International Journal of Medical & Pharmaceutical Sciences
DOI: https://doi.org/10.31782/IJMPS.2023.13102

Review Article

IJMPS
Section: Pharmaceutical Sciences

Recent Formulation Development Advances and Drug Delivery Insights for Medicated Chewing Gums

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ABSTRACT

Oral medication delivery system research has resulted in the development of new formulations and technology. Such studies demonstrate the importance of the oral route among patients. We've gone through all of the benefits and drawbacks of medicated chewing gum as a contemporary medication delivery system, including the history, benefits and drawbacks, production processes, composition variations, assessment tests, and samples of different medicated chewing gum kinds. The acceptance of medicated chewing gum has grown over time. Chewing gum's advantages and therapeutic benefits encourage its development, as shown by the fact that new formulations including new pharmaceuticals have been generated in the past and will be found in the market by the formation of new medicated chewing gums. Medicated chewing gums have a broad range of potential uses that will be identified in the future. Chewing gums now have the same qualification criteria as pills. Patients' compliance is improved by using medicated chewing gums as a delivery strategy in patient-centered research.

Keywords: Medicated chewing gum, Formulation, Drug delivery, Manufacturing, Evaluation, Products

1. INTRODUCTION

1.1. Modified release dosage forms

Modified release dosage forms are developed to deliver drugs to the specific part of the body wherever it will be absorbed, to change dosing schedules, associated to assure that concentration of the drug is maintained over an acceptable interval. Modified release dosage forms are more acceptable compared to conventional dosage forms, there are a lot of improvements in terms of formulation development and product design [1]. Modified dosage forms are getting approval worldwide and many researchers are showing their interest in this direction. To improve bioavailability and to achieve better acceptability, newer technologies are developed to modify normal conventional tablets. Tablets that come under modified release dosage forms are oral disintegrating tablets, lozenges, medicated chewing gums, effervescent tablets, sublingual and buccal tablets, extended-release tablets, etc., medicated chewing gum can be used as a convenient novel drug delivery system [2]. Today, medicated chewing gums meet a similar high-quality standard as tablets and they are developed in a way that the different drug release profiles may be outcome thereby it target different patient groups (**Figure 1**). From ancient times man had a habit of chewing the chewing gum. These days it is one of among the foremost popular dosage forms used for delivering numerous active substances [3].

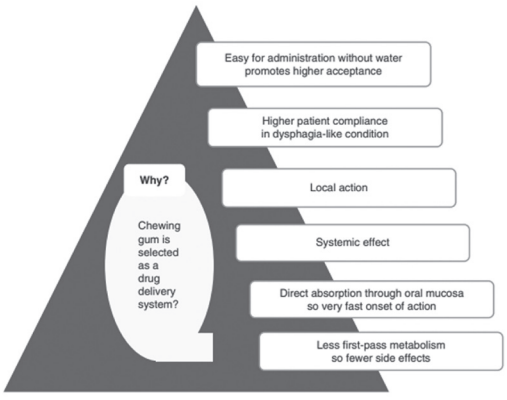

Figure 1: Reasons for selecting medicated chewing gums as a therapeutic agent.

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ISSN: 2231-2188 (Print) **ISSN:** 2231-685X (Online)

Received: 18.11.2022 **Revised:** 25.12.2022 **Accepted:** 05.01.2023 **Published:** 31.01.2023

1.2. Anatomy and Physiology of Oral Mucosa

The oral cavity is an attractive site for delivering medicines locally or systemically. Anatomy and physiology of the oral cavity show the direct influence on oral mucosal drug delivery systems [4]. The oral mucosa can be subdivided into 2 general regions they are the outer vestibule and the oral cavity (**Figure 2**).

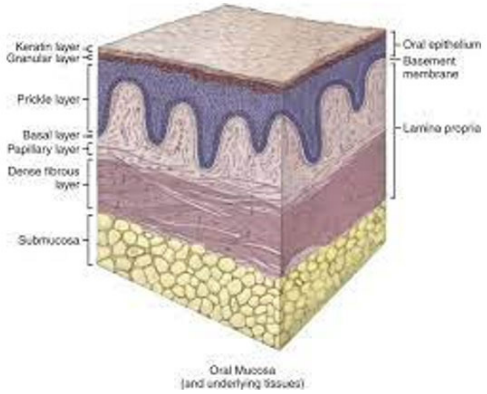

Figure 2: Oral epithelium anatomy.

