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A Comprehensive Review on the Advancements and Applications of Medicated Chewing Gum in Healthcare

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ABSTRACT

Oral drug delivery system is most common route of administration which is highly accepted by the patients. The reasons behind such popularity are due to its ease of administration. Chewing gums are mobile drug delivery systems unlike chewable tablets medicated chewing gums are not supposed to be swallowed and may be removed from the site of application without resorting to invasive means. Chewing gum has been used for centuries to clean the mouth or refresh the breath. Medicated chewing gum has more potential uses in pharmaceuticals, Over the counter medicines and nutraceuticals. Medicated chewing gum are not only used by some special population groups who are having swallowing difficulties such as geriatric and pediatric but also popular among the young generation. Today medicated chewing gum meets the same high-quality standard as tablets. This review article covers composition, method of preparation and its limitation, factors affecting drug release, characterization of gum base, evaluation, application, and Medicated chewing gum marketed products.

INTRODUCTION

As oral drug delivery is simple, most convenient, safest, non-invasive, and most economical, it continues to be the preferential route of administration. The most facing challenges in oral delivery are to overcome problems like pill swallowing difficulty, delivery of unpalatable drugs and reducing dosing frequency. Pill swallowing difficulty primarily affects the patients having dysphagia, geriatric and paediatric populations. The most facing challenges in oral delivery are to overcome problems like pill-swallowing difficulty, delivery of unpalatable drugs and reducing dosing frequency. Pill swallowing difficulty primarily affects the patients having dysphagia, geriatric and paediatric populations.[1]

The intraoral route is the most preferred due to its convenience and rapid onset of action. Intraoral dosage forms have evolved as an alternative to conventional tablets, capsules and liquid preparations. Most of the intraoral dosage forms are intended to disintegrate, dissolve or release the drug in the oral cavity, where it has opportunity to be locally absorbed, in part or whole and alternatively may be swallowed and subsequently absorbed along the gastro-intestinal tract (GIT).[2]

Medicated Chewing Gum (MCG) is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and is intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. MCG is considered as vehicle or a drug delivery system to administer. Medicated chewing gum is a solid or semisolid dosage form which consists of one or more active ingredient (water soluble or insoluble) incorporated in water insoluble base.[3]

Medicated chewing gum is defined by the European Pharmacopoeia and guidelines for pharmaceutical dosage form issued in 1991 by the committee for medicinal product for human use as “A single-dose, solid preparation with tasteless masticatory gum base, mainly consisting of gum which is intended to be chewed and not swallowed, providing a slow steady release of the medicine contained”.[4]

Most of the chewing gum were used for smoking cessation (containing the nicotine) and used for oral and dental hygiene, motion sickness and freshening of the breath. In addition, many chewing gum of chewing gum intended for caries prevention, xerostomia alleviation, tooth whitening and vitamin/mineral supplementation.[5]

Mechanism of drug transport.

During the chewing process, the drug contained in the gum product is released from the mass into saliva and it could be absorbed through the oral mucosa or swallowed reaching the stomach for gastro-intestinal absorption. Thus, two absorption pathways are possible to introduce the active ingredients into the systemic circulation, giving rise to a systemic effect. Drug absorbed directly via the buccal membrane avoids metabolism in the gastro-intestinal tract and the first past effect of the liver, it might therefore be possible to administer a reduced dose in chewing gum compared to other oral delivery systems.[6]

Advantages [7]

1. Increased rate of effectiveness rather than other oral delivery systems.

2. Removal of gum at any time; therefore, termination of drug delivery.

3. Reduced risk of overdosing.

4. Requiring no water to drink.

5. Protection of the susceptible drugs contained from chemical or enzymatic attack in gastrointestinal (GI) tract.

6. Both systemic and local drug delivery.

7. High acceptance by children and teenagers.

8. Low first-pass effect so reduced dose is formulated in chewing gum compared to other oral delivery systems.

9. Fewer side effects.

10. Reduced risk of intolerance to the gastric mucosa.

11. Annihilation of xerostomia.

12. Reduced pains and difficulties in swallowing following tonsillectomy.

13. Fast bowel recovery after GI surgery.

14. Reduced hypoglycaemic shocks in people taking antidiabetic drugs.

Disadvantages [7]

1. Allergic reaction to artificial sweeteners.

2. Continuous stress on jaws that may cause temporomandibular joint disorder.

3. Teeth decay through being coated by sugar.

4. Stomach irritations, aches, gastric ulcers through continuous swallowing of saliva and even flatulence because of presence of sorbitol in some formulations.

