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REVIEW ARTICLE……!!!

MEDICATED CHEWING GUM: AN ENGROSSING APPROACH

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KEYWORDS:

Medicated chewing gums, Chewing gum, Patient Compliance, Mobile drug delivery system.

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ABSTRACT

In the recent years scientific and technological advancements have been made in the research and development of oral drug delivery systems. The reasons that the oral route achieved such popularity may be primarily due to its ease of administration. Chewing gum is one of the very popular oral confectionary products. It is a potentially useful means of administering drugs either locally or systematically via, the oral cavity. The medicated chewing gum has through the recent years gained increasing acceptance as a drug delivery system. Chewing gum known as gum base (insoluble gum base resin) contains elastomers, emulsifiers, fillers, waxes, antioxidants, softners, sweeteners, food colorings, flavoring agents, and in case of medical chewing gum, active substances. It offers various advantages over conventional drug delivery systems. Unlike chewable tablets, medicated chewing gums are not supposed to be swallowed and may be removed from the site of application without resorting to invasive means. Moreover medicated chewing gums require the active and continuous masticatory activities for activation and continuation of drug release. An In-vitro apparatus was specially designed and constructed for release testing of medicated chewing gums. Medicated chewing gums are excellent mobile drug delivery systems for self-medication as it is convenient and can be administered discretely without water.

INTRODUCTION:

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 a drug is maintained over an acceptable interval. Modified release dosage forms are more acceptable compared to the conventional dosage forms, there are a lot of improvements in terms of formulation development and product design. Modified dosage forms are getting approval worldwide and many researchers are showing their interest in this direction [1]. To improve bioavailability and to achieve better acceptability, newer technologies are developed to modify normal conventional tablets [2]. 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., Chewing gum can be used as a convenient novel drug delivery system. 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 outcomes thereby it target different patient groups. From ancient times man has a habit of chewing the chewing gum. These days it is one of the foremost popular dosage forms used for delivering the numerous active substances [3,4,5]. In the U.S.A, in the year of 1948, the first commercially marketed chewing gum was 'State of Maine Pure spruce gum'. The first patent was issued in 1869 to Dr. WF. Semple. This chewing gum was manufactured as dentifrices but it was never been marketed. In 1928, the first medicated chewing gum “Aspergum” was launched. The active medicament present in this gum was Aspirin, it 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 [6-8]. 2 But, today technology is improved and extended, people may know how to develop medicated chewing gum with 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 preparation with a base consisting mainly of gum that is intended to be chewed but not to swallowed [9,10]. The medicated chewing gums contain gum base with one or more medicaments that are released after chewing for a certain period, 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 GI absorption. Then, the remaining mass was spat out after the drug is released out [11,12,13]. 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.

ADVANTAGES: [14,15,16,17]

1. It 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. G.I.T 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. The 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 shows 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 MCG.
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.

LIMITATIONS:

1. Flatulence and diarrhea may be caused by sorbitol which is present in MCG.
2. Excipients used in MCG 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 earaches in children due to prolonged chewing.

Anatomy and physiology of oral mucosa: [18,19,20] The oral cavity is the attractive site for delivering the medicines locally or systemically. Anatomy and physiology of the oral cavity show a

direct influence on oral mucosal drug delivery systems. The oral mucosa can be subdivided into 2 general regions they are the outer vestibule and oral cavity.

Oral mucosa consists of 3 main layers:

• Oral epithelium

• Lamina propria

• Submucosa

Oral epithelium: The epithelium of 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). Non keratinized epithelium is somewhat flexible and is found in areas like the tender palate, the floor of 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.

Lamina propria: It is a sheet of connective tissue containing collagen elastic fiber and cellular components in 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. **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 secretions supplied by parotid, the submaxillary and the sublingual glands. Saliva constantly washes the surface of the mucous membrane.

The presence of saliva in the mouth is essential for these main reasons: Drug permeation across moist membranes occurs more easily than across the nonmucous membranes, compared to drug absorption across the GIT and skin. The oral route is an important one to administer most of the drug substances. 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.

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. [21] Drug transport across buccal mucosa follows simple Fickian diffusion. [6]

$J = DKp/\Delta ce$

Where: J = Drug flux

D = Diffusifivity

Kp = Partition coefficient

Δce = Concentration gradient

The drug permeation across the oral mucosa is by 2 pathways:

1. Transcellular/intracellular route

2. Paracellular/intercellular route.

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.

COMPOSITION OF MCGS: [7,23,24,25] 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 a 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.