Oral mucosa consists of 3 main layers:

1.2.1. Oral epithelium

The epithelium of the mouth includes stratified, squamous epithelium, which may also be keratinized. Keratinized epithelium is dehydrated, chemically resistant, and mechanically tough. It is found in the oral cavity subjected to mechanical stress such as mucosa of the gingival and hard palate (roof of the mouth). The non-keratinized epithelium is somewhat flexible and is found in areas like the tender palate, the floor of the mouth, cheeks, and lips. The epithelium of the oral cavity is supported by the basement membrane, which separates the epithelium from the underlying connective tissue layer. The oral epithelium is similar to stratified squamous epithelia, it is found somewhere else in the body for example the skin [5].

1.2.2. Lamina propria

It is a sheet of connective tissue containing collagen elastic fiber and cellular components in a hydrated ground substance. It also carries blood capillaries and nerve fibers. The drug moieties can enter into systemic circulation through the blood vessel in the lamina propria [6].

1.2.3. Salivary Glands

Saliva is a watery secretion, hypotonic in nature containing mucus, enzyme, antibodies, and inorganic ions. 0.5 to 2 L of saliva is daily produced by the salivary glands which are important secretion supplied by the parotid, the submaxillary, and the sublingual glands. Saliva constantly washes the surface of the mucous membrane [7].

The presence of saliva in the mouth is essential for these main reasons:

1. Drug permeation across moist membranes occurs more easily than across the non-mucous membranes, compared to drug absorption across the GIT and skin.
2. The oral route is the important one to administer most of the drug substances.
3. The drug needs to therefore first dissolve in saliva before it can be absorbed i.e., the drug can't be absorbed directly from the dosage form [8].

1.2.4. Mechanism of drug transport

During the mastication process, the drug is released into saliva and is either absorbed through buccal mucosa or swallowed and absorbed through GIT. Drug transport across buccal mucosa follows simple Fickian diffusion [9].

$$J = DKp/\Delta ce$$

Where, J = Drug flux; D = Diffusivity; Kp = Partition coefficient; Δce = Concentration gradient

The drug permeation across the oral mucosa is by 2 pathways (**Figure 3**):

1. Transcellular/intracellular route
2. Paracellular/intercellular route

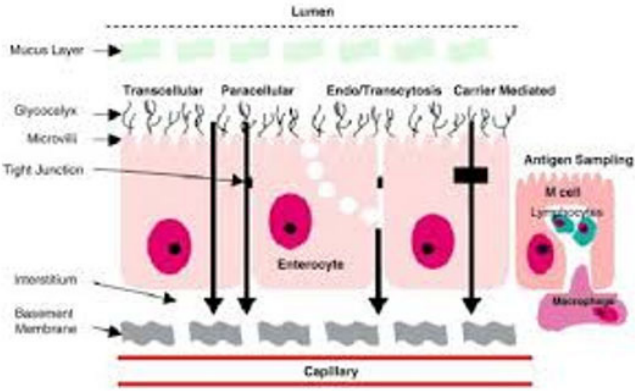

Figure 3: Drug transport pathways.

The drug transport pathways across oral mucosa may be studied using:

1. Microscopic techniques using fluorescent dyes,
2. Autoradiography, and
3. Confocal laser scanning microscopic procedures

2. MEDICATED CHEWING GUM

In the USA, in the year of 1948, the first commercially marketed medicated chewing gum **(Figure 4)** was 'State of Maine Pure spruce gum'. The first patent was issued in 1869 to Dr. W. F. Semple. This chewing gum was manufactured as dentifrices but it was never been marketed [10]. In 1928, the

first medicated chewing gum "Aspergum" was launched. The active medicament present in this gum was Aspirin, which is still available in the market. The chewing gum containing "Dimenhydrinate" is also available commercially for motion sickness. But until 1978 i.e., after the development of nicotine chewing gum, chewing gum did not get acceptance as a useful drug delivery system [11]. But, today technology is improved and extended, people may know how to develop medicated chewing gum with the required properties. Different types of active substances can be incorporated into the gum base because it is a convenient novel drug delivery system. Chewing gum was approved as a Pharmaceutical dosage form in 1991, by the commission of the European Council. According to European Pharmacopoeia, and guidelines, medicated chewing gums are defined as solid single-dose preparations with a base consisting mainly of gum that is intended to be chewed but not to swallow [12].

Figure 4: Medicated chewing gum.

2.1. Formulations

2.1.1. Development

The medicated chewing gums contain a gum base with one or more medicaments which are released after chewing for a certain period of time, to deliver the dose, after that remaining mass is discarded. The drug was released into saliva, during the chewing process and absorbed through the oral mucosa or some of the drugs were swallowed for GIT absorption. Then, the remaining mass was spit out after the drug is released out. Medicated chewing gums are used for either local treatment of mouth diseases or to produce systemic action. Medicated chewing gums are the newly approved drug delivery systems with potential uses in pharmaceuticals, OTC medicines, and nutraceuticals [13].

2.1.2. Complexation and encapsulation for taste masking

2.1.2.1. Ion exchange resin complexation

Complexation of lipophilic active ingredients to ion exchange resins such as polacrillin potassium provides sustained drug delivery. This approach is useful to mask the taste of bitter drugs [14].

2.1.2.2. Cyclodextrin complexation

Cyclodextrin complexation have been used to increase the solubility, stability, and bioavailablity of a variety of active ingredients in formulations, and also explored for masking the taste of certain active ingredients [15].

2.1.2.3. Microencapsulation

Microencapsulation by water-soluble or water-insoluble polymers is one of the successful methods for sustaining the release of active ingredient sweetener or flavorant from medicated chewing gum [16].

2.2. ADVANTAGES OF MEDICATED CHEWING GUMS

1. Does not need water to swallow, therefore it can be taken anywhere.
2. It is a better option for patients having difficulty in swallowing.
3. Useful for acute medication.
4. Counteracts dryness, prevents fungal infection and tooth decay.
5. Extremely acceptable by children.
6. The bioavailability of drugs increases because of no first-pass metabolism when absorbed from the oral cavity.
7. Fast onset of action because active medicament is rapidly released into the buccal cavity and subsequently absorbed into the systemic circulation.
8. GIT suffers less from the effects of excipients because gum does not reach the stomach.
9. Reduced risk of irritation to gastric mucosa because there is no direct contact of the stomach with a high concentration of active principles.
10. Fraction of drug reaching the stomach is carried by saliva, delivered continuously and regularly. Hence, the duration of action is increased.
11. Medicated chewing gums commercially available are containing aspirin, caffeine, and dimenhydrinate show faster absorption through medicated chewing gums than tablets.
12. It is intended to produce both local and systemic action.
13. If treatment is to be stopped, it can be terminated at any time by spitting away medicated chewing gum.
14. The drugs that are delivered from chewing gum after chewing are introduced into GIT either dissolved or suspended in saliva and thus the drug will be present in a readily bioavailable form.
15. Lesser side effects [18].

2.3. LIMITATIONS OF MEDICATED CHEWING GUMS

1. Flatulence and diarrhea may be caused by sorbitol which is present in medicated chewing gum.
2. Excipients used in medicated chewing gum like liquorice cause hypertension, cinnamon can cause ulcers.
3. Chewing gum has been shown to stick to different degrees to enamel dentures and fillers.
4. It can cause pain in facial muscles and earache in children due to prolonged chewing [19].

2.4. COMPOSITION OF MEDICATED CHEWING GUMS

Chewing gum is a mixture of active pharmaceutical ingredients and a mixture of natural or synthetic gums and resins, sweetened with sugar, corn syrup, artificial sweeteners, flavoring, and coloring agents. The basic material is the natural gum chicle obtained from the sapodilla tree. Chicle is a very costly material and difficult to obtain therefore other natural gum or synthetic materials like polyvinyl alcohol and other polymers are used as a gum base [20]. Medicated chewing gum formulations mainly consist of 2 parts:

1. Water-insoluble portion
2. Water-soluble portion

2.4.1. Active pharmaceutical ingredients

The active pharmaceutical ingredients may be enclosed or embedded in the core or coat or in both in the medicated chewing gum. Its proportion may vary from 0.5-30 % of final gum weight [21].

2.4.1.1. Physicochemical properties of drug

1. pH-independent solubility
2. High salivary solubility
3. Tastelessness

2.4.1.2. Patient-related factors

1. Non-toxic to or mucosa and salivary ducts.
2. Non-carcinogenic.
3. Should not cause any tooth decay.
4. Should not cause teeth and or mucosa staining.
5. Should not affect salivary flow [20].

2.4.2. Water-insoluble portion

It mainly consists of elastomers, resins, fats and oils, and inorganic fillers [21].

2.4.2.1. Elastomers

It includes natural (chicle, crown, nispero, etc.) and synthetic (butadiene, polyisobutylene, styrene copolymers, isobutylene isoprene copolymers, etc.). It provides elasticity and controls the gummy texture. These are used in the concentration range of 15-45% [22].

2.4.2.2. Elastomer solvents

To soften the elastomer, elastomer solvents are added. They mainly include terpinene resins such as polymers of α-pinene / β-pinene, natural resin esters such as partially hydrogenated resin, pentaerythritol esters of resin or glycerol esters of partially hydrogenated wood or gum resin and partially dimerized resin of glycerol esters, these are used in the concentration range of 45-70% [23].

2.4.2.3. Plasticizers

They are used to produce different types of desirable textures and consistency properties and regulate the cohesiveness of the product. Two types of plasticizers are used *i.e.*, Natural or Synthetic [24].

2.4.2.4. Fillers/Texturizers

It gives good consistency or texture to the preparation, is intended to give better chewability, and increases bulkiness of low dose drugs. Eg: $MgCO_3$, $CaCO_3$, ground limestone, Mg and Al silicate, clay alumina, talc, TiO_2, and mono-/di-/tri-calcium phosphate [25].

2.4.3. Water-soluble portion

It includes bulk sweeteners, high-intensity sweeteners, flavoring agents, softeners, emulsifiers, colors, and antioxidants [26].

2.4.3.1. Softeners and Emulsifiers (0.5-15%)

To improve the chewability and mouth feel these softeners are used. Eg: tallow, hydrogenated tallow, glycerin, lecithin, mono-/di-/tri-glycerides, fatty acids like stearic acid, palmitic acid, oleic acid, and linolenic acid [27].

2.4.3.2. Sweeteners (50-65% of gum base composition)

Sweeteners are of 2 types:

2.4.3.2.1. Aqueous sweeteners

These can act as softeners to mix the ingredients and to retain the moisture. Eg: sorbitol, corn syrup, hydrogenated starch hydrolysates, etc [28].

2.4.3.2.2. Bulk sweeteners

Sugar components like sucrose, dextrose, maltose, dextrin, fructose, galactose, and corn syrup. Sugarless components are sugar alcohols like sorbitol, xylitol, mannitol, hydrogenated starch hydolysate, etc. Nowadays high-intensity artificial sweeteners are used, which give longer-lasting sweetness and flavor perception. Eg: sucralose, aspartame, salt of acesulfame, alitame, saccharin, etc [29].

2.4.3.3. Flavoring agents

To improve the esthetic feel of chewing gum flavoring agents are added. These agents include essential oils such as citrus

oil, peppermint oil, spearmint oil, fruit essences, clove oil, mint oil, and oil of wintergreen, artificial flavoring agents are also to be used [30].

2.4.3.4. Colorants and whiteners

FD&C type dyes, lakes, vegetable, and fruit extracts are used as colorants and TiO_2 as a whitener [31].

2.4.3.5. Antioxidants

Butyl hydroxytoluene, butyl hydroxyanisole, propylgallate, etc. are used as antioxidants [32].

2.4.4. Compression adjuvants

To improve the compression characters some suitable compression adjuvants are used like silicon dioxide, Mg stearate, talc, etc. Lubricants are to be used in the concentration of 0.4-1% by weight of the tabletted chewing gum composition. Glidants are to be used in chewing gum from 0.5-5% by weight of tabletted chewing gum composition. Anti adherents are used to prevent the sticking of granules to punches and to die cavity and sticking to one another. Eg: silicates, silicon dioxide, talc, and mixtures preferably about 0.3-0.6% by weight are used [33].

2.5. MANUFACTURING PROCESSES

Chewing gums are manufactured mainly by 3 processes:

2.5.1. Conventional method or traditional method (melting method)

Initially, gum base is softened or melted by taking it in a kettle mixture. At a definite time, all other ingredients like active ingredients, sweeteners, syrups, and other excipients are added (**Figure 5**). This prepared gum is passed through rollers to form into a thin, wide ribbon-like mass, while passing through the rollers, finely powdered sugar or sugar substitutes are added to reduce the sticking and to improve the flow. Then it is cooled for 48 hrs to set properly. Finally formed mass is cut into desired size and shape [34].

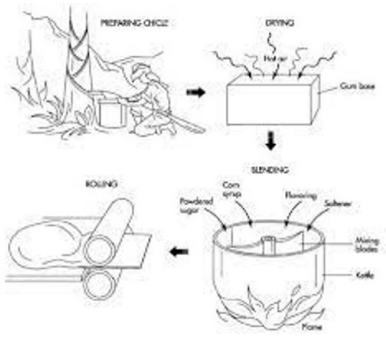

Figure 5: Traditional method for developing medicated chewing gums.

2.5.2. Cooling, grinding, and tableting method

To lower the moisture content, this method has been developed and reduces the problems which are observed in the conventional method (**Figure 6**). After taking required amounts of chewing gum ingredients at a particular temperature where the chewing gum composition is brittle, it is to be cooled. This cooling temperature is determined by observing the properties of cooled chewing composition. The temperature of the refrigerated mixture is generally 15°C lower. For cooling of chewing gum composition, various cooling agents are used like liquid nitrogen, hydrocarbon slush, or solid CO_2 is preferred as it can give temperature as low as -78.5°C upon warming the mixture it sublimes and not adhered, not interact adversely with processing apparatus and not leave any undesirable or hazardous residue. The cooled mixture is ground to get small fragments or pieces of composition. Some additives can be added to the cooled gum composition to facilitate cooling, grinding, and to get desired properties of chewing gum. The additives include anti-caking agents, grinding agents. Anti-caking agents like silicon dioxide are used and they can be mixed with chewing gum composition and solid CO_2 before the size reduction or grinding process. It prevents the formation of agglomerates. Grinding agents are used to prevent the sticking of gum to the grinding apparatus, 2-8% of grinding aid like alkaline metal phosphate, an alkaline earth metal phosphate, or maltodextrin can be incorporated. But, because of their incompatibility with acidic ionizable therapeutic agents, it has limited use. From the therapeutic and safety point of view, also it is problematic because it is remains in the chewing gum composition and final chewing gum tablet. Then the composition is made into a powder, the coolant is removed by allowing it to evaporate. Then powdered mass is warmed to room temperature which is removed from the refrigerated state. After removal of coolant from the powder, the powder is mixed with other additives such as binders, lubricants, coating agents, sweeteners in a suitable blender such as a sigma mill or a v-cone blender and compressed into a tablet [35].

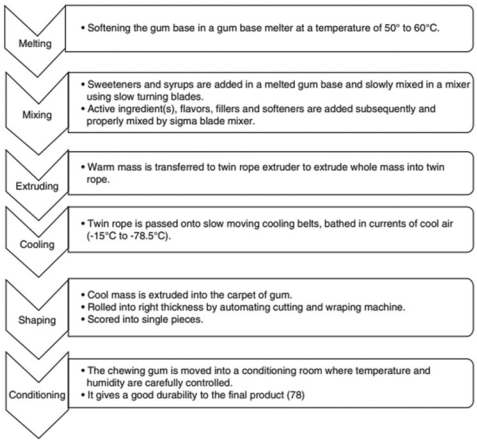

Figure 6: Cooling, grinding, and tableting method.

2.5.3. Direct compression method

The manufacturing process became easy if a directly compressible chewing gum excipient is available. By using this excipient we can overcome the problems of the melting and freezing method (**Figure 7**). SPI Pharma developed directly compressible chewing gum excipient "Pharmagum". It is a mixture of polyol(s) or sugars with a chewing gum base. By using this excipient, which is available as a directly compressible and free-flowing powder, it can be formulated into a gum tablet. Pharmagum is available in 3 forms i.e. Grade S,M,C. Pharmagum 'S' has 50% less gumbase compared to pharmagum 'M'. Gumbase and sorbitol present in Pharmagum 'S'. Gumbase, mannitol, and isomalt are present in pharmagum 'M'. By using traditional tableting machine chewing gum can be prepared. Medicated chewing gum's prepared by directly compressible excipients are 10 times harder and crumble when pressure is applied that resulting in faster release than conventional methods [36].

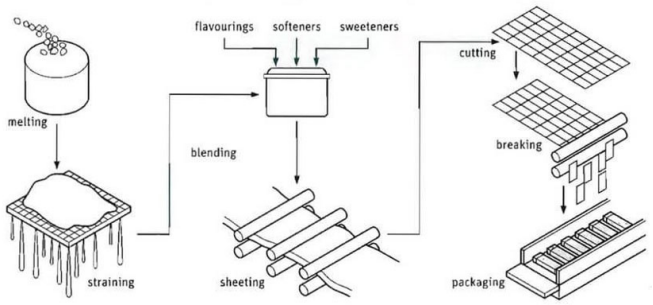

Figure 7: Direct compression method for manufacturing medicated chewing gums.

2.6. EVALUATION TESTS

2.6.1. Content uniformity

Ten medicated chewing gums are selected randomly then their contents are measured, if each single content is between 85% and 115% of average content, it will comply with the test, but if one single preparation is out of this range the preparation will not comply with the test [37].

2.6.2. Mass uniformity

Twenty medicated chewing gums are selected randomly and weighed, not more than two single mass should vary the average mass [38].

2.6.3. Dissolution test

Mastication devices are designed to simulate human chewing behavior. To mimic a drug release in these devices or machines, the following test is specified. This test determines the dissolution rate of active ingredients in medicated chewing gum, a part of medicated chewing gum is placed in the chamber of an apparatus which contains [39]:

1. Chewing chamber.
2. A vertical piston and
3. Horizontal pistons with sealed rings. Medicated chewing gum is chewed by horizontal pistons and is fixed by vertical piston.

During each chewing cycle, apparatus speed and pistons' movements should be controlled not to interfere with each other's work. Actually, horizontal and vertical pistons are, respectively, instead of teeth and tongue. One of the first chewing machines constructed by Christrup and MØller consists of two pistons, a reservoir, a thermostat and a regulator of the rate of chewing chamber (**Figure 8**). The chewing machine was developed again. The dissolution medium is swirled by ribs. The machine provides the rotation speed of 20 rpm and cycle frequency of 30 cycles per minute [40].

Figure 8: Christrup and MØller medicated chewing gum.

In another apparatus designed by Wennergren (**Figure 9**), they considered the effect of occlusal surfaces, rotary and shearing movements and the medium temperature on drug release. In the first apparatus adopted by EP, a defined volume of dissolution medium is shed into mastication chamber, the acidity of medium reaches to pH 6.0 by phosphate buffer and the temperature should be 37°C ± 0.5°C, the piston speed is 60 rpm. The usual number of chews per minute of a normal person is 60 strokes/min, then a part of medicated chewing gum or the whole gum is placed into the chamber and the apparatus is set and the procedure is started. The machine is stopped at determined time, the remaining part of the gum is then removed and a sample of dissolution medium is prepared, the content of active agent(s) is determined by a suitable method, after each sampling, dissolution medium could have been replaced by a new and fresh medium so that the dilution

factor should be calculated. The content of active agent(s) in the gum residue could be determined too. This test is carried out on three medicated chewing gums for three times [41].

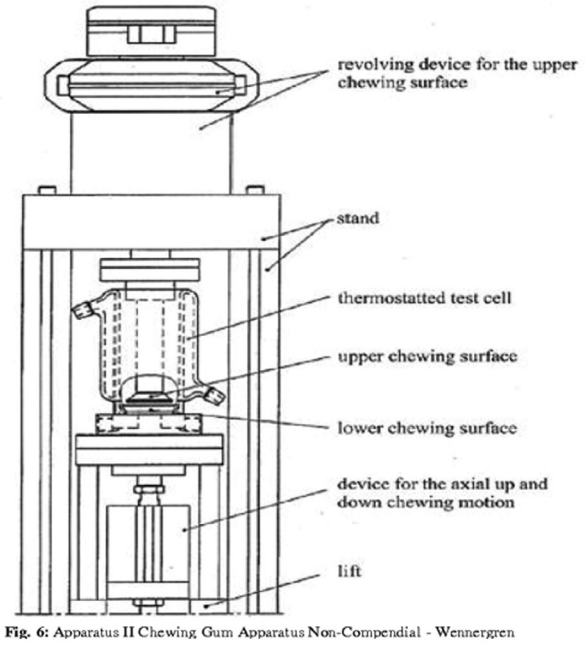

Fig. 6: Apparatus II Chewing Gum Apparatus Non-Compendial - Wennergren

Figure 9: Wennergren medicated chewing gum.

2.6.4. Organoleptic properties

Organoleptic properties refer to those which affect sense, taste and feelings of people who use a product, so the vital role of these properties should not be disregarded because they impress acceptance by individuals and even marketing. The organoleptic characteristics of prepared gums comprise softness/stiffness, adherence to teeth, taste, bulk volume and perdurability of taste. A Latin-square designed should be held on 10 volunteers to score their points of view. The Latin-square design is a statistical method; this means that testing units (volunteers and formulations) are divided into two blocking factors. For differentiation, we allocate rows to volunteers and columns to formulations or contrariwise. In this case no testing unit should be repeated in each row and column [42].

2.6.5. Taste

A Latin-square design should be carried out using a taste panel of some trained and healthy volunteers and then asking them to score to their points of view according to a series of scales like Likert scale. To finally diagnose the best and most desirable flavor among volunteers; a further taste panel test can be performed [43].

2.6.6. Mechanical properties

Simply that is a test in which the chewing gum specimens are subjected to a tension until such time as failure occurs. The load required for elongation before fracture is recorded by computer. The tensile testing machine is set for the determination of force-elongation properties. Engineering stress and strain are obtained as describe below [44]:

Stress = $\sigma = P/A_o$ (Load/Initial cross-sectional area)

Strain = $e = \Delta l/l_o$ (Elongation/Initial gage length)

The first part of the curve obeys Hook's law where the ratio of stress to strain is constant, and a linear relationship can be observed.

The shape, size, width, thickness, and gauge length are to be specified precisely because we wish to avoid having a break or non-uniformity within the area being gripped. Hence, the specimen should be suitably prepared for gripping into the jaws of the testing machine according to the standards. The major parameters obtained from the test and the explanations of the stress-strain curve are tensile strength, yield strength, and fracture strength as expressed by percent elongation and reduction in area, the highest stress the specimen sustains during the test and before failure is typically recorded as ultimate tensile stress. After yield strength, we enter the plastic region where the chewing gum will not revert to its first shape by removing the load [45].

2.7. FACTORS AFFECTING RELEASE RATE AND AMOUNT

In vivo and *in vitro* release of drug from medicated chewing gum is dependent not only to formulation factors but also to active ingredients' portion and individual chewing characteristics [46].

2.7.1. Water solubility

When the active ingredient is water-soluble, the release of drug gets to the end rather than other active ingredients with slight water-soluble properties, and lipid-soluble drugs face further release problems than others because they are bound to lipophilic substances and gum bases and slowly released into oral cavity [47].

2.7.2. Formulation factor

Mixing of active ingredients with hydrophilic compounds or hydrophobic compounds affects the release of the drug. Sometimes faster release does not mean more complete release of drug; rather formulations with slower release profiles often show more complete release of drug [48].

2.7.3. Physicochemical properties

Ingredients more soluble in saliva will be immediately released within few minutes of chewing, but highly lipid-soluble ingredients are first released into gum base then into

saliva. Stability of gum base and its components to salivary enzymes, molecular mass, and ionization play an important role in release and absorption of drug through mucosa [49].

2.7.4. Individual characteristics

Speed, intensity, frequency, and type of chewing characteristics of different individuals affect the release of active ingredients; EP recommends 60 chews/min for appropriate release of active ingredients. But these numbers of chews depend also on the retention time of medicated chewing gum in the mouth, which in clinical trials, the ordinary and suitable time is about 30 min of chewing. These differences lead to variable results of drug release. The problem of adhering of many lipophilic ingredients to gum base and other lipophilic compounds and, therefore, slow release of the drug into saliva may be solved by encapsulation of active ingredients or coating them with appropriate substances [50].

2.8. STABILITY

Chewing gum is a very stable product due to its low moisture content and less reactive nature than that of other oral ingredients. A major challenge in the production of chewing gum is its shelf life, storage conditions and effect of some ingredients that impress stability. Water content can lead to growth of microorganisms and chemical degradation, but water can be bound to other compounds, so that is not noticeably available to active agents, but even if few water existing in the chewing gum is determined annihilator and dangerous for other components, no water can be employed in the manufacturing method. To avoid oxidation of the drug, antioxidants are needed but due to the low content of water, presence of preservatives is not essential. Holding water content with no significant change at low or high concentration of moisture at atmosphere needs a major amount of gum base and xylitol as a bulking agent. Such made chewing gums are stable at extreme conditions and are capable of adding more desired ingredients and active agents. No stiffening, compacting or softening are observed in terms of moisture stability in these kinds of gums [51].

Xylitol would also enhance storage stability in the gum; it means that in low or high humid conditions the gum's water content remains at its favorable level and the gum flexibility, elasticity, splitting, and softness do not encounter major changes. Effect of xylitol on the crystalline structure and its water binding properties are responsible for these changes. In general, the stability of the active substance is good because chewing gum holding drug protects it from oxygen, light, and humidity. High temperature for some heat-sensitive components to facilitate mixing can be avoided by increasing other powers, instead. Undesired interactions between different components can be prevented by encapsulation or coating of some ingredients by suitable substances so that less contact between compounds occurs. One other important parameter involved in this topic is appropriate packaging and storage of gum to prevent water and moisture penetration and light exposure. The costly and expensive packaging and wrapping can be eliminated by spotting above notes. Finally, the freshness and stability of gum would remain for a long period of time and problem of staling, brittleness, and/or growth of microorganisms can be greatly reduced [52].

2.9. PACKAGING

The advantages of chewing gum packaging are clear to the world since it extends shelf-life of the product by preventing aroma and flavor to disappear. It also provides moisture retention and gum stability. There are too many packaging methods with a wide range of options. In almost all of packaging types, we need a wrapping machine that receives and wraps the sticks of gums; in some cases, the wrapper machine seals the end of the package. In the following, a formed blister pack may be used then a foil will be heat-sealed at the back or a traditional packaging may be applied by lining the pellets up in a row and wrapping then sealing the both ends. The manufacturing and packing steps should be performed at about 20-25°C and relative humidity of 57%. Packaging has a substantial portion in the whole process both in terms of cost and time. Undoubtedly, packaging influences attraction of product among consumers, thus a well-favored and stylish design can attract more consumers to buy the specific product. Therefore, besides protecting the content, avoiding impurity, expediting transport and improving storage, packaging can influence consumers' willingness to buy the product and capture his attention during purchase competition [53].

4. CONCLUSION

We can conclude that chewing gum will be much more familiar to patients and the market in the coming years, based on the benefits of chewing gum as a novel drug delivery, such as concurrently supporting both local and systemic delivery, protection against acids and enzymes, low first pass metabolism, elevating alertness and cognitive function, good stability, and much more. However, their new and old applications demonstrate our point, as it can be seen that effective chewing gums containing at least one drug as active agent can be used to treat motion sickness, pain, smoking, dental caries, tooth decay, otitis media, GIT problems, oral fungi, inflammatory problems, and more. Because there is much more information and knowledge to be investigated for manufacturing chewing gums, the technology to deliver

chewing gum to market and to the health system as a dependable substitute for various types of tablets has not yet been established and completely understood. But, thankfully, the procedure's development is permissible. New chewing gum formulations should be considered by scientists and researchers in order to increase chewing gum variants owing to patient preferences and provide a suitable release pattern for chewing gums containing medications.

CONFLICTS OF INTEREST

No conflict of interest is declared.

ACKNOWLEDGEMENT

The author acknowledges the college management, principal, teachers, non-teaching staffs, and colleagues for their kind support.

FUNDING INFORMATION

No agency provided funds.

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