Review Article

A Review on Medicated Chewing Gum as a Novel Drug Delivery System

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ABSTRACT

New formulations and technologies have been developed through oral drug delivery systems' research. Such research display significance of oral route amongst patients. We have reviewed all the features associated with medicated chewing gum as a modern drug delivery by introducing the history, advantages and disadvantages, methods of manufacturing, composition differences, evaluation tests and examples of varieties of medicated chewing gums. Acceptance of medicated chewing gum has been augmented through years. The advantages and therapeutic benefits of chewing gum support its development as we can see new formulations with new drugs contained have been produced from past and are going to find a place in market by formulation of new medicated chewing gums. Potential applications of medicated chewing gums are highly widespread as they will be recognized in future. Nowadays standards for qualifying chewing gums are the same as tablets. Patient-centered studies include medicated chewing gums as a delivery system too which creates compliance for patients.

Keywords: Oral drug delivery, medicated chewing gum, patient compliance.

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INTRODUCTION

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 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 [1].

Medicated chewing gums are solid or semi-solid pharmaceutical dosage forms and contain one or more active pharmaceutical ingredients (API) and water soluble or insoluble excipients blended with a water-insoluble gum base. The drug product is intended to be chewed in the oral cavity for a specific period of time, after which the insoluble gum base is discarded [2] . During chewing, the drug contained in the gum is released into the saliva. The released drug has got two fates; either it could be absorbed through the oral mucosa or may reach the stomach for GI absorption. In fact, both these two fates may occur simultaneously. So, medicated chewing gums offer both local and systemic effect [3]. This drug delivery system offers absorption by two pathways. Drug absorbed directly via the buccal membrane avoids metabolism in the gastrointestinal tract and thus the chance of first pass effect of the liver. As a result drug formulation as medicated chewing gum may require reduced dose compared to other oral drug delivery systems[4]

Advantages of medicated chewing gum[5-10]

- No need of water to swallow so can be taken anywhere.
- Accuracy of medication.
- Counteracts dry mouth, prevents candidacies and caries.
- Highly acceptable by children.
- Less first-pass metabolism and improved bioavailability.
- Gum does not reach the stomach. Hence gastrointestinal tract suffers less from the effects of excipients.
- Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa.
- Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly duration of action is increased.
- The treatment can be terminated at any time.
- Aspirin, Dimenhydrinate and Caffeine shows faster absorption through MCG than tablets,
- Stimulates flow of saliva in the mouth,
- Neutralizes plaque acids that form in the mouth after eating fermentable carbohydrates

- Helps whiten teeth by reducing and preventing stains.

Disadvantages of medicated chewing gum[11-14]

- Prolonged chewing of gum cause pain in facial muscles and ear ache in children.
- Risk of over dosage as compared to chewable tablets or lozenges.
- Sorbitol present in medicate chewing gum cause flatulence, diarrhoea.
- Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers.
- Additives like flavouring agent, cinnamon present in gum cause ulcers in oral cavity and liquorice cause hypertension
- Because of its unpleasant taste and staining properties to teeth and tongue, Chlorhexidine oromucosal application is limited to short term use.

Types of Chewing Gum[15]

Cut and wrap

Figure 1: Cut and wrap chewing gum

The gum bases for this type of line need a certain elasticity to withstand the stretching that takes place in the cooling tunnel. Chewing gum formulation should be softer than other chewing gum, due to the bigger size of the piece which is achieved by adding more liquids in the formula (glucose and sweeteners)

Stick and tabes chewing gum

Figure 2: Sticks and tabs chewing gum

Gum bases for laminated product should have the necessary plasticity to allow them to be shaped by the rolls and after the curing time, become hard enough to be wrapped properly. Laminated chewing gum usually have higher gum base percentage than cut and wrap gum. Besides that, the glucose contents needs to be adjusted to afford the necessary hardness for the packaging process while maintaining sufficient elasticity to ensure that the pieces do not break when bent.

Pellets/pillows

Figure 3: Pellets/pillows chewing gum

Similar to sticks, chewing gum is shaped in pellet form. Gum bases for laminated product should have the necessary plasticity to allow them to be shaped by the rolls and after the curing time, becomes hard enough to withstand the cooling process.

Hollow balls

Figure 4: Hollow balls chewing gum

Gum bases for revolutionary products must have certain elasticity (less than cut and wrap product) and have the necessary plasticity to maintain their shape and prevent leaks (if filled). Once the center is cured, it must be hard enough to withstand the coating process.

Liquid filled gums

Figure 5: Liquid filled gums

Gum bases for stamped chewing gum should have special characteristics:

- ✓ Sufficient elasticity to withstand the equalizing steps where the stretching takes place.
- ✓ Correct plasticity to quickly adopt the shaped produced by the dies of the forming machine.

The chewing gum should have a gum base percentage range that allows for good formation and a good seal. A deficiency or excess in the gum base content will lead to product deformation.

Gum filled candy

Figure 6: Gum filled candy

All bubble gum bases can usually be used for this type of product, however due to high temperature of the candy, gum bases with lower viscosities may be more difficult to work with because they can become liquid.

Compressed chewing gum

Figure 7: Compressed chewing gum

They are made of a powder ready to be compressed for functional and Pharmaceutical industries.

Components Required for Medicated Chewing Gum Formulation[16- 17, 19, 27]

Table 1: Water insoluble gum base

Ingredients	Function	Example
Elastomers	Provides elasticity and controls gummy texture	Natural- chicle gum, nispero, rosadinha, jelutong, periollo, lechicapsi, sorva etc.) Synthetic rubbers- (butadiene, styrene, polyisobutylene, polyethylene mixtures, polyvinyl alcohol etc.)
Elastomeric solvents	Softening the elastomeric base component	Terpinene resins (polymers of alpha-pinene or betapinene), modified resins or gums (hydrogenated, dimerized or polymerized resins)
Plasticizers	To obtain a variety of desirable textures and consistency proper-ties	Lanolin, palmitic acid, oleic acid, stearic acid, glyceryl triacetate, propylene glycol monostearate, glycerine, natural and synthetic waxes, hydrogenated vegetable oils, paraffin waxes, fatty waxes, sorbitol monostearate, propylene glycol
Fillers or texturizers or mineral adjuvant	Provide texture, improve chew ability, provide reasonable size of the gum lump with low dose drug	Calcium carbonate, magnesium carbonate, aluminum hydroxide, talc, aluminum silicate.

Table 2: Water soluble gums base

Ingredients	Function	Example
softeners and emulsifiers	These are added to the chewing gum in order to optimize the chew ability and mouth feel of the gum	Glycerin, lecithin, tallow, hydrogenated tallow, mono/di/ tri glycerides.
Colorants and whiteners	Gives the formulation soothing color and improves acceptability of the formulation	Titanium dioxide, natural food colors and dyes suitable for food, drug and cosmetic applications
Sweeteners	To provide the desired sweetness of the product	Water soluble sweetening agents (xylose, ribulose, glucose, mannose, galactose, sucrose, fructose, maltose, monellin, sugar alcohols like sorbitol, Mannitol etc.), Water soluble artificial sweeteners (sodium or calcium saccharin salts, cyclamate salts etc.), Di-peptide based sweeteners (aspartame, alitame etc.), Naturally occurring water soluble sweeteners, chlorinated derivatives of ordinary sugar (sucralose), protein based sweeteners (thaumatin I and II)
Antioxidants	Prevent any possible microbial growth	Butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate
Flavoring agent	To enhance acceptability	Essential oils (citrus oil, fruit essences, peppermint oil, spearmint oil, mint oil, clove oil and oil of wintergreen) and synthetic or artificial flavors
Bulking agent	Used if low calorie gum is desired	Polydextrose, oligofructose, inulin, fructooligosaccharides, guargum hydrolysate, indigestible dextrin
Compression adjuvant	To ease compression process	Silicon dioxide, magnesium stearate, calcium stearate, talc.

Manufacturing Procedure of Medicated Chewing Gum

- conventional or traditional method
- cooling, grinding and tabletting method
- Direct compression method

Conventional or traditional method [18 - 19]

Gum compoents →melted and placed in a kettle mixer→gum sent throught a series of rollers→thin, wide ribbon formed 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 up to 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.

Limitations[20-21,]

- Elevated temperature used in melting restricts the use of this method for thermolabile drugs.
- Due to melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult.
- Gum components having 2-8% moisture content would jam the grinding machine, stick to blades, screens adhere to punches and would be difficult to compress.

Cooling, Grinding and Tabletting Method[22-24]

Aim of the method-to lower the moisture content and alleviate the problems faced in conventional method

Cooling

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. General temperature of the refrigerated mixture is -15oC or lower. Temperature which is required for cooling is determined by the composition of the Chewing Gum and empirically by observing the properties of the cooled chewing gum composition. Coolants used are liquid nitrogen, hydrocarbon slush, carbon dioxide. Carbon dioxide is preferred as it can give temperatures as low as 78.50oC. 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.

Grinding

Cooling of grinding apparatus is done 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

Steps involved

- ✓ Mixture of chewing gum composition, solid carbon dioxide and precipitated silica is ground in a mill grinder.
- ✓ Additional solid carbon dioxide and silica are added to the ground composition, and the composition is further ground.
- ✓ This two step grinding process advantageously keeps the chewing gum composition at a very low temperature. The presence of solid carbon dioxide enhances the efficiency of the grinding process. The same process can be made multiple by incorporating additional carbon dioxide and/or precipitated silica at every 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.

Tableting

Compression can be carried out by any conventional process like punching. Similar to the Conventional process even this process requires careful monitoring of humidity during the tabletting process

Direct Compression Chewing Gum[5 ,24 -25,]

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. 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.

Factors Effecting Release Of Drug Ingredients[24 ,26-27]

Contact Time

Both the local or systemic effect is depending on time of contact of Medicated Chewing Gum in oral cavity. In clinical trial chewing time of 30 minutes was considered close to ordinary use. Average chewing rate is 60 chews /minute.

Physicochemical properties of active ingredient
Physicochemical properties of active ingredient plays very important role in release of drug from Medicated Chewing Gum. Saliva soluble drugs immediately released within few minutes and lipid soluble drugs released first into the gum base and then released slowly.

Inter individual variability

The chewing frequency and chewing intensity which affect the drug release from Medicated Chewing Gum may vary from person to person. In-vitro study prescribed by European Pharmacopoeia suggest 60 cycles per minute chewing rate for proper release of active ingredient.

Formulation factor

Composition and amount of gum base affect rate of release of active ingredient. If lipophilic fraction of gum is increased, the release rate is decreased.

FORMULATION ASPECTS FOR MEDICATED CHEWING GUM[18 ,21, 28-29]

Microencapsulation by water-soluble or water-insoluble polymer is one of the successful methods for sustaining the release of active ingredient sweetener or flavorant from MCG. Cyclodextrin complexes have been used to increase the solubility, stability and bioavailability of a variety of active ingredients in formulations and also explored for masking the taste of certain active ingredients. Hard gum may retard the release whereas increased amount of softeners and emulsifiers in gum base fasten release. Complexation of lipophilic active ingredients to ion exchange resins such as polacrillin potassium provides sustained drug delivery. Also, this approach is useful to mask the taste of bitter drugs

EVALUATION PARAMETERS

As per specifications given in European Pharmacopoeia[5,26]

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.

Product performance test

Two different types of tests are performed to assess the drug product characteristics:-product quality and product performance tests.

***In-vitro* drug release from MCG**

Unofficial single module chewing apparatus[30]

Figure 8: *In vitro*-drug release from MCG

One of the unofficial apparatus for carrying out dissolution studies of MCG was designed by Wennergren. This apparatus consists of a two-piston and temperature-controlled reservoir for dissolution medium. 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 dissolution medium, which is equilibrated to a temperature of 37oC. 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 analyzed to evaluate percentage drug release.

Official MCG chewing apparatus

The official modified dissolution apparatus[31]

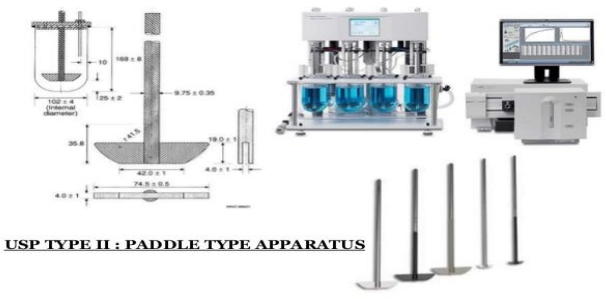

Figure 9: Official dissolution apparatus

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 own axis to each other to attain maximum mastication. The temperature of the chamber can be maintained at 37±0.5oC and the chew 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.

***In vivo* 'chew-out' studies[32]**

The in-vivo release of active ingredient from chewing gum during mastication can be studied by recruiting a panel of sufficient numbers of tasters and scheduled chew-out Studies. For the duration of the chewing process the drug contained within the MCG is released in the saliva and then it is either absorbed through oral mucosa or, if swallowed, it is absorbed through the gastrointestinal tract.

Release of drug in saliva

Panel of volunteers is asked to chew the drug delivery device for a certain period of time and to assess the remaining quantity of active substance in the residual gum.

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.

Urinary excretion profile of medicated chewing gum

This method can be applicable only to those drugs which are excreted via urine. In that minimum four healthy human volunteer are selected for the study of formulations. Volunteers are strictly instructed that they should not take any medicine in the last 48 hour. They are fasted overnight and emptied their bladder in the volumetric flask. Sample collection starts from blank of zero hour urine. Then sample collection is done on the 15 min, 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 24 hour intervals 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 value 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. C. Stability33 The stability of chewing gum is comparable to that of most other solid delivery systems. Chewing gum normally contains little water (2.5%). If the water content is very critical for the stability of drug, the chewing gum can be manufactured without water (less 0.2%). This will however, often make the product hygroscopic and will affect the texture. The low water content also inhibits microbial growth in the chewing gum during storage. Furthermore, the product can be protected against oxidation by a sealed coat and by an appropriate packing. For every temperature-labile component, e.g. enzymes, the process temperature of 50-60o C during mixing may create a stability problem. It is however possible to operate the process at a lower temperature to avoid this issue

Therapeutic Application[15,34]

Table 3: Therapeutic Application

Therapeutic use	Specific example	Marketed products
Smoking cessation	Nicotine	Nicorette
Pain relives	Aspirin	Alka seltzer
CNS stimulation, improvement of memory	Caffein	Stay alert
Treatment of oddities media	Xylitol	Spry
Treatment of dental carries	Chlorhexidine,	Advanced +
Treatment and management of motion Sickness	Dimenhydrinate	Travvell
Acid neutralization	Antacid	Chooz

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 surgical procedure are available for treatment of some disease was 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. The application scope for medicated chewing gums, however, is wide and more products will become available. Medicated chewing gum is a valid alternative to standard, chewable or orally disintegrating tablet presentations.

CONCLUSION

In the future, we may see drugs formulated into chewing gum in preference to other delivery systems to deliver drugs locally to the oral cavity. A chewing gum formulation must have a pleasant taste and texture. Most active substances have an unpleasant, bitter, or metallic taste. Since the active substance will be released in the oral cavity and remain there for a longer period of time than is the case with ordinary delivery forms, unique expertise in

taste definition, taste masking, and taste modification are essential to the success of a medical chewing gum product. As chewing gum as a drug delivery system is to be expanded into additional therapeutic areas, it is important that the delivery form is acceptable to the endusers. 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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