MCG formulations mainly consist of 2 parts:

1. Water-insoluble portion

2. Water-soluble portion

Active pharmaceutical ingredients: Active pharmaceutical ingredient may be enclosed or embedded in core or coat or in both in the MCG. Its proportion may vary from 0.5-30 % of final gum weight. Optimal properties of drugs include: Physicochemical properties of drug:

1. pH-independent solubility

2. High salivary solubility

3. Tastelessness Patient-related factors:

1. Non-toxic to oromucosa and salivary ducts

2. Noncarcinogenic

3. Should not cause any tooth decay

4. Should not cause teeth and oromucosa staining

5. Should not affect salivary flow

Water-insoluble portion: It mainly consists of elastomers, resins, fats and oils, and inorganic fillers. Elastomers: It includes natural (chicle, crown, nispero) and synthetic (butadiene, polyisobutylene, styrene copolymers, isobutylene isoprene copolymers). It provides elasticity and controls the gummy texture. These are used in the concentration range of 15- 45%.

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 rosin and partially dimerized resin of glycerol esters, these are used in the concentration range of 45-70%.

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

Fillers/Texturizers: It gives good consistency or texture to the preparation, intended to give better chewability and increases the bulkiness of low dose drugs. Eg: MgCo3, CaCo3, ground limestone, Mg. and Al silicate, clay alumina, talc, Tio2, and mono/di/tricalcium phosphate. 1.5.3. **Water-soluble Portion:** It includes bulk sweeteners, high-intensity sweeteners, flavoring agents, softeners, emulsifiers, colors, and antioxidants.

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/triglycerides, fatty acids like stearic acid, palmitic acid, oleic acid, and linolenic acid.

Sweeteners (50-65% of gum base composition): Sweeteners are of 2 types: Aqueous sweeteners, Bulk sweeteners

• Aqueous sweeteners: These can act as softners to mix the ingredients and to retain the moisture. Eg: sorbitol, corn syrup, hydrogenated starch hydrolysates

• 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 hydrolysate. Nowadays high-intensity artificial sweeteners are used, which give longer-lasting sweetness and flavor perception. Eg: sucralose, aspartame, salt of acesulfame, alitame, saccharin

Flavoring agents: To improve the aesthetic 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.

Colorants and whiteners: FD&C type dyes, lakes, vegetable, and fruit extracts are used as colorants and TiO2 as a whitener.

Antioxidants: Butyl hydroxyl toluene, butyl hydroxy anisole, propyl gallate are used as antioxidants

Compression adjuvants: To improve the compression characters some suitable compression adjuvants are used like silicon dioxide, Mg.stearate, talc. Lubricants are to be used in the concentration of 9 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 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.

Manufacturing processes: [26] Chewing gums are manufactured mainly by 3 processes:

1.Conventional or traditional method (melting method)

2.Freezing, grinding and tableting method

3.Direct compression method

The 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. This prepared gum is passed through rollers to form into 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 the desired size and shape.

Limitations:

1. It is not useful for thermolabile substances, because high temperatures are used for melting.
2. Difficult to achieve accuracy and dose uniformity.
3. Uniform shape or weight is not obtained.
4. It requires stringent manufacturing conditions, so it is not easily adaptable to technology.
5. By using this melted gum base we can't prepare tablets because of moisture content. If this gum base is ground and compressed it obstructs the grinding machine, stick to punches and die cavity.

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.

Cooling and grinding: After taking the 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 15o 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 -78.5oC 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 anticaking agents, grinding agents. Anti-caking agents like Silicon dioxide are

used and it can be mixed with chewing gum composition and solid CO2 before size reduction or grinding process. It prevents the formation of agglomerates. Grinding agents used to prevent sticking of gum to 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 a therapeutic and safety point of view also it is problematic because it 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 warmed to room temperature which is removed from the refrigerated state.

Tableting: 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 sigma mill or a v-cone blender and compressed into a tablet.

Limitations: This process requires careful monitoring of humidity during the compression process.

Direct compression method: The manufacturing process became easy if directly compressible chewing gum excipient is available. By using this excipient we can overcome the problems of melting and freezing methods. 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 gum base compared to pharmagum 'M'. Gum base and sorbitol present in Pharmagum 'S'. Gum base, mannitol, and isomalt are present in pharmagum 'M'. By using traditional tableting machine chewing gum can be prepared. MCG's prepared by directly compressible excipient are 10 times harder and crumble when pressure is applied that results in faster release than conventional methods.

FACTORS AFFECTING THE RELEASE OF API: [27]

Time of contact: The release is dependent on how much of time chewing gum is in contact with the oral cavity to produce a local or systemic effect. In general 30 minutes was considered as chewing time. The intensity of chewing is an important factor.

Physicochemical properties of active ingredient: The release of drugs from chewing gum is dependent on the physicochemical properties of the drug substance. The ingredients which are soluble in saliva are released at a faster rate compared to ingredients which are not soluble in saliva, because these are first released into the gum base then slowly released into saliva.

Inter-individual variability: The drug release may vary from person to person because it depends on persons chewing frequency and chewing intensity. According to European Pharmacopoeia 60 cycles per minute, chewing rate is ideal.

