REVIEW ARTICLE

Medicated chewing gum, a novel drug delivery system

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New formulations and technologies have been developed through oral drug delivery systems' researches. Such researches display significance of oral route amongst patients. We've 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.

Key words: Oral drug delivery, medicated chewing gum, patient compliance

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INTRODUCTION

Chewing gum is a drug delivery system which 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.[1]

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.[2]

First marketing of chewing gums was at 1848 when chicle from Sapodilla tree was sapped. 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.[3,4]

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.[3,4]

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.[4-7]

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.[8]

Medicated chewing gums which are marketed for therapeutic purposes are so various; a brief list is given in Table 1.

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Table 1: Therapeutic use and examples of MCGs

Therapeutic use/indication	Drug
Treatment of motion sickness	Dimenhydrinate hydrochloride,[9] Diphenhydramine hydrochloride,[10] Ginger[11]
Smoke cessation	Nicotine[12]
Pain reliever	Aspirin, lobeline, silver acetate[6]
Anti-plaque and gingivitis, preventing of dental caries and tooth decay	Xylitol,[13] chlorhexidine,[14] *Salvadora persica L.*[15]
Oral antifungal	Miconazole[16]
Treatment of otitis media	Xylitol[13]
Alertness and CNS stimulant	Caffeine[17]
Antioxidant	Green tea[18]
Anti-nausea and anti-emetic (prevention of motion sickness), effective in GI problems	*Ginger*[11]
Antioxidant, anti-inflammatory and anti-septic and healing	*Aloe vera*[19]

MCG = Medicated chewing gum; CNS = Central nervous system; GI = Gastrointestinal

The aim of this article was to review on advantages and disadvantages of MCGs and methods for formulation them.

Ability of chewing gums to release active ingredients into the oral cavity, steady and rapid action, capability of both systemic and local delivery, make it appropriate for extensive use in food and pharmaceutical industries.

Advantages of medicated chewing gums

1. Increased rate of effectiveness rather than other oral delivery systems.[20,21]
2. Removal of gum at any time; therefore termination of drug delivery.[20,21]
3. Reduced risk of overdosing while it's whole swallowed.[20,21]
4. Requiring no water to drink.[20,21]
5. Protection of the susceptible drugs contained from chemical or enzymatic attack in gastrointestinal (GI) tract.[21]
6. Both systemic and local drug delivery.[20,21]
7. High acceptance by children and teenagers.[20,21]
8. Low first-pass effect so reduced dose is formulated in chewing gum compared to other oral delivery systems.[20]
9. Good for rapid delivery.[20-22]
10. Fewer side effects.[21]
11. Reduced risk of intolerance to gastric mucosa.[21]
12. Good stability against light, oxygen, and moisture.[20]
13. Annihilation of xerostomia and help tasting and swallowing in people with dry mouth.[6,7-22]
14. Reduced pains and difficulties in swallowing following tonsillectomy.[6]
15. Improving work performance and cognitive function[23]
16. Fast bowel recovery after GI surgery.[7]
17. Reduced hypoglycemic shocks in people taking anti-diabetic drugs.[7]
18. Stimulating alertness through increased blood flow to brain.[24]
19. Help reduce food cravings.[24]

Disadvantages of medicated chewing gums

1. Disappearing of drug in oral cavity following salivary dilution.[8,25]
2. Different release profiles because of chewing style differences.[8,25]
3. Short time of administration due to eating, speaking, and drinking.[8,25]
4. Allergic reaction to artificial sweeteners.[26]
5. Continuous stress on jaws that may cause temporomandibular joint disorder.[7,26]
6. Teeth decay through being coated by sugar.[7,26]
7. Masseter problems.[26]
8. Stomach irritations, aches, gastric ulcer through continuous swallowing of saliva and even flatulence because of presence of sorbitol in some formulations.[22,26]
9. Getting choked by swallowing gum in under-aged children.[7]

Composition

Chewing gum is a mixture of ingredients-either natural or synthetic-that comprises water-soluble bulk portion and water insoluble gum bases. These two portions are responsible to carry different ingredients which are listed in Table 2.[27,28]

Gum base is the nonnutritive part of gum which is not dissolve while chewing, gum bases are mixture of natural gums, latex, plastics, solid paraffin, bees' wax but modern gum bases use no natural rubber at all or just a minimal amount, 15-30% of chewing gum is gum base.[5]

Elastomer is a polymer with high elongation properties and elasticity, which make them flexible against its breaking or cracking. Natural and synthetic elastomers are two different materials applied in chewing gum formulations. The ability of formulation process depends on types and amounts of elastomers.[21,28,29]

Emulsifier allows two indissoluble phases to disperse in one another and can improve softness and ability to make bubble gums. It contributes to mixing and softness during shelf life and hydration effect while chewing.[21,28,30,31]

Plasticizer is a material to make chewing gum composition softened and consumer-friendly. It promotes gum texture by applying plasticity and reducing brittleness and renders the elastomers soft.[21,31,32]

Table 2: Chewing gum composition, water-soluble bulk portions[31-36]

Component	Function and proportion	Example
Water soluble bulk portion		
Bulk sweeteners		
Sugar sweeteners	30-60%, saccharide-coating components	Sucrose, dextrose, maltose, dextrin, dried invert sugar, fructose, levulose, galactose, corn syrup
Sugarless sweeteners		Sorbitol, mannitol, xylitol, hydrogenated starch hydrolysate, maltitol
High-intensity artificial sweetener	0.02-8%	Sucralose, aspartame, salts of acesulfame, alitame, saccharin
Flavoring agent	0.01-1%	Essential oils, synthetic flavors, mixture (citrus oils, fruit essences, peppermint oil, spearmint oil, clove oil, oil of wintergreen and anise)
Softener (plasticizer)	0.5-15%, regulating the cohesiveness and modifying the texture	Glycerin, lecithin, aqueous sweetener solutions, sorbitol, hydrogenated starch hydrolysate, corn syrup, tallow, cocoa butter, glycerol monostearate, glycerol triacetate, fatty acid (palmitic, stearic, olic…)
Emulsifier	15-45%, dispersing immiscible compounds	Mono-, di-, tri-, stearyl acetate, lactylic esters
Colorants (FD and C type dye and lake)	0.1%	Fruit and vegetable extracts, titanium oxide
Antioxidant	0.02% of the gum base	Ascorbic acid, tocopherol, butylhydroxytoluene
Anti-tack agent	0.2-0.6%, something that helps chewing gum not adhere to denture fillings and natural teeth	Slip-agent can be used as this purpose which may be comprised of α-cellulose and vegetable proteins Alkaline metal phosphate, malto dextrin
Anti-caking agent	0.5-2%, preventing agglomeration	Precipitated silicon dioxide, solid carbon dioxide
Water insoluble gum base		
Elastomers		
Natural	15-45%, provides elasticity and cohesiveness	Smoked or liquid latex, guayule, jelutong, lechi-caspi, perillo, sorva, rosadinha, chicle, massaranduba balata, massaranduba chocolate, nispero
Synthetic		Polyisobutylene, isobutylene, -isoprene copolymer, styrene-butadiene copolymers, polyvinyl acetate
Rubber/fat/resin phase (elstomeric plasticizer)	15%, softening elastomeric material	Estrugums: glycerol esters, pentaerythritol esters of rosins (hydrogenated dimerized and polymerized rosins) Synthetic: terpene resins
Filler/texturizer	Up to 50%, modifying the texture of gum base	Magnesium and calcium carbonate, ground limestone, silicate types, clay, alumina, talc, titanium oxide, mono-, di-, tri-calcium phosphate, cellulose polymers
Wax (the base may be wax-free)		

Texturizer supplies overall texture and facilitates blending and other processing stages. Cud size, chewing ability, and stretch are the effects of texturizers' level.[21,31,32]

Rubber is also associated with the manufacture of bubble gum, it's just the resin used in formulations which also acts as elastomeric plasticizer as well as a binding agent between elastomers and texturizers.[21,31,32]

Sweeteners provide the sweetness of formulation and improve the taste. Aqueous sweeteners which include corn syrup, hydrogenated starch, and sorbitol, help to retain moisture and freshness of the final product. They also act as a plasticizer or softening agent and binding agent.[21,32,33]

High-intensity artificial sweeteners also provide the sweetness, but a lower calorie is produced by them due to the partial absorbance in the intestine.[33]

Flavoring agents provide an acceptable flavor for the product and can act as taste-masking agents for bitter drugs to cover the taste of active ingredient.[21,33]

Colorants improve the color of the formulation by producing gentle and soft color.[21]

Anti-oxidants prevent the growth of microorganisms by inhibiting oxidation.[21,32]

Anti-tack agents eliminate self-adhesiveness known as blocking especially rubbers which have a tendency to stick together. It reduces fragmentation of the gum during mastication and prevents attaching to the teeth.[34,35]

Anti-caking agents are used to prevent caking and forming lumps. These materials improve flowability and rehydration and help for good packaging. They are

added to the formulation to extend shelf life and detract dispersibility.[33,36,37]

Manufacturing process

Fusion method

The first step of a typical process for manufacturing chewing gum is to melt and soften the gum base at about 60°C and place it in a kettle mixer, in which blades soften the base, then other ingredients such as sugar, glycerin, sweeteners, taste-masking agent are added to the softened base, lately the flavoring agent is added in the mixing procedure at 40°C, then cooling and rolling steps would be done, and the rolled chewing gum would then be cut into pieces of desired shapes and sizes. To make a coated gum tablet, a coating agent should be sprayed to form a uniform surface.[6,12]

Second type of this method is somehow different: The primary step of preparation is to set up a mixer (the mixer could be sigma blade or other types of mixers), if a sugar-containing gum is needed, the first step is to add corn syrup to the mixer, and then finely powdered sugar is added gradually. Sugar, used in this step, could be powdered sucrose, dextrose, fructose, corn syrup solids or combination of them.

After adding these sweeteners, plasticizers are added to modify the texture and regulate the cohesiveness. Glycerin is the most preferably plasticizer used. Other components specified in Table 2 could be added to the matrix according to required characteristics, such as fillers, colorants, and flavorings. But it is recommended that flavorants being added to the matrix at the end of procedures when gum base is totally and completely homogenized because most flavorants are relatively volatile.

The proportions of components in the matrix are variable between sources and depend to desired characteristics. But powdered sugar has approximately the most proportion.

The mechanical forces of mixer, that is, compressive and shear and heat can ease the softening process. When no heat is applied, a higher power is demanded. The mixing process continues until a homogenous mass is formed. The mixing process should last about 8 min.

Another way of mixing ingredients is to add sugar gradually till the end of adding other components.[25,38]

After matrix preparation and completely mixing it, the commercially prepared particles of gum base are added to the chamber all at once. But it is believed that these particles should have been heated and mixed before adding all other ingredients to the mass of gum base. In this stage, mixing will continue for 10-20 min.[38,39]

The difference between this almost new method from the conventional (fusion) method in mixing techniques is wherein the sweetener matrix is first formed then gum base particles as pellets are added, but in conventional (fusion) method, the sweeteners and other ingredients are added to the molten gum base.

This new processing method has advantages over the previous way of processing, that is, the probability of producing sugar lumps is less than before.[39,40]

Cooling, grinding, and tableting method

One other method to provide a chewing gum with desired taste, color, and flavor is to mix gum base with favorable and suitable sweeteners, corn syrups, starches, flavoring agents, and colorants, and then refrigerate and cool it by a freezer apparatus or by contacting with a coolant like carbon dioxide to a temperature below −15°C which is therefore crushed and pulverized with a cutter or grinding apparatus to obtain minute particles then these finely ground particles are heated to a temperature which makes them adhere to each other and form a slick and uniform bulk with consistent texture and low specific gravity. If the fragments are such that they do not self-adhere, low pressure would be applied manually or mechanically before they are warmed to the normal room temperature to thereby promote self-adhesion.

The cooling and grinding steps can be combined by cooling the grinding apparatus. After the grinding step, we can let the coolant (if used) evaporate and disappear from our desired composition.

The minute particles may be coated by edible substances or premixed with powdery materials.

For tabletization, compressing punches may be needed but an anti-adherent agent should be applied to avoid sticking to surfaces of punches.[25]

Direct compression

A new technology to make a chewing gum tablet is direct compression and tableting at high-speed standard machine, but as explained in a patent, this way of forming chewing gum tablets provides a quickly dissociable chewing gum, but after a few seconds of chewing, particles adhere together to form a uniform and homogenous mass. In this method; we need a granulating agent, most preferably that is sorbitol which can also act as a sweetener. A lubricant such as magnesium stearate, talc, stearic acid, hydrogenated vegetable oils, and sodium stearyl fumarate is added to formulation before tableting. First step of this method is dry mixing of gum base, granulating agent and at least one processing material then adding active ingredient, sweeteners, and other needed ingredients to

the formulation in free flowing form of materials then directly compressing the chewing gum into tablets. In the first step, the temperature should not raise higher than the melting point of the gum base. After obtaining a uniform and slick mass, the temperature would lower to add other ingredients.

The compressed tablet is capable of releasing the active ingredient into the mouth cavity, after 2-10 chews dissociation reaches to maximum.

We can formulate many sensitive active substances in model of compressed chewing gum that is advantage over previous methods, other significant benefits are:

1. Fast release.
2. fast absorption, and
3. high content uniformity. Bi-layered compressed chewing gum tablets are now found in new pharmaceutical products.[22,41,42]

Problems associated with manufacturing chewing gums

1. Capping, lamination, picking, and sticking are the most common processing problems.[43]
2. In the first method, one of the problems is that the inordinate content of moisture in the matrix may cause a low viscosity which reduces the shear and compressive forces, indeed more gum base particles are more likely to dissociate and float.[25]
3. Heating and melting can make controlling the accuracy and uniformity of the drug difficult.[25]
4. It is hard to provide sanitary conditions to make MCGs.[25]
5. In the second method, moisture content of chewing gum may cause the gum jam to the blades and punches of apparatus, screens, surfaces, and chamber's wall.[43]
6. In the second method caking and balling of the gum prevent formation of gum fragments.[25]
7. In the third method, ejection of final compressed mass from the mixer is difficult and may stuck up into the tubes and stick to punches.[44]
8. Forming a low calorie chewing gum has resulted in a gum with hard chew, poor texture, and bad taste or off-taste.[45]
9. Bad smell and undesired taste of ingredients applied in the compound.[46]
10. Sugar spots or lumps may appear in the final texture and cause undesired feeling.[38]
11. Some ingredients and active agents can irritate mucosa.[46]
12. High temperature to facilitate the mixture of gum base, leads to spoil other ingredients.[46]
13. Water elimination from final formulation requires advanced techniques to avoid the hardness of gum.[46]

Evaluation tests

Content uniformity

Ten MCGs 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.[1]

Mass uniformity

Twenty MCGs are selected randomly and weighed, not more than two single mass should vary the average mass.[1]

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 MCG, a part of MCG is placed in the chamber of an apparatus which contains:

1. Chewing chamber.
2. A vertical piston and
3. Horizontal pistons with sealed rings. MCG 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.[1] Actually, horizontal and vertical pistons are, respectively, instead of teeth and tongue.[47]

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. 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.[6,48]

In another apparatus designed by Wennergren (Kvist *et al.*) they considered the effect of occlusal surfaces, rotary and shearing movements and the medium temperature on drug release.[49]

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 MCG 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 MCGs for three times.[1]

Evaluation of 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.[12, 50]

1	2	3
2	3	1
3	1	2

Evaluation of chewing gums 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.[12,51]

Evaluation of mechanical properties of chewing gums

Tensile test

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:

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 nonuniformity 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.[12,52,53]

Factors affecting release rate and amount

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

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
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
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
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 MCG 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.[6,34,54]

Stability

Chewing gum is a very stable product due to its low moisture content and less reactive nature than that of other oral ingredients.[24]

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.[3]

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.

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.[31]

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.[9]

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.[1,3,55]

Chewing gum 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.[56] 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.[55]

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.[57]

Future trends

Future of chewing gum will reveal all of the scientists' efforts for the development of chewing gum as a modern drug delivery system and progress of chewing gum production technology. In the future, other attempts will be seen to formulate more drugs using chewing gum as a drug delivery system. Treatment of fungal diseases, prevention of caries and other dental health issues, smoking cessation, etc., are common health work of MCGs. But remineralization of teeth, cold relief, energy enhancing, anti-nausea and so many new advantages of this novel drug delivery system are going to play an important role through future studies. MCGs are admissible alternatives of chewable or standard tablets and oral disintegrated dosage forms.

Actually, it takes time for chewing gum to get acceptance by people as a drug delivery system, but we hope that MCG finds its real place in industry and market and between patients soon, through its numerous advantages.

Long lasting flavored, filled gums, timed-release, and other new MCGs formulated for diseases that previous delivery systems have been used for, are trendy products to be seen in the future as a new kind of chewing gum which is made biodegradable and can be dissolve in around 1 month.

We predict a brighter future for MCG as a novel drug delivery system than previous oral systems.[58]

CONCLUSION

According to the benefits of chewing gum as a novel drug delivery, like concurrently supporting both local and

systemic delivery, protection against acids and enzymes, low first pass metabolism, elevating alertness and cognitive function, good stability and a lot more; we can conclude that chewing gum will be much more familiar to patients and market in the next few years. However, their new and old applications prove our statement as it can be seen that there are treatments for motion sickness, pain, smoking, dental caries, tooth decay, otitis media, GI problems, oral fungi, inflammatory problems etc., by formulating efficient chewing gums that contain at least one drug as active agent.

The technology to bring chewing gum to market and health system as a reliable alternative for different kinds of tablets has not been ready and fully understood yet because there are much more information and knowledge to be explored for manufacturing chewing gums. But, fortunately, the progress of this procedure is admissible.

Scientists and researchers should also consider new formulations for chewing gums for increasing variations of chewing gum due to patients' different styles and providing appropriate release pattern for chewing gums containing drugs.

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AUTHOR'S CONTRIBUTION

All authors have contributed in designing and conducting the study. All authors have assisted in preparation of the first draft of the manuscript or revising it critically for important intellectual content. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

REFERENCES

1. Directorate for the Quality of Medicine and Health Care of the Council of Europe. European Pharmacopoeia. 7th ed. Strasbourg: Directorate for the Quality of Medicine and Health Care of the Council of Europe; 2009. p. 289, 709.
2. Available from: http://www.candyfavorites.com/shop/education.php [Last accessed on 2013 July 2].
3. Rathbone MJ, Hadgraft J, Roberts MS. Modified-Release Drug Delivery Technology, New York: CRC Press; 2002.
4. Jacobsen J, Christrup LL, Jensen NH. Medicated chewing gum. Am J Drug Del 2004;2:75-88.
5. Available from: http://www.madehow.com/Volume-1/Chewing-Gum.html [Last accessed on 2013 July 15].
6. Rassing MR. Chewing gum as a drug delivery system. Adv Drug Deliv Rev 1994;13:89-121.
7. Madan N, Rathnam A. Chewing gums for optimal health. Chron Young Sci 2011;2:7.
8. Surana AS. Chewing gum: A friendly oral mucosal drug delivery system. Int J Pharm Sci Rev Res 2010;4:68-71.
9. Mehta F, Trivedi P. Formulation and texture characterization of medicated chewing gum delivery of dimenhydrinate hydrochloride. Pharmacia Lett 2011;2:129-40.
10. Mehta F, Kartikayen C, Trivedi P. Formulation and characterization of medicated chewing gum delivery of diphenhydramine hydrochloride. Pharmacia Sin 2011;2:182-93.
11. Aslani A, Ghannadi A, Rostami F. Design, formulation and evaluation of Ginger chewing gum. Adv Biomed Res 2015;4:Under publication.
12. Aslani A, Rafiei S. Design, formulation and evaluation of nicotine chewing gum. Adv Biomed Res 2012;1:57.
13. Uhari M, Kontiokari T, Koskela M, Niemelä M. Xylitol chewing gum in prevention of acute otitis media: Double blind randomised trial. BMJ 1996;313:1180-4.
14. Pandey S, Goyani M, Devmurari V. Development, *in-vitro* evaluation and physical characterization of medicated chewing gum: Chlorhexidine gluconate. Pharm Lett 2009;1:286-92.
15. Aslani A, Ghannadi A, Mortazavi S, Torabi M. Design, formulation and evaluation of medicinal chewing gum by the extract of *Salvadora persica* L. Life Sci J 2013;10:47-55.
16. Rindum JL, Holmstrup P, Pedersen M, Rassing MR, Stoltze K. Miconazole chewing gum for treatment of chronic oral candidosis. Eur J Oral Sci 1993;101:386-90.
17. Aslani A, Jalilian F. Design, formulation and evaluation of caffeine chewing gum. Adv Biomed Res 2013;2:72.
18. Aslani A, Ghannadi A, Khalafi Z. Design, formulation and evaluation of green tea chewing gum. Adv Biomed Res 2014;3:142.
19. Aslani A, Ghannadi A, Raddanipour R. Design, formulation and evaluation of *Aloe Vera* chewing gum. Adv Biomed Res 2015;4:Under publication.
20. Imfeld T. Chewing gum - facts and fiction: A review of gum-chewing and oral health. Crit Rev Oral Biol Med 1999;10:405-19.
21. Asija R, Patel S, Asija S. Oral dosages forms: Medicine cntaining chewing gum: A review. J Drug Delivery Ther 2012;2:90-5.
22. Heema N, Stuti G. Medicated chewing gums-updated review. Int J Pharm Res Dev 2010;2:66-76.
23. Smith AP, Woods M. Effects of chewing gum on the stress and work of university students. Appetite 2012;58:1037-40.
24. Available from: http://www.gumassociation.org. [Last accessed on 2013 July 15].
25. Athanikar NK, Gubler SA. Process for Manufacturing a Pharmaceutical Chewing Gum. US Patent No. 6,322,828; 2001.
26. Available from: http://www.chewinggumfacts.com/chewing-gum-benefits/chewing-gum-negative-effects/ [Last accessed on 2013 July 15].
27. Khatun S, Sutradhar KB. Medicated chewing gum: An unconventional drug delivery system. Int Curr Pharm J 2012;1:86-91.
28. Bumrela SB, Kane RN, Dhat SP. Medicated chewing gum: A new reformulation technique. Pharma news 2005;3:1.
29. Available from: http://www.dupont.com/products-and-services/plastics-polymers-resins/elastomers/articles [Last accessed on 2013 Aug 24].
30. Available from : http://www.alsiano.com/Food/container/container/Food/Confectionery/Chewing-gum.aspx [Last accessed on 2013 Aug 24].
31. Patel MM, Reed MA, Yatka RJ. Environmentally Stable Chewing Gum Composition Containing Xylitol. US Patent No. 4,931,294; 1990.
32. Nagasamy VD, Toprani PS, Mukherejee S, Tulasi K. Medicated chewing gums - A review. Int J Pharm Sci 2014;4:581-6.
33. Gadhavi AG, Patel BN, Patel DM, Patel CN. Medicated chewing gum-A 21st century drug delivery system. Int J Pharm Sci Res

2011;2:1961-74.
34. Sameja K, Raval V, Asodiya H, Patadiya D. Chewing gum: A modern approach to oral mucosal drug delivery. Int J Pharm Res Dev 2011;4:001-16.
35. Cosgrove T, Erol AH, Voss MG. Chewing Gum Composition. US Patent Application No. 12/449,622; 2008.
36. Gavaskar B, Venkataramana D, Rao YM. Medicated chewing gum: A novel approach to improve patient compliance. Int J Res Pharm Biomed Sci 2011;2:23-32.
37. Ortega-Rivas E, Juliano P, Yan H. Food Powders: Physical Properties, Processing, and Functionality. Springer; 2006. p. 342.
38. Kubota RM, Thomas SM, Chapdelaine AH, Courtright SB. Method of Making Chewing Gum. US Patent No. 4,806,364; 1989.
39. Harikae N, Sato Y, Shibata M, Tezuka S. Process for Preparation of Chewing Gum. US Patent No. 4,329,369; 1982.
40. Mochizuki K, Yokomichi F. Process for the Preparation of Chewing Gum. US Patent No. 4,000,321; 1976.
41. Amin AF, Norman GT. Chewing Gum Formulation and Method of Making the Same. US Patent No. 7,208,186; 2007.
42. Available from: http://fertin.com/expertise/gum/ [Last accessed on 2013 Aug 25].
43. Cherukuri SR, Bikkina K. Tabletted Chewing Gum Composition and Method of Preparation. US Patent No. 4753805; 1988.
44. Chaudhary SA, Shahiwala AF. Directly compressible medicated chewing gum formulation for quick relief from common cold. Int J Pharm Investig 2012;2:123.
45. Cherukuri SR, Hriscisce F, Wei YC. Reduced Calorie Chewing Gums and Method. US Patent No. 4,765,991; 1988.
46. Bindi GC, Vipul PP, Tushar RD. Medicated Chewing Gum: A Review, Pharmatotur-Art-1047, 2011;1-5.
47. Caudhary SA, Shahiwala AF. Medicated chewing gum-A potential drug delivery system. Expert Opin Drug Deliv 2010;7:871-85.
48. Christrup LL, MØller N. Chewing gum as a drug delivery system. Arch Chem Sci 1986;14:30-6.
49. Kvist C, Andersson SB, Fors S, Wennergren B, Berglund J. Apparatus for studying in vitro drug release from medicated chewing gums. Int J Pharm 1999;189:57-65.
50. Available from: http://mathworld.wolfram.com/LatinSquare.html [Last accessed on 2013 Sept 1].
51. Likert R. A technique for the measurement of attitudes. Arch Psychol 1932;140:1-55.
52. Brown R. Physical testing of rubber. New York: Springer; 2006.
53. Available from: https://www.nde-ed.org/EducationResources/CommunityCollege/Materials/Mechanical/Tensile.htm [Last accessed on 2013 Sept 12].
54. Ughade MA, Wasankar SR, Deshmukh AD, Burghate RM, Makeshwar KB. Medicated Chewing Gum: Modern Approach to Mucosal Drug Delivery. Asian J Res Pharm Sci 2012;2:150-9.
55. Bahoshy BJ, Klose RE, Sjonvall RE, Szczesniak AS. Chewing gum with improved storage qualities. US Patent No. 4,000, 320. 1976.
56. Available from: http://www.wrigley.com/global/about-us/how-gum-made.aspx [Last accessed on 2013 Sept 22].
57. Lidón I, Rebollar R, Serrano A, Martín J. Evaluation of the perception of sensory and experience levels for chewing gum packs. Selected Proceedings from the 15th International Congress on Project Engineering. Huesca, 6-8 July 2011;186-92.
58. Available from: http://www.business-review-webinars.com/webinar/Pharma/Medicated_chewing_gum_formulation_and_production-pQ1rK3ZM [Last accessed on 2013 Oct 10].

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