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REVIEW ARTICLE

CHEWING GUM: A BOON FOR ORAL DRUG DELIVERY

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Abstract

Different types of formulations including; mouth wash, lozenges, gargles, mouth dissolving films and pellets, chewing gums, etc. are being used to combat bad breath. Chewing gums have been used as a means of cleansing teeth and for removing bad breath odor, since a very long time. The prevalent use of chewing gums by people of all age groups has prompted interest of formulations scientist towards manufacturing of chewing gums for different purposes. Chewing gums are preferred for delivering drugs for localized effect as medicated chewing gums. Herbal ingredients are known to have a very pleasant and persistent mouth feel, however their use in the form of chewing gums is least explored. In this review authors have tried to compile the basic concept of formulating chewing gum, its method of production, characterizing parameters, various applications in different areas, future scope.

Keywords: Mouth feel, formulation, chewing gums.

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1. Introduction

Chewing gums are the agents which offer an alternative as well as a novel drug delivery system (1). Chewing gum have an old and long history (2). The Greeks used mastic, a resin from the bark of mastic tree for cleaning their teeth and improving the smell of breath. The Mayan Indians obtained gum from the sapodilla tree, a member of the family Sapotaceae for the same purpose (3). Due to certain limitations and the shortage of the natural gum, this paved out the way for synthetic gum during the period of World War 2 (4). Then after at the end of world war i.e. in the year 1948 for the first time chewing gum was marketed and commercialized by the name "state of Maine pure spruce gum"(4).

The first medicated chewing gum (MCG) containing an analgesic, acetylsalicylic acid (aspirin) was marketed in the 1928 by the name "aspergum" (5). However, it was not accepted in public domain un till 1978. With the introduction of nicotine chewing gum in the 1980s, the chewing gum begins to be accepted for use (6). Another chewing gum dimenhydrinate was commercially available for the treatment of motion sickness.

For the prevention and treatment of various oral diseases, an alternate class of antimicrobials comprising of naturally occurring antimicrobial peptides have been developed in the form of MCG. The aim of formulating such MCG was to effectively delivery and maintain a sufficient anti-bacterial dose within the oral cavity. Chewing gums have potential for sustained delivery of active agent, since they reside in the oral cavity for a longer period of time as compared to lozenges, tooth paste etc. and hence are preferred for the treatment of diseases pertaining to oral cavity (7).

This increasing use of chewing gum led the committee for medicinal products for human use (CPMP) to define medicated chewing gum as "A solid dose preparation with a base consisting mainly of a gum that are intended to be chewed but not to be swallowed, providing a slow steady release of medicine contained" this is reflected in European pharmacopoeia and the guidelines for pharmaceutical dosage form. Chewing gum has travelled such a huge path from the Mayan Indians to the present day, mainly due to it is ease of administration, easy and a quick manufacturing process, quick onset of drug release along with ease of termination to drug release (4). Pros and cons of chewing gum are described in table 1. Major advantages of oral drug delivery:

- By passing the gastrointestinal tract and hepatic portal system so fewer side effects
- Provides rapid onset of action (direct absorption through oral mucosa) and the formulation can be removed if the therapy is to be terminated
- Higher patient compliance

Table 1: Pros and cons of chewing gum

Pros	Cons
• A rapid onset of action is obtained. • The rate of salivation increases which modifies pH and helps in the treatment of acidity of gastric mucosa. • The drug has high bioavailability. • The drug released is in soluble form, which is an advantage over tablet dosage form. • They are ready to use type of dosage form. • It has a high patient compliance as it's administration does not require water. • It provides a pleasant taste. • It rules out the problem of swallowing tablets and hence is hi ghly accepted by children and patients. • It has very less side effects. • It helps in prevention of dental caries. • It removes the condition of dry mouth (xerostomia) • It helps in relieving stress • The released drug has high bioavailability due to very less first pass metabolism. • Highly attractive from the marketing perspective due to the product's distinctiveness.	• Salivary dilution causes a decrease in concentration of drugs. • Involuntary swallowing from oral cavity of the saliva causes wastage of the drug. • Drug release differs from patient to patient as per the patients chewing habit. • The risk of over consumption is high as compared to chewable tablets, lozenges etc. • Diarrhea and flatulence are caused by sorbitol containing chewing gum. • Chewing gum is found to st ick to the enamel dentures and fillers. • Earache in children and jaw pain in adults is observed by prolonged use of chewing gum.

2. Composition of chewing gum (8, 9)

A piece of chewing gum consists of gum core composed of the gum base. The gum base consists of the elastomer, plasticizers, fillers, elastomer solvent, etc. The amount of powdered sugar used for the coating determines the brittleness of the chewing gum. Chewing gum consists of both water soluble and water in soluble portion. The water-insoluble phase consists of gum base (insoluble gum base resin), elastomers and emulsifiers. While, the water-soluble phase consists of fillers, antioxidants, softeners, sweeteners, food colorings, flavoring agents etc. In the case of medicated chewing gum an active pharmaceutical ingredients (API) is present in addition to the above-mentioned ingredients. Generally, the water content of chewing gum is very less and so there is no need of preservatives (10). The details of excipients with their proportional representation and purpose of addition are mentioned in table 2.

Table 2: Excipients used for formulating chewing gum (11).

Excipient	General range	Function	Example
Elastomers	15-45%	Controls the gummy texture and provides elasticity to the gum base.	**Natural:** Chicle gum, crown gum, nispero etc. **Synthetic:** Butadiene-styrene copolymer, polyisobutylene, isobutyleneisoprene copolymers
Elastomers solvent	45-70%	Provides softness to the elastomeric base.	**Natural**: Partially Hydrogenated rosin, pentaerythritol esters or glycerol ester of rosin, glycerol esters of demineralized rosin. **Synthetic:** Terpenes (D -limonene, α and β-pinene)

Plasticizers	---	Provides Proper consistency and desirable texture to the gum base.	Lanoline, glyceryl triacetate, glycerine, propylene glycol monostearate, vegetable oil and different waxes from natural and synthetic origin.
Bulking agent	Quantity sufficient	Used to enlarge the bulk consistency in case of low calorie gum and in highly potent chewing gum.	Guar gum hydrolysates, indigestible dextrin, polydextrose, insulin, oligofructose, and fructooligosaccharide.
Softening agent	0.5-15%	They enhance the mouth feel and chew ability of chewing gum	Glycerin, lecithin and fatty acids(oleic acid, palmitic acid, linoleic acid, stearic acid, succinic acid)
Sweetening agents	<50%	To obtain desired amount of sweetness.	Sugars(sucrose, dextrose, glucose) Sugar alcohols (xylitol, Mannitol, sorbitol), aspartame.
Flavoring agent	0.01-1%	Provides different aroma and enhances the texture acceptability.	Volatile essential oils from both natural and artificial source like clove oil, fennel oil etc.

Coloring agent	0.1%	Provides a soothing color to the chewing gum and when used in corelationship with flavoring agent it increases acceptability.	Titanium dioxide, extracts obtained from plant and animal origin and the coal tar dyes approved by FD & C.
Antioxidants	0.02%	Prevents microbial growth.	Propyl gallate, butylated hydroxyl toluene, and butylated hydroxyl anisole.
Filling agents or compression adjuvants	<50%	They are used as aid in compression process.	Magnesium stearate, magnesium aluminum silicate, calcium carbonate, tricalcium phosphate, bentonite and talc.

Various ingredients used for formulating a medicated chewing gum are described in detail below (12):

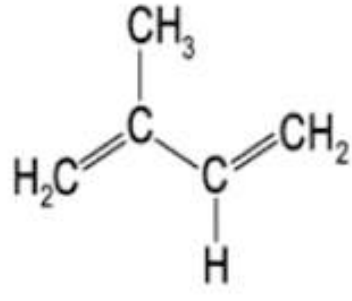
A) Gum base (1)

The gum base can be obtained from two types of sources - 1.) Natural and 2.) Synthetic

1) Natural

Gum base is obtained from trees are chicle like rubbery latexes or are the milky juices obtained by putting a cut on the plant part.