5. Getting choked by swallowing gum in under-aged children.

TYPES OF CHEWING GUM [8]

1. Cut and wrap:

To endure the stretching that occurs in the chewing gum, the gum bases for this type of line must be rather flexible. To survive the stretching that occurs in the cooling tunnel, the gum bases for this kind of line must be moderately flexible. Due to the larger piece size, the chewing gum formulation should be softer than traditional chewing gum. This is accomplished by adding more liquids to the mixture (glucose and sweeteners).

Fig No. 01 Cut and wrap

2. Sticks and tabs:

For laminated items, the gum bases need to be both flexible enough to be molded by rollers and stiff enough to wrap well after curing. Typically, laminated gum has a lower gum base percentage than cut and wrap gum. In addition, the glucose content needs to be controlled to maintain the necessary elasticity to stop the pieces from breaking when bent while still providing the necessary hardness for the packaging process.

Fig No. 02 Sticks and tabs

3. Pellets/pillows:

Gum for chewing comes in stick-like pellet form. Gum bases for laminated items should be flexible enough to be moulded by rollers and harden sufficiently to withstand cooling after curing.

Fig No. 03 Pellets/pillows

4. Hollow balls:

For gum bases to maintain their shape and avoid leaking, they need to have a certain level of plasticity and elasticity (less than goods that are cut and wrapped) (if filled). The centre needs to be sturdy enough to withstand coating once it has dried.

Fig No. 04 Hollow balls

5. Liquid-filled gums:

The following qualities should be present in gum bases for stamped chewing gum:

a) Enough elasticity to withstand stretching during equalizing stages.

b) Enough plasticity to easily take the shape that the shaping machine's dies produce. The chewing gum's gum base percentage range should enable the best formulation and seal. If the gum base content is either low or too high, the product will distort.

Fig No. 05 Liquid-filled gums

6. Gum-filled candy:

Lower-viscosity gum bases could be trickier to work with because they might become liquid at the high temperature of the confection.

Fig No. 06 Gum-filled candy

7. Compressed chewing gum:

They are made of a compressible powder for the pharmaceutical and functional markets.

Fig No. 07 Compressed chewing gum

Table no: 01 Composition of MCG.[9]

Sl no	Ingredients	Concentration	Functions	Examples
1	Active pharmaceutical ingredients	0.5-30%	Provide therapeutic effect	Vitamins, nicotine, Analgesics, antacids, Antitussive, antihistamine.
Gum base (water soluble)				
2	Elastomers	40-70%	Provide elasticity and gummy texture.	Nature rubber-like latex or natural gum such as jelutong, lechi capsi, puerile, chicle.
3	plasticizers	3-20%	Regulate cohesiveness of product	Natural plasticizers- natural resins esters like glycerol esters or partially hydrogenated resin, polymerised glycerol esters etc Synthetic plasticizers – terpene resins.
4	Fillers or texturizers	2-60%	Provide texture, improve chewability and provide reasonable size	Magnesium and calcium carbonate, limestone, clay, alumina, talc, titanium oxide.
Water soluble ingredients				
5	Softners and emulsifers	0.5-15%	Optimize chewability and provide softness to the mixture.	Glycerine, lecithin, tallow, hydrogenated tallow, mono/di/tri glycerides, steraic acid, palmitic acid, linoleic acid etc.
6	Colorants and whiteners	Less than 1%	Provide colour	FD &C types dyes and lakes
7	sweeteners	50-65%	Provide sweetness to the product	Sorbital, mannitol, glycyrrhizin, sucrose, maltose, xylose, glucose, galactose, fructose, corn syrup, sucralose, aspartame, saccharin etc
8	Bulking agent	Qs	Use when low calorie gum is required	Polydextrose, oligofructose, inulin, fructooligosaccharides, guargum hydrolysate, indigestible dextrin.
9	Flavouring agents	1-5%	Enhance flavour and consumer acceptability	Citrus oil, peppermint oil, spearmint oil, mint oil& clove oil
10	Anti caking agents	0.2-1%	Prevent formulation of agglomerate of ground chewing gum particles	Silicon dioxide, magnesium oxide
11	Grinding agents	0.2-1%	Prevent sticking	Alkaline metal phosphate, alkaline earth metal phosphate.
12	antioxidant	0.02%	Prevent oxidation	BHT, tocopherol, propyl gallate etc