Formulation factor: Composition and gum base amount used in the preparation affects the release rate of the drug from the chewing gum. If the amount of lipophilic fraction of gum is high, the release rate is decreased.

Quality control tests for MCG'S: [28,29,30,31]

Uniformity of content: MCG's containing with an amount of active ingredient 2 mg or less than 2 percent of total mass comply with this test for a single dose preparations uniformity of content. 1

Uniformity of mass: For single-dose preparations, uniformity of mass is required. If for all the active substances uniformity of content is prescribed, uniformity of mass test is not required.

In vitro drug release: This test is officially prescribed in European Pharmacopeia and is determined by applying a mechanical pressure to a piece of gum in a small chewing chamber that contains a required amount of buffer solution.

Apparatus I: Compendial chewing gum apparatus: This apparatus consists of a chewing chamber, 2 horizontal pistons and a third vertical piston (tongue). The vertical piston works on the on other hands with 2 horizontal pistons and verifies whether the gum stays in the correct place between chews. If necessary, it is practical to construct the machine so that at the end of the chewing the horizontal pistons rotate around their own axis in inverse direction to each other to get maximum chewing.

Apparatus II: Non compendia chewing gum apparatus: Wennergren developed one of the noncompendia apparatus which was commercially available. The chewing strategy comprises of responses of the lower surface in combination with a shearing development of the upper surface that gives mastication of the chewing gum and in the meantime, satisfactory agitation of the test medium.

In vivo 'chew out' studies: A sufficient number of volunteers are selected, they are asked to chew the gum. The drug contained within the MCG is released into saliva and then it is either absorbed through oral mucosa or if it is swallowed, absorbed through the gastrointestinal tract.

Drug release in saliva: Optimized formulations with good consistency can be selected for determining the drug release in saliva. The healthy human volunteers are first advised to rinse their mouth with distilled water and allowed to chewing the medicated chewing gum for 30 min., where the maximum release of the drug has to be observed. Then samples are collected after 5, 10, 15, 20, 25, 30 min and samples are made diluted in specific solvent and measure absorbance by using suitable analytical methods.

Urinary excretion profile of chewing gum: The drugs which are excreted via urine, this method can be applied. Healthy human volunteers are selected for this study and volunteers are instructed not to take any medicine for the last 48 hrs and they are fasted overnight and ask them to empty their bladder. Samples are collected for 15 min, 1,2,3,4,6,7,8,10,11,12,24 hr intervals after administration of MCG. The volunteers are advised to drink water at regular intervals of 30 min and by using analytical methods the collected urine samples are analyzed.

Buccal absorption Test: Volunteers are asked to swirl constant volume of drug solutions of known concentrations at different pH values of 1.2, 5.6, 6.5, 7, 7.5, 7.8 and 8 in the oral cavity for 15min, and expelled out. Then collected saliva is analyzed for drug content and back-calculated for buccal absorption.

Safety Aspects:[32] Generally, today it is perfectly safe to chew chewing gum. Previously, hard chewing gum has caused broken teeth. Extensive chewing for a long period of time may cause painful jaws muscle, and extensive use of sugar alcohol containing chewing gum may cause diarrhea. Long term frequent chewing of gum has been reported to cause increased release of mercury vapors from dental amalgam fillings. However, medicated chewing gum does not normally require extensive chewing, or consumption to great extent. Flavors, color etc. may cause allergic reactions. Overdosing by use of chewing gum is unlikely because a large amount of gum has to be chewed in a short period of time to achieve this. Swallowing pieces of medicated chewing gum will only cause the minor release of the drug because the drug can only be released from the gum base by active chewing. As a general rule, medicated chewing gum (like other medicines) should be kept out of reach of children, if required; drug delivery may be promptly terminated by removal of the gum.

Future Trends: Chewing gum not only offers clinical benefits but also is an attractive, discrete and efficient drug delivery system. A few decades ago, the only treatment for some diseases was surgical procedure but now more and more diseases can be treated with Novel Drug Delivery Systems. Generally, it takes time for a new drug delivery system to establish itself in the market and gain acceptance by patients, however chewing gum is believed to manifest its position as a convenient and advantageous drug delivery system as it meets the high-quality standards of pharmaceutical industry and can be formulated to obtain different release profiles of active substances. The potential of MCG for buccal delivery, fast onset of action and the opportunity for product line extension makes it an attractive delivery form. Reformulation of an existing product is required for patent protection, additional patient benefits and conservation of revenues.

CONCLUSION AND DISCUSSION:

Thus, it can be concluded that the chewing gum can be used, as a carrier for vast categories of drugs where extended-release and the local action is desired. Chewing gum can be used without water, at any time. Medicated Chewing gums can produce both local effects as well as systemic effects in the oral cavity. They can be used for the purpose of taste masking of certain drugs too.

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