Natural gum chicle is commonly obtained from sapodilla tree *(Manilkara zapota L.)* belonging to the family sapotaceae. Chemically chicle is polyterpene which consists of thousands of C5H8 isoprene subunits (2-methyl-1,3-butadiene)



Isoprene unit

These gums as are obtained from natural origin are costly, has batch to batch variations etc. natural origin related disadvantages. Due to these reasons, it paved the way out for the use of synthetic materials as a gum base in chewing gum.

Example: Gum *(Pistachi mutica, Schiiuis molle),* Latex *(Asciepias eriocarpa, Euphorbia iorifera),* Resin *(E. agathisaustralls, Silpthum lacinatum),* Root bark *(Actinella siennis),* Ground bark *(B. lnuginosa),* Juice *(Tygodesmia juncea)* etc.

2) Synthetic:

Basic copolymers like butadiene-styrene, isobutylene-isoprene copolymer (butyl rubber), polyvinyl acetate, polyisobutylene, polyethylene etc. are used as synthetic gum base in chewing gum.

To reduce the adherence of the gum with teeth known as detackifier can be reduced by the usage of polyvinyl alcohol and polyvinyl acetate of different molecular mass it also aids in cutting down the chewing gum into pieces during chewing.

Gum base is the most important component of the chewing gum as it is present in highest amount (15-40%) so its amount determines the basic property of chewing gum such as texture, softness, hardness, elasticity, crumbliness, stickiness and mouth feel.

The gum base used are lipophilic in nature and as the most API are lipophilic in nature they adhere with the gum base by forming weak chemical bonding and so a slow release or incomplete release of API is observed.

To overcome this condition buffering or solubilizing agents can be added or coating/ encapsulation of API can be performed. While, the hydrophilic API gets released easily from the gum base and it needs to slow down its release by either encapsulating or by increasing the lipophilic content of the API.

B) Elastomers (2)

Elastomers provides elasticity to the gum base and also gives gummy texture to the chewing gum and are incorporated in to the chewing gum in the range of 15-45%.

Elastomeric solvents are added which aids in providing elasticity and softness to the chewing gum.

C) Plasticizers (13)

Plasticizers are added to the gum base to obtain proper consistency to the gum base and to give desirable texture to the chewing gum they are added to the chewing gum in varying concentration depending on the desired texture.

D) Bulking agent (3)

They are the agents used to increase the bulk of the chewing gum. The need to increase the bulk consistency of the chewing gum is needed in case of the MCG containing a very potent drug or for the drug which is to be given in very low

dose. It's also helpful for the diabetic patient by using a low-calorie gum.

E) Softening agents:

Softening agents increases the chew ability and enhances mouth feel by providing enormous softness during chewing.

F) Sweetening agents:

Sweetening agents are used to provide desired sweetness to the chewing gum

Sweetening agents can broadly be classified into two categories i.e. aqueous and bulk. While, the bulk sweeteners can be further classified into nutritive and non-nutritive bulk sweeteners.

The sweetening agents are selected for a formulation based on their safety, organoleptic qualities such as taste, odor and based on its stability in different pH conditions.

G) Flavoring agent:

Flavoring agent are used to provide the formulation a suitable flavor and also to increase the aroma of the chewing gum which enhances the acceptability of the product. They are generally added to musk out the taste of another undesired component used in the chewing gum. They are also used to overcome the bitter taste of the chewing gum. They are selected on the basis of another excipients and color used in the formulation.

Various flavors used for taste masking of different kind of drug are described in table 3.