Table no: 02 Factors affecting the release of active ingredients.[10]

Parameters	Effects on drug release behavior
Physicochemical Property of API	• Saliva soluble ingredients will be immediately released within few minutes. • Lipid soluble drugs are released slowly.
Contact time	• The local or systemic consequences is dependent on contact time of Medicated chewing gum in oral cavity.
Interindividual variability	• The chewing gum incidence and chewing concentration which affects the drug release from MCG may vary from person to person.
Formulation factors	• The rate of release of API is mainly dependent upon the composition and the amount of the gum base. • The release rate is decreased if lipophilic fraction of gum is increased.

Manufacturing processes

Different methods employed for the manufacturing of MCG can be broadly classified into three main classes namely.

1. Conventional/Traditional method (fusion method) [11]

Gum components ⟶ melted and placed in a kettle mixer

(Contain sweetener, syrup, active ingredients, and other excipients)

⇩

Gum sent through 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 [12]

1. Elevated temperature used in melting restricts the use of this method for thermolabile drugs.

2. Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult.

3. Lack of precise form, shape or weight of dosage form.

4. Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for the production of pharmaceutical products.

5. 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.

2. Freezing, Grinding and Tabletting Method (Thermoliable) [13]

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

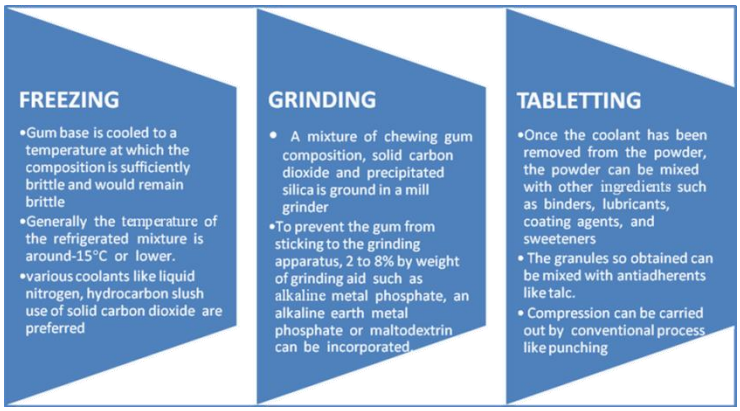

Figure No 08: Steps of manufacturing by freezing, grinding and tableting

Limitation:

- High-tech, expensive equipment's are required.
- Careful monitoring of humidity during manufacturing process becomes a challenge.

3. Direct compression method

New technology to make a chewing gum tablet is direct compression and tableting. This cost-effective method involves compression of gum bases mixed with active ingredients. In this method a granulating agent, most preferable 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.

Other significant benefits of this method are as follows- fast release, fast absorption, and high content uniformity. Medicated chewing gums by direct compression method are 10 times harder and crumble when pressure is applied resulting in faster release than medicated chewing gum formed by fusion method.[14]

The manufacturing process can be accelerated if a directly compressible chewing gum excipient is available. The limitations of melting and freezing can be overcome using these. Pharmagum is one such compactable gum system. Pharmