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A REVIEW ON MEDICATED CHEWING GUM

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Abstract:

Chewing gums are mobile drug delivery systems. Unlike chewable tablets medicated gums are not supposed to be swallowed and may be removed from the site of application without resort to invasive. Medicated chewing gum is solid, single dose preparation with a base consisting mainly of gums that are intended to be chewed but not swallowed. Several ingredients are now incorporated in medicated chewing gum, e.g. Fluoride for prophylaxis of dental caries, chlorhexidine as local disinfectant, nicotine for smoking cessation, aspirin as an analgesic, and caffeine as a stay alert preparation. In addition, a large number of chewing gum intended for prevention of caries, xerostomia alleviation, and vitamin/ mineral supplementation are currently available. As for as patient convenience is concerned it is discrete and easy administration without water promotes higher compliance. Since it can be taken anywhere, a chewing gum formulation is an excellent choice for acute medication. The advantages for children and for patients who find swallowing tablets difficult are obvious. Today improved technology and extended know how have made it possible to develop and manufacture medicated chewing gum with predefined properties. The present review article is nicely discussed advantages, disadvantages, formulation, manufacturing process, limitation of manufacturing process, factors affecting release of active substance, quality control tests for chewing gum.

Keywords: *Chewing gum, non adhesive, drug delivery, sustain release*

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INTRODUCTION:

Pharmacologically Active Agents or Drugs are formulated into variety of dosage forms like Tablets, Capsules, Injectables, Inhalers, Ointments etc considering Physicochemical properties, Pharmacokinetic & Pharmacodynamic parameters and Biopharmaceutical aspects of Drugs; however, recently in addition to its confectionary role, Chewing Gum also has proven great value as a delivery vehicle for pharmaceutical and nutraceutical ingredients. It can be taken discreetly without water and the drug is allowed for local and systemic delivery[1]. It can be employed for treatment of diseases of the oral cavity and throat e.g. for caries prevention, or it can release drugs that can be absorbed through oral mucosa directly into the systemic circulation. In addition, drug that is not absorbed by the oral cavity membranes can be dissolved in the saliva before swallowing, thus leading to a more rapid onset of action. The Medicated Chewing Gums (MCG) can also be utilized for site specific activity in case of oral cancer[2]. Chewing gum is going to advance more and more in nowadays researches and it seems to get more standardized in future industry because it can deliver either pharmaceuticals or nutrients which are known as medicated chewing gum (MCG) and NonMCG. MCG is supposed to act as an extended release dosage form that provides a continuous release of medicine contained[3].

Figure 1 Medicated Chewing gum

Ancient Greeks used to get a chewable resin from a tree called mastic but due to archaeological diggings chewing gum-like substances or masticatory resins back to 5000 years ago. Resin pieces have even been found with teeth traces in Finland and Sweden. First marketing of chewing gums was at 1848 when chicle from Sapodilla tree was sapped[4]. John Curtis and his son boiled spruce tree sap and added sugar, flavor, and fillers, then rolled it and first made masticatory sticks which they wrapped in papers and sold them. Over time their company prospered, it was then that the son found they need to improve the company and machines, so he developed a machine which mass-produced gums.

In 1869, Doctor William F. Semple from Ohio issued the first patent for chewing gum both as a confection and a pharmaceutical to protect teeth. The first MCG was launched in 1924 in United States of America which was called Aspergum but an admission of chewing gum as a drug delivery system did not gain until nicotine chewing gum was released at the market[5]. Thomas Adams first manufactured MCGs with natural latex-base and issued the first patent of chewing machine to render chicle kneaded, and smooth but modern chewing gums often consist of synthetic resins. There is a monograph in European pharmacopoeia (EP) that defines MCG but the term “chewing gum” was first listed in guidelines as pharmaceutical dosage forms in 1991 and approved by the commission of European communities[6]. Due to acceptance of oral drug delivery systems among people, chewing gums soon became friendly to people all around the world because of convenient administration. Besides its enjoyable taste and good feeling, it provides proven health, nutrition, and cognitive benefits.

ADVANTAGES OF MEDICATED CHEWING GUMS [7]

- Increased rate of effectiveness rather than other oral delivery systems.
- Removal of gum at any time; therefore termination of drug delivery.
- Reduced risk of overdosing while it's whole swallowed.
- Requiring no water to drink.
- Protection of the susceptible drugs contained from chemical or enzymatic attack in gastrointestinal (GI) tract.
- Both systemic and local drug delivery.
- High acceptance by children and teenagers.
- Low first-pass effect so reduced dose is formulated in chewing gum compared to other oral delivery systems.
- Good for rapid delivery.
- Fewer side effects.
- Reduced risk of intolerance to gastric mucosa.
- Good stability against light, oxygen, and moisture.
- Annihilation of xerostomia and help tasting and swallowing in people with dry mouth.

- Reduced pains and difficulties in swallowing following tonsillectomy.
- Improving work performance and cognitive function
- Fast bowel recovery after GI surgery.
- Reduced hypoglycemic shocks in people taking anti-diabetic drugs.
- Stimulating alertness through increased blood flow to brain.
- Help reduce food cravings.

DISADVANTAGES OF MEDICATED CHEWING GUMS [8]

- Disappearing of drug in oral cavity following salivary dilution.
- Different release profiles because of chewing style differences.
- Short time of administration due to eating, speaking, and drinking.
- Allergic reaction to artificial sweeteners.
- Continuous stress on jaws that may cause temporomandibular joint disorder.
- Teeth decay through being coated by sugar.
- Masseter problems.
- Stomach irritations, aches, gastric ulcer through continuous swallowing of saliva and even flatulence because of presence of sorbitol in some formulations.
- Getting choked by swallowing gum in under-aged children.

FORMULATION OF CHEWING GUM

The characteristic component of all Chewing Gums is the gum base. Other component added to Chewing Gums typically includes sweetening agents, flavoring agents and aromatics. In medicated Chewing Gum active drug is incorporated. A gum base comprises of a complex mixture of elastomers, natural of synthetic resins, fats, emulsifiers, waxes, antioxidants, fillers and flavoring agents[9].

1. Elastomers: They provide elasticity and cohesion to the chewing gum. Natural elastomer, Natural rubbers like Latex or Natural gums such as Jelutong, Lechi Caspi, Perillo, Chicle and synthetic elastomers like polyisobutylene and butyl rubber are used.

2. Resins: They serve two functions; one, as mastication substance and other as binding agent between elastomers and fillers they contribute to the balance between the properties of elasticity and plasticity. Glycerol esters from pine resins are examples of natural resins. Synthetic resin polyvinyl acetate can be used. It reduces the tendency of the gum to adhere to the teeth (detackifier) and to be divided into pieces during chewing. It has only a slight taste with good stability[10].

3. Emulsifiers and fats: These are used to soften the mixture and give the required chewing consistency and mouth feel. Emulsifiers promote the uptake of saliva into the chewing gum during mastication. Monoglycerides, diglycerides and partly hardened vegetable and animal fat are used.

4. Plasticizers: Natural and Synthetic plasticizers are used to regulate cohesiveness of product. Natural Plasticizers include Natural rosin esters like Glycerol Esters or partially hydrogenated Rosin, Glycerol Esters of Polymerized Esters, Glycerol Esters of Partially dimerized Rosin & Pentaerythritol Esters of Rosin. Synthetic Plasticizers include Terpene Resins derived from a-pinene and/or d-limonene[11].

5. Antioxidants: They may be added to protect the gum base and flavors from oxidation. Ascorbic acid, tocopherol, butylhdroxytoluene have been used.

6. Fillers: They provide the right texture for the gum base. Talc, calcium carbonate can be used.

7. Colorants and Whiteners: It may include FD & C type dyes and lakes, fruit and vegetable extracts, Titanium Dioxide.

8. Sweeteners: Sugar Components include Saccharides like Sucrose, Dextrose, Maltose, Dextrin, Fructose, Galactose, and Corn Syrup. Sugarless Components include sugar alcohols such as Sorbitol, Mannitol, Xylitol, hydrogenated Starch hydrolysate[12]. High intensity artificial sweeteners can also be included to provide longer lasting sweetness and flavor perception e.g. Sucralose, Aspartame, salt of Acesulfame, Alitame,Saccharin, Glycerrhizin, Dihydrochalcones. Aqueous Sweeteners can also be used as softeners to blend the ingredients and retain moisture. These include Sorbitol, hydrogenated Starch hydrolysates and Corn Syrups. Corn syrup keeps gum fresh and flexible.

9. Flavouring Agents: A variety of flavouring agents are used to improve flavour in chewing gum includes essential oils, such as Citrus oil, fruit essences, Peppermint oil, Spearmint oil, Mint oil, Clove oil & Oil of Wintergreen. Artificial flavouring agents can also be used. 10. Active Pharmaceutical Drugs: In medicated chewing gum active pharmacological agent may be present in core or coat or in both. The proportion of which may vary from 0.5-30% of final gum weight. A small, unionized, lipophilic and

enzymatically stable active agent is likely to be absorbed more readily[14]. A saliva soluble ingredient will be completely released within 10-15 minutes of chewing whereas lipid soluble ingredient will dissolve in the gum base and thereafter be slowly and completely absorbed. MCG consists of masticatory gum core that may be coated. The core is composed of an aqueous insoluble gum base which can be mixed with Sweeteners and Flavors. The coating can be applied as a film of polymers, waxes, sweeteners, flavors and colour or a thick layer of sugar or sugar alcohol.

METHODS OF PREPARATION

Different methods can be employed for the manufacturing of Chewing Gum; however, these can be broadly classified into three main classes namely: [15]

- Conventional/ traditional Method (Melting).
- Cooling, grinding and tabletting Method.
- Direct Compression Method

1.CONVENTIONAL/ TRADITIONAL METHOD

Components of gum base are softened or melted and placed in a kettle mixer to which sweeteners, syrups, active ingredients and other excipients are added at a definite time. The gum is then sent through a series of rollers that forms into a thin, wide ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavor. In a carefully controlled room, the gum is cooled for upto 48 hours. This allows the gum to set properly. Finally the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity[16]. However, the conventional method has number of limitations like elevated temperature used in melting, restricts the use of this method for thermo labile drugs. Controlling of accuracy and uniformity of drug dose becomes difficult due to melting and mixing of highly viscous gum mass makes. Such a chewing gum composition is difficult to form into chewing gum tablets because of their moisture content (2-8%). If attempted to grind and tablet such a composition would jam the grinding machine, stick to blades, screens adhere to punches and would be difficult to compress. Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.

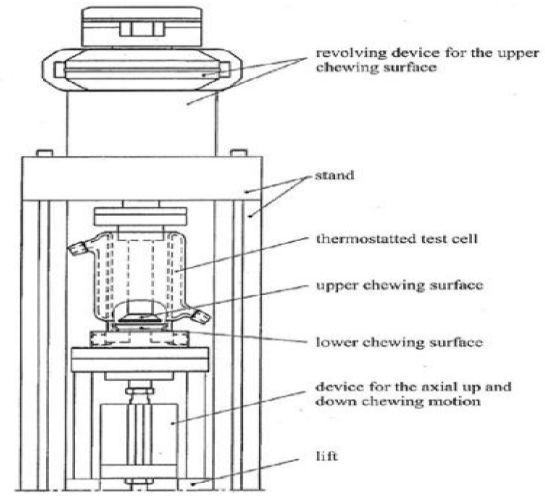

Fig. 6: Apparatus II Chewing Gum Apparatus Non-Compendial - Wennergren

Figure 2 Chewing gum apparatus

2. COOLING, GRINDING AND TABLETTING METHOD

This method has been developed with an attempt to lower the moisture content and alleviate the problems faced in conventional method. The Chewing Gum composition (base) is cooled to a temperature at which the composition is sufficiently brittle and would remain brittle during the subsequent grinding step without adhesion to the grinding apparatus. The temperature required for cooling is determined in part by the composition of the Chewing Gum and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperature of the refrigerated mixture is around -15oC or lower[17]. Amongst the various coolants like liquid nitrogen, hydrocarbon slush use of solid carbon dioxide is preferred as it can give temperatures as low as 78.50C. The solid carbon dioxide sublimes readily on warming the mixture and is not absorbed by the chewing gum composition. It does not interact adversely with the processing apparatus and does not leave behind any residue which may be undesirable or potentially hazardous. 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 chewing gum composition can be combined into a single step.

The grinding apparatus itself is cooled by keeping the grinding apparatus in contact with a coolant or by placing the grinding apparatus in a cooling jacket of liquid nitrogen or other cold liquid. For more efficient cooling, the chewing gum composition can be pre cooled prior to cooling to the refrigeration temperature. Sometimes a mixture of chewing gum composition, solid carbon dioxide and precipitated silica is ground in a mill grinder in a first grinding step. Additional solid carbon dioxide and silica are added to the ground composition, and the composition is further ground in a second grinding step[18]. This two step grinding process advantageously keeps the chewing gum composition at a very low temperature. The presence of solid carbon dioxide also serves to enhance the efficiency of the grinding process. The same process can be made multiple by incorporating additional carbon dioxide and/or precipitated silica at each step. Certain additives can be added to the chewing gum composition to facilitate cooling, grinding and to achieve desired properties of chewing gum. These include use of anti-caking agent and grinding agent. Once the coolant has been removed 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 mill or a high shear mixer. Alternatively a Fluidized Bed Reactor (FBR) can also be used[19]. The use of FBR is advantageous as it partially rebuilds the powder into granules, as well as coats the powder particles or granules with a coating agent thereby minimizing undesirable particle agglomeration. The granules so obtained can be mixed with antiadherents like talc. The mixture can be blended in a V type blender, screened & staged for compression. Compression can be carried out by any conventional process like punching. Cooling, Grinding and Tabletting Method thus overcomes the limitations of Conventional technique. However, it requires equipment other than conventional tabletting equipment thus making it expensive process as compared to Conventional process. Similar to the Conventional process even this process require [20]

3. DIRECT COMPRESSION CHEWING GUM

SPI pharma has developed a compatible gum system known as Pharmagum. Pharmagum is a mixture of polyols and of sugar with gum base. Pharmagum® S consists primarily of gum base and sorbitol. Pharmagum® M contains gum base, Mannitol and Isomalt. These are free flowing powders, which are directly compressible. The gum is manufactured under CGMP conditions and complies with food chemicals. Direct compression chewing gum can be directly compressed on a traditional tabletting machine, thus enabling rapid and low cost development of a gum delivery system. [21]

Formulation Aspect:

- Hard gum retards the drug release, which can be increased by increasing the amount of softeners and emulsifiers in gum base.
- Drugs with poor water solubility can be complexed with Cyclodextrin or can be subjected to solubilisation technique to increase its aqueous solubility
- A solid system of lipophilic active ingredients bound to the cation exchange resin permits a sustained drug delivery system.
- Microencapsulation or agglomeration is the method to modify and control the release of AI.

FACTORS AFFECTING RELEASE

The release rate of an active substance is determined not only by the formulation of the chewing gum but also by the properties of the active substance and of the individual chewing the gum[22]. The chewing gum – The water content of gum base is very low and the gum binds lipophilic substances very firmly. In order to obtain the optional formulation it is possible to

- Decrease the release rate of highly hydrophilic substances
- Increase the release rate of lipophilic substances
- Achieve a more complete release of lipophilic substances
- Prolong the release
- Changing the water solubility of the active substance will increase or delay the release. A similar effect may be obtained by changing the hydrophilic/lipophilic balance of the chewing gum formulation.

The simplest way of achieving this is to increase or decrease the amount of gum base. An increase in the gum base will make the formulation more lipophilic and thus reduce the release rate of a given active substance. In principle, it is possible to manufacture products with a very low gum base content, but in practice a portion of chewing gum containing less than 20% gumbase will have inferior chewing properties and may not be considered a viable formulation[23]. Instead of changing the gum base content, it is far more effective to change the release properties by adding solubilizers to the formulation. This method enables release from the chewing gum

of even highly insoluble substances, e.g.Miconazole. However using solubilizers requires specially designed gum bases as thesolubilizer affect the texture of chewing gum. This may result in residual product be coming soft to an unacceptable degree after a very short period of chewing. Other methods are available for instance nicotine can be formulated as complex bound to a cation exchange resin leading to a prolonged release. This ion exchange principle could of course, also be used for other ionic substances. It is also possible to granulate the active substance with hydrophilic components, melted lipids, or to mix the active substance with a melted polymer.[24]

Figure 3- Crewing apparatus

The active substance

The release rate of an active substance depends on the solubility of the active substance in water and saliva. Highly hydrophilic substancewill be almost completely released within 10 to 15 minutes. Substances withsolubility in water or less than 0.1 – lg/100ml are lipophilic components of the gumbase and thereby show a slow and incomplete release. Active substances may befound in the form of salts or compounds with different solubilities, e.g. pro-drugs,thus the compound offering the best properties for achieving optimal release may be selected. Chlorhexidine can serve as an example apart from pure chlorexidine,chlorhexidine is available as different salts with different solubility. A specialcompound or pro-drug may be obtained by formulating a complex with an activelipophilic substance, e.g. by using cyclodextrines. This will result in a compound withhigher water solubility and consequently increased release. It is also possible to increase or delay the release of an active substance by changing the physical form through a variety of coating and encapsulating techniques of the substance particles. A hydrophilic or a hydrophobic coating may encapsulate the active substance. To reduce the release rate a coating with ethyl cellulose can be used.[25]

The individual

For medical chewing gum as for other pharmaceutical products is an inter-patient variance. Additional to conventional pharmaceutical formulations, other inter-patient variations apply for a chewing gum formulation. When the individual is chewing the gum it may be regarded as an extraction process. Consequently, the release is related to the time the gum is being chewed to the frequency and intensity by which the individual is chewing, and it depends on the amount and composition of the individual's saliva.

QUALITY CONTROL

- **Test for Uniformity of Content:** Unless otherwise prescribed or justified and authorized medicated chewing gum with content of 2 mg or less than 2 percent of the total mass of gum comply with test.
- **Uniformity of mass:** Uncoated medicated chewing gum and unless otherwise justified and authorized coated medicated chewing gum comply with the test for uniformity of mass of single- dose preparations.
- **Drug release from medicated chewing gum:** It has been reported commercially that the drug release from medicated chewing gum as per the specification given in European Pharmacopoeia and is determined by applying a mechanical kneading procedure to a piece of gum placed in a small chewing chamber containing a known volume of buffer solution[26].

SAFETY ASPECT

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, colour 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 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.[27]

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 disease was surgical procedure but now more and more disease 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[28]. 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.

Trade Mark	Active Substance	Aim	Commercially Available
Aspergum	Aspirin	Pain relief	North America
Nicorette	Nicotine	Smoking cessation	Worldwide
Nicotinelle	Nicotine	Smoking cessation	Western Europe, Australia, New Zealand
Trawell	Dimenhydrinate	Travel illness	Italy, Switzerland,
Superpep	Dimenhydrinate	Travel illness	Germany, Switzerland
Chooz	Calcium carbonate	Stomach acid neutralization	USA
Endekay Vitamin C	Vitamin C	General health	Middle East, United Kingdom
Source Vitamin C	Vitamin C	General health	Australia
Brain	DHA & CCE	Enhanced brain activity	Japan
Stay Alert	Caffeine	Alertness	USA
Cafe Coffee	Caffeine	Alertness	Japan
Buzz Gum	Guarana	Alertness	United Kingdom
Go Gum	Guarana	Alertness	Australia
Chroma Slim	CR	Diet	USA
Fluorette	Fluoride	Cariostatic	USA
Vitaflo CHX	Chlorhexidine	Preventing Tooth decay	USA
Travvel	Dimenhydrinate	Motion sickness	USA, Australia

Figure 4- Medicated Chewing gums in the market

CONCLUSION:

Chewing gum is an excellent drug delivery system for self medication, as it is convenient and can be administered discretely without water. It offers several advantages compared to chewable tablets, lozenges and other related formulations. Hence in forth coming years it will become a much more common and popular drug delivery system.

The potential of MCG for buccal delivery, fast onset of action and the opportunity for product-line extension makes it an attractive delivery form. Medicated Chewing gums can produce both local effects as well as systemic effects in the oral cavity[29]. They can be used for the purpose of taste masking of certain drugs too. Chewing gum for smoking cessation will also remain despite the fact that nicotine patches have grown in popularity lately. This is because the very act of chewing gum also provides a physical substitute for the smoking habit and thereby increases the possibility of successful quitting.

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