Table 3: Approved flavoring agents of taste specific masking (10)

Taste of drugs	Flavors
Sweet	Honey, vanilla, bubble gum, Fruit and berry
Bitter	Wild cherry, raspberry, coffee, chocolate, mint, grapefruit, passion fruit, peach, orange, lemon, lime, anise
Acidic sour	Lemon, lime, orange, cherry, grapefruit, liquorice
Alkaline	Mint, chocolate, cream, vanilla
Metallic	Burgundy, berries, grape, marshmallow, Guyan
Salty	Butterscotch, maple, apricot, peach, melon, vanilla, wintergreen, mint

H) Coloring agent:

Coloring agent are used to provide soothing color to the chewing gum. They are generally used in accordance with the flavoring agents as both of them collectively increases the general acceptance of the chewing gum.

General source of coloring agent is various extract obtained from plant (chlorophyll-green, cur cumin-yellow) and animals (cochineal-red); various dyes obtained from the coal tar which are approved for its application in food and cosmetics by FD&C of various nations like brilliant blue, fast green, tartarazine, sunset yellow etc. Various synthetic opacifiers such as titanium dioxide and magnesium oxide are used to provide whiteness to the final product.

I) Anti-oxidants

Anti-oxidants are the agents used as a preservative which does not allow the oxidation of the chewing gum and thus has an anti-microbial property. It helps in increasing the general stability of the chewing gum and also helps in increasing the shelf life of the final product.

J) Filling agents:

They are also called as compression adjuvants. They aid in the compression process of chewing gum preparations as they deform very easily on compression, they also improve the flow property of the material and are used as a lubricant.

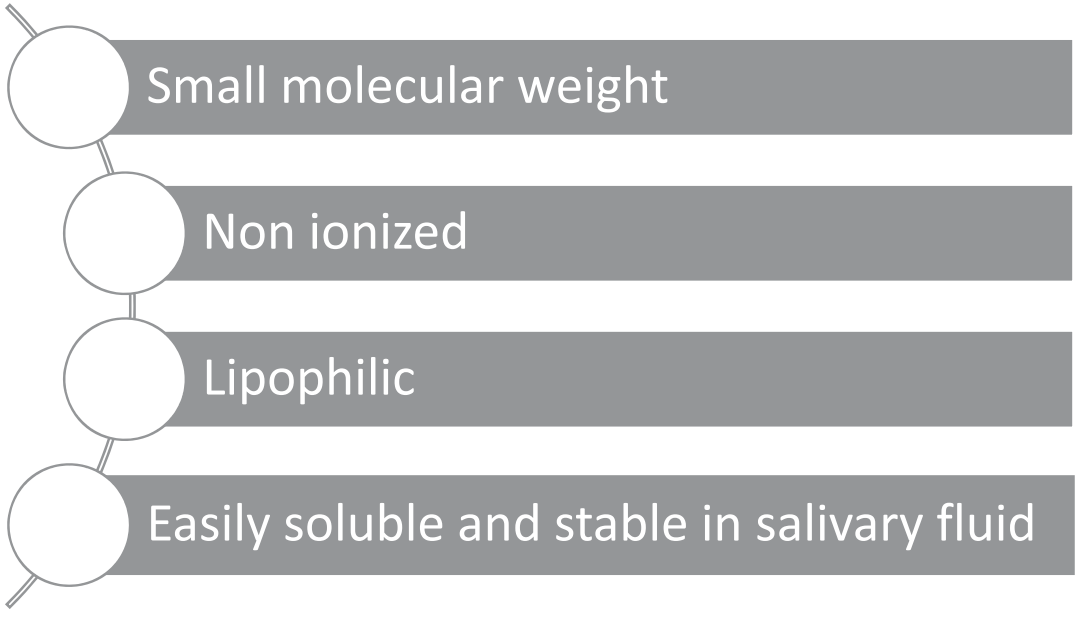


Figure 1. Desirable properties of drug (API)

3. METHOD OF PREPARATION OF MEDICATED CHEWING GUM (14)

1. Conventional method

This method is also called as fusion method. In this method, the gum base is softened or melted using a mixer. The active ingredient and other excipients are added to the melted gum base in a sequence. The resultant gum mixture is passed through a series of rollers that produce thin and wide ribbons. This are then allowed to cool and set properly. Finally, the gum is then cut into desired size and shape, followed by packing.

Thermolabile drugs cannot be incorporated as melting of gum base requires high temperature. Also, content uniformity cannot be achieved.

2. Freezing, Drying and Tableting Method

Freezing

The gum base is cooled such that it remains sufficiently brittle and would not adhere to the grinding apparatus during further processing. The temperature is usually set to 15° C or below.

Grinding

The previously refrigerated gum base is crushed to obtain fine fragments of the mixture. Additionally, anti caking agent like- silicon dioxide, are added to prevent adhesion during the process.

Tableting

The grinded gum base is mixed with active ingredient and other excipients such as, binder, lubricant, coating agent, sweetener, flavoring agent, etc., using a suitable blending machine. The blend is then mixed with anti-adherent talc or magnesium stearate. The final step involves compression with the aid of tablet compression machine.

3. Direct compression method:

The gum base is taken into a blender like v-shaped, cone shaped to this active agent is mixed directly for a specific period of time. Binder, sweetener, flavor and other excipients are added with continuous mixing.

The blend obtained is then mixed with talc or magnesium stearate in order to maintain the flow of the blend and prevent adhesion during compression. Lastly the blend is subjected to compression using tablet compression machine.

Factors affecting release of active ingredient

- Physicochemical properties of active ingredient: the saliva soluble ingredients will be able to give immediate release and quick onset of action. While poorly soluble ingredients will be slowly released.

- Formulation related factors: Amount and composition of the gum base effects the release of active ingredient.

- Contact time: The contact time of MCG has a direct impact on the local and systemic effect of the active ingredient incorporated.
- Inter patient variability: The chewing frequency, intensity and time affect the release of active ingredient from the MCG.

Table 4 : Factor affecting the release of API form MCG

Factors affecting the release of API from MCG	
1.)	Contact time
2.)	Chewing rate
3.)	Physical and chemical property of API
4.)	Physical and chemical property of API
5.)	Person to person variation
6.)	Formulation factors
7.)	Environmental factor
8.)	Rate and amount of saliva production
9.)	Manufacturing process
10.)	Pka value of the drug

4 CHARACTERIZATION OF MCG (11, 15)

1 Pre-compression parameters

1.1 Bulk density (16, 17)

The bulk density of the powder is the mass of the powder divided by the volume occupied by the powder. The bulk density is determined by allowing the dispersed powder to settle down under the influence of the gravity inside a specific container. Powders consisting of the high structural strength resist settling down and possesses low bulk density. While the one with low structural strength settles down easily and possesses high bulk density. Bulk density is defined by the following equation:

Bulk density = Mass/Volume

1.2 Tapped bulk density (18)

The tapped density of a specific powder can be obtained by tapping the container containing the dispersed powder sample.

The tapping is performed at a specific rate for a specific period of time from a definite height until the constant volume of the powder is obtained.

The powder possessing high cohesive force shows a high amount of reduction of volume on tapping. While the free-flowing powder does not show any significant amount of reduction on tapping.

Tapped density =
(Mass of tapped material) /
(Volume of tapped material

1.3 Carr's index (19)

Carr's index is also known as carr's compressibility index. It is used to study the compressibility of a powder.

$$C = 100 ((Vb-Vt)/Vb)$$

Where Vb is the volume of powder occupied when let to settle freely, Vt is the volume occupied by the same amount of powder after tapping.

Carr's index is frequently used to determine the flowability of the powder. The free-flowing powder has a very small difference between the Vb and Vt, giving the small amount of carr's index. While poor flowing powder has high carr's index.

1.4 Hausner's ratio (20)

Hausner's ratio is the ratio of the tapered bulk density to the aerated bulk density. It is helpful in the measurement of the cohesion property of the powder. A decrease in the hausner's ratio directly corresponds with the decrease in the cohesiveness of the powder and vice-versa.

$$H = \rho t/\rho b$$

Where, ρt is freely settled bulk density of material, ρb is tapped density of material

2.0 Sensory evaluation of MCG (14)

With the help of the panel of human volunteer's sensory evaluation can be performed. The volunteers can be guided to chew the chewing gum for specified period. A score card for the evaluation of can be made based on which the appropriateness felt by them on following parameters:

2.1 Chewability

2.2 Grittiness

2.3 Taste

2.4 Sweetener lasting time

3.0 Texture profile analysis

In order to determine the softness of the MCG, texture profiling can be done. This analysis gives a graph of load vs time, which gives estimate of the chewability.

4.0 In vitro drug release (9, 21, 22)

For the in vitro drug release study of MCG two different types of chewing apparatus has been proposed. (a) Unofficial single-module chewing apparatus and (b) official MCG chewing apparatus.

(a) Unofficial single-module chewing apparatus:

Weenergren designed the first dissolution studying apparatus which consisted of two horizontal pistons and a reservoir whose temperature can be controlled. A jaw with the flat lower surface is parallel to central part of the lower surface. A brim is angled upward at about 45° so that lower surface functions as a bowl preventing the gum to from sliding during mastication. On compression of piston the MCG gets compressed and makes a twisting association.

(b) Official MCG chewing apparatus:

The apparatus for MCG was adopted by the European pharmacopoeia in the year 2000. It consists of two horizontal the pistons known as teeth, a chewing chamber and a vertical piston known as the tongue. The tongue works alternatively with the teeth its function is to ensure that gum is positioned in correct place during the mastication process. The horizontal piston is rotated in opposite direction on its own axis which gives the maximum mastication.

The temperature of the chewing chamber is maintained at 37±0.5° Celsius. The chew rate, the volume of the medium, jaws distance, twisting angles etc. can be varied according to the requirements. The European pharmacopoeia recommends the usage of 40ml of chewing chamber consisting of 20ml of the buffers (pH around 6) and with a chew rate of around 60 strokes per minute.

5.0 Applications of MCG (15)

5.1 Smoking cessation

Due to masticatory effect of MCG containing nicotine in very mild quantities, it gives aids by giving a feeling of smoking sensation. This prevents the patient for actually undergoing the act of smoking. Thus, chewing the MCG can reduce smoking.

5.2 Bad smell

The ingredients used in MCG have a strong flavor and mouth feel. This helps to remove the bad smell occurring after eating some strongly flavored eatables like onion, garlic etc.

5.3 Dental caries

Pediatric and geriatrics age group people suffer from dental caries. It is difficult for doctors to treat them. Hence MCG serve the purpose. These age group people are given MCG containing drugs which cure dental

caries. The more they chew the chewing gum the more is the drug released in mouth cavity and thus provides relief from dental caries

5.4 Pain

MCG provides relief from the tooth and gum related pain.

5.5 Fungal infections

Fungal infections in mouth cavity are difficult to cure. Since the mouth cavity is full of moisture all through day and night. MCG aids in curing fungal infection by continuously releasing the loaded medicament within the mouth cavity. Thereby providing relief from fungal infections.

5.6 Treat xerostomia caused by drugs like opioids, antidepressants and sedatives.

5.7 Other indications like anxiety, motion sickness, allergy, cold and cough, acidity, diabetes etc.

6.0 Future trends

Since old age, chewing gums have been able to attract people of different age groups as a mouth freshener. The use of chewing gum as a drug delivery system is a new trend and as it has got several benefits over conventional drug delivery system like- it has got both local and systemic effect, it bypasses first pass metabolism effect, fewer chances of toxicity, high patient compliance etc. since new and new NDDS are being formulated to reduce the surgical remedy of the disease, MCG can be seen as a reliable drug delivery system. While, economically chewing gum has become a multi- million-dollar industry and about one and a half million tons of chewing gum is sold in a year. The U.S. food and drug administration has accepted chewing gum as non-carcinogenic as the sugar substitutes are not used up by the oral bacteria. Hence, the MCG has a bright future ahead.

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