size of components must be kept below 100 μ m which avoids an unpleasant gritty feeling during chewing and the risk of damaging the enamel of the teeth.

CHARACTERIZATION

There are two types of evaluation tests performed to assess the drug product characteristics, viz. physical evaluation parameters and quality parameters:

Physical evaluation of medicated chewing gum

Uniformity of content^{3, 6}

Content of 2mg or less than 2% of the total mass of gum comply with this test.

Uniformity of mass^{3, 6}

Uncoated and coated medicated chewing gum comply with the test for uniformity of mass of single-dose preparation.

Weight variation^{3, 5}

This test is performed to determine the weight variation present in one batch of product. Weight of 10 medicated chewing gum was taken from one batch. Average weight calculated and from that standard deviation calculated.

Stickiness^{3, 5}

Medicated chewing gum was placed on a planar surface. Cylindrical hammer colloids on medicated chewing gum with a frequency of 30 strokes per minute. This process carried out for ten minutes. Afterward sticking of mass to the hammered surface was observed and reported.

Hardness / plasticity^{3, 5}

This test was performed by using Monsanto type hardness tester for all types of medicated chewing gum formulation.

Chew out the study^{3, 5, 8}

The protocol of this test was formulated based on input from Fertin Pharma Pvt. Ltd. Denmark (one of the largest manufacturers of medicated chewing gum). Various

parameters are included in the initial phase of chew-out study such as texture, elasticity, smoothness, crankiness, softness, cooling effect, hardness, juiciness, cheesiness and lubricating feel.⁵ In this test, in vivo release of the incorporated drug studied. The chew-out study can be carried out in four ways as:

Drug release in saliva

The panel of volunteers is asked to chew the drug delivery device for a certain time and to assess the remaining quantity of an active substance in the residual gum. The gums are really chewed in this way and the formulation is subjected not only to the mechanical stresses of an artificial machine but also it undergoes all the phenomena involved in this process (increase of salivary secretion, saliva pH variation, swallowing and absorption by the oral mucosa, etc.) which can strongly influence the performance of the dosage form and the amount and rate of drug release. It is possible to select optimized formulations with excellent consistency to release the drug into saliva. Minimum Four human volunteers can be selected (two males and two females). Volunteers are instructed to rinse their mouths with distilled water and allowed to chewing the medicated chewing gum for 15 minutes so that its maximum release has to be taken. The saliva sample is drawn after 2, 4, 6, 8, 10, 12, 14, 15 min. The saliva samples are made diluted in the required solvent and absorbance is analyzed by a suitable analytical method.

Dissolution test of residual medicated chewing gum

In this experiment, gums are tested by a panel of volunteers to verify the drug release process from the drug delivery system. Each person chews one sample of the tableted gum for different periods (1, 5, 10, 15 min). The residual gums are cut into tiny fragments, frozen and ground until a fine powder is obtained. The content of the remaining drug is determined using the appropriate analytical method. The amount of drug released during mastication is calculated by subtracting the amount of residual active ingredient present in the gum from the total content, whereas pharmacokinetics can be determined from withdrawn blood samples at specific time intervals. A few constraints of chew-out research are the prerequisites of human volunteers, inter-individual variability in chewing patterns, chewing frequencies, composition of individual saliva and saliva flow rate.

Urinary excretion profile of medicated chewing gum

This method can be applied only to those drugs which are excreted via urine. For the study of formulations, at least four healthy human volunteers are chosen. Volunteers are strictly instructed that they should not take any medicine in the last 48 hours. They are fasted overnight and emptied their bladder in the volumetric flask. The sample collection starts from a blank of zero-hour urine. Then sampling is performed at intervals of 15 min, 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 24 hours after administration of medicated chewing gum. The volunteers are asked to



drink water at regular intervals of 30 min. and urine samples are analyzed by suitable analytical methods.

Buccal absorption test

Human volunteer swirled fixed volume of drug solution of known concentration at different pH values of 1.2, 5, 6, 6.5, 7, 7.5, 7.8, 8, in the oral cavity for 15 min and then expelled out. The expelled saliva is analyzed for drug content and back-calculated for buccal absorption.

In vitro drug release^{3, 5, 6, 8}

The gum piece was placed in a temperature-controlled chewing chamber of the chewing machine. The compressed air chewed it by two electronically-controlled horizontal pistons and the third vertical piston confirms that the gum placed in the proper position. The chamber temperature can be maintained at $37\pm 0.5^\circ\text{C}$. Other various parameters such as chew rate, medium volume, the distance between the jaws and twisting movement of the piston varied according to the need. The European Pharmacopoeia recommends an unspecified buffer (20ml, pH 6) in a chewing chamber (40 ml) with a chew rate (60 strokes/minute).

Unofficial single-module chewing apparatus

One of the unofficial apparatus for carrying out dissolution studies of medicated chewing gum was designed by Wennergren. This apparatus consists of a two-piston and temperature-controlled reservoir for dissolution medium, as shown in a schematic representation in Fig. 4. The upper jaw has a flat surface that is parallel to the central part of the lower surface. The small brim of the lower surface is angled upwards (45 degrees) so that the lower surface functions as a small bowl with a flat bottom. This bowl prevents the chewing gum from sliding during mastication. Throughout one cycle of chewing, one piston on each side shift towards each other. When they get together, they press the MCG between them and then make a twisting association before returning to the preliminary point. To carry out a drug release test, a known quantity of chewing gum is placed in the 20 ml volume of the dissolution medium, which is equilibrated to a temperature of 37°C . The pressing and twisting forces are transmitted to the gum through the pistons at a chewing rate of 60 strokes a minute. At specified time intervals, that is, 3, 5 and 10 min, samples are collected and analysed to evaluate percentage drug release.

Official medicated chewing gum chewing apparatus

The official modified dissolution apparatus for assessing drug release from medicated chewing gum, as per European Pharmacopoeia, is depicted in Fig.5. In this apparatus, in addition to the pair of horizontal pistons ('teeth'), the chewing chamber is supplied with a vertical piston ('tongue') working alternate to the horizontal pistons, which ensures that the gum is always positioned in the correct place during the mastication process. If required, it is possible to construct the machine so that at

the end of the chew the horizontal pistons rotate in opposite directions around their axis to each other to attain maximum mastication. The temperature of the chamber can be maintained at $37\pm 0.5^\circ\text{C}$ and the chewing rate can be varied. Other adjustable settings include the volume of the medium, the distance between the jaws and the twisting movement.

The European Pharmacopoeia recommends 20 ml of unspecified buffer (with a pH close to 6) in a chewing chamber of 40 ml and a chew rate of 60 strokes a minute. This most recent device seems promising, competent and uncomplicated to operate. Several studies have been carried out using the European Pharmacopoeia apparatus and the results indicate the methodology is rugged and reproducible.

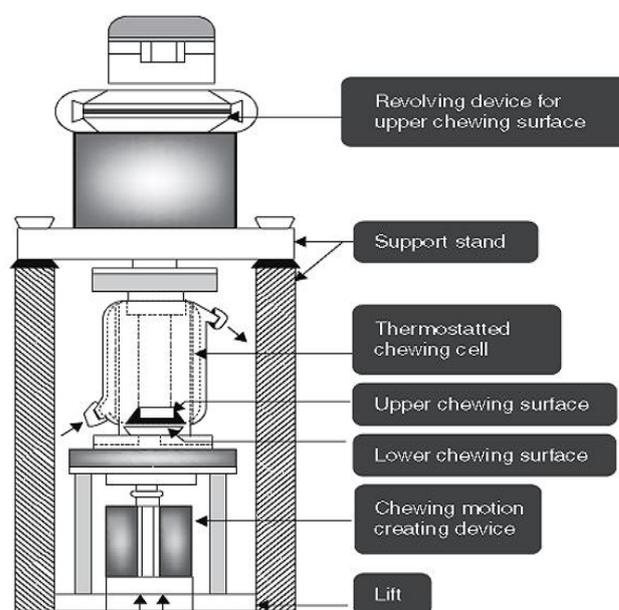


Figure 4: Schematic representation of unofficial single module chewing apparatus⁸

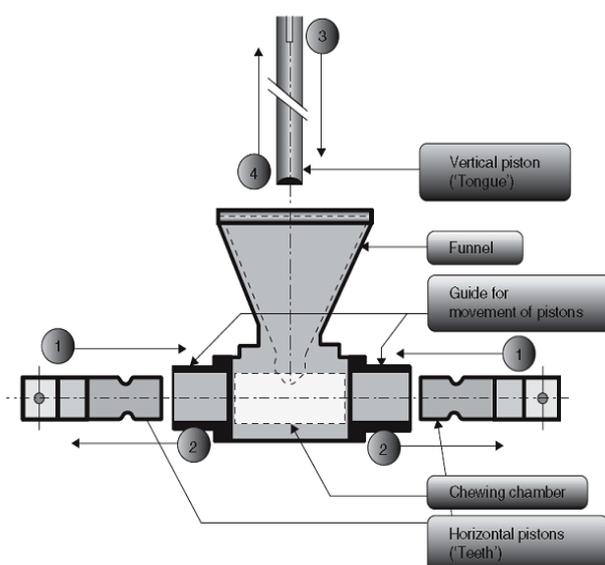


Figure 5: Schematic representation of modified dissolution apparatus as per European Pharmacopoeia,

where numbered arrows indicate the sequence of motion⁸

Stability study^{3, 5, 6}

Synthetic gum base (10 gm) was stored in the bottle for six months at 30°C ± 2°C/65% RH ± 5% RH as according to WHO guidelines. The gum was examined for signs of aging and physical deformities.

A. Quality parameters²

1. Texture:
2. Flavor:
3. Sensory:

Applications

The medicated chewing gum can also be used as an alternative tool for buccal and sublingual tablets. It acts locally as well as systemically because the drug is released more uniformly and covers a maximum area of absorption in the oral cavity. Medicated chewing gum widely used for local effects in various conditions (plaque acid neutralization, fresh breath, dental caries, anti-plaque, fungal, and bacterial infections) and systemic effects in various conditions (vitamin C deficiency, pain & fever, alertness, motion sickness, and smoking cessation). Some of the major applications of medicated chewing gum are described below:

Local therapy

The main target of chewing gum formulation is to prevent and treat oral diseases. From this formulation, the active drug substances release in a controlled manner and show local effects against dental caries. Low plaque pH plays a significant role in the origin of dental caries. Therefore, sugar-free chewing gum is suggested and recommended after meals in caries prevention treatment.

Dental caries^{3, 5, 7, 8}

- i. To prevent and cure oral disease is the main target place.
- ii. To control the release rate of active substances and to provide a prolonged local effect.
- iii. Lowers intensity and frequency of dental caries by relegate plaque pH.
- iv. Fluoride chewing gum can be used to prevent dental caries in children.
- v. Chlorhexidine chewing gum can be used to treat various infections (gingivitis, periodontitis, oral and pharyngeal infections) and cause less staining of the teeth.
- vi. To mask the bitter taste of various drugs such as Chlorhexidine.

Oral candidiasis^{3, 4, 7}

Fungal infections have become major causes of morbidity microorganisms to conventional treatment is becoming a challenge, researchers are trying to identify potential drugs and alternatives treatments with better and improved therapeutic effects and fewer adverse effects. Studies are underway to create a medicated chewing gum with a mixture of essential oils as active ingredients to treat oral candidiasis effectively.

Systemic therapy^{3, 5, 7, 8}

Medicated chewing gum formulations provide better absorption through the buccal mucosa after systemic drug delivery. Systemic therapy of medicated chewing gums offers the treatment of adults, children, and adolescents due to its various advantages such as quick and critical treatment, easy, no need for water, easy administration, reduced risk of gastrointestinal tract side effects, and no attention drawn to the condition requiring medication. Medicated chewing gums could be advantageous to several indications such as,

Pain^{3, 5, 7}

Chewing gum formulation containing NSAIDs has been clinically treated with minor pains, headaches, and muscular aches. The oldest medical chewing gum available is Aspergum[®], a chewing gum containing acetylsalicylic acid.

Smoking cessation^{3, 4, 5, 7}

Nicotine, silver acetate and lobeline containing formulations have been clinically tested as assistances to smoking termination. Aslani and Rafiei (2012) formulated nicotine-containing chewing gum by direct compression technique to assist smokers to quit smoking. The result showed that the final formulation had optimal chewing hardness, adhering to teeth, and plumpness characteristics, as well as the most pleasant taste and highest acceptability to smokers. Nicotine chewing gum can be regarded as a convenient formulation for breaking an "oral habit" like smoking.

Obesity^{3, 5, 7}

Active substances like chromium, guarana, and caffeine-containing formulations are proved to be efficient in treating obesity. Caffeine and guarana have demonstrated to increase the metabolic rate and stimulate lipolysis and reduce the feeling of hunger. Aslani and Jalilian (2012) prepared caffeine-containing chewing gum to increase alertness and decrease fatigue. Chromium reduces obesity due to improved blood glucose balance.

Other indications^{3, 5, 7}

- i. Beneficial in various other diseases such as xerostomia, allergy, motion sickness, acidity, cold, cough, diabetes, anxiety, etc.



- ii. Chewing gum is known to be a potent stimulant of salivary secretion.
- iii. Pilocarpine incorporated formulations increased in salivary secretion.
- iv. Stimulated saliva has a buffering capacity and may, therefore, help reduce the acidity of gastric fluid.
- v. Antacids containing formulations reduce the postprandial reflux.
- vi. Caffeine-containing chewing gum produces a positive stimulating effect on memory.
- vii. Active substances such as Dimenhydrinate, scopolamine, and dolasetron containing formulations are used for the prevention and treatment of diarrhea and nausea.

Future Trends^{3,5,7}

Medicated chewing gum is a gorgeous, distinct and well-organized drug delivery system that offers clinical benefits. A few decades ago, surgical procedure is one of the ways for the treatment of diseases but now it replaced with novel drug delivery systems. Chewing gum is believed to mark its place as an appropriate and favorable drug delivery system as it encounters the high-quality values of the pharmaceutical industry and can be framed to achieve different release profiles of dynamic ingredients (proved by clinical trials and market research reports). In the coming years, these new formulations (medicated chewing gum) established successfully in the market as a drug delivery system and gain acceptance by both professionals and patients.

Marketed products of medicated chewing gum

Several marketed products of medicated chewing gum are given in table no. 3.

Table 3: Marketed products of medicated chewing gum^{3,7}

Product	Commercial availability	Drug	Indication
Advanced	Worldwide	Chlorohexidine	Prevention of dental caries
Aspergum	North America	Aspirin	Analgesic
Brain	Japan	DHA, CCE	Enhanced brain activity
Buzz gum	United kingdom	Guarana	Alertness
Café coffee	Japan	Caffeine	Alertness
Chooz	USA	Calcium carbonate	Stomach acid, neutralization
Chroma slim	USA	Chitosan C with Chromium Picolinate	Diet
Endekay Vit C	United kingdom	Vitamin C	General health
Fluorette	Japan	Fluoride	Prevention of dental caries
Go gum	Australia	Guarana	Alertness
Hexit	Australia	Chlorhexidine	Antibacterial
Nicorette	Worldwide	Nicotine	Smoking cessation
Nicotinelle	Western Europe	Nicotine	Smoking cessation
Niquitin CQ	Worldwide	Nicotine	Smoking cessation
Stamil Vit C	Australia	Vitamin C	General health
Stay alert	USA	Caffeine	Alertness, motion sickness
Superpep	Germany, Switzerland	Dimenhydrinate	Travel illness
Travell	Italy, Switzerland	Dimenhydrinate	Travel illness
Vitaflo	USA	Chlorhexidine	Antibacterial
V6	United kingdom	Xylitol	Prevention of dental caries

Safety Aspects^{3,5,7}

Difference commercial chewing gums have been shown stick to a different degree to dentures, fillers, and crowns. Previously, some problems associated along with chewing gum such as broken teeth (due to hard nature), painful jaw muscles (due to extensive chewing for longer duration of period), diarrhea (due to extensive sugar alcohol), allergic

reactions (due to flavors & colors) and cause increased discharge of mercury vapors from dental amalgam paddings. Like other medical substances, medicated chewing gum should be kept out of reach of children, if required.



SUMMARY AND CONCLUSION

Medicated chewing gum is an exceptional drug delivery system as compared to chewable tablets, lozenges, and other related formulations. Due to its unique characteristics, it can be concluded that the medicated chewing gums can be used, as a carrier for vast categories of drugs where extended-release and can produce both local and systemic effects in the oral cavity. Medicated chewing gum is assumed to evident its situation as an appropriate and beneficial drug delivery system as it encounters the high-quality standards of Pharm. Industry and can be formulated to obtain different release profiles of active substances. Finally, in the future, we may see medicated chewing gum become the first choice as a comparison to other delivery systems to deliver drugs locally to the oral cavity due to its unique characteristic properties such as easy to administer anywhere, anytime, convenient, and its pleasant taste increases the product acceptability and patient compliance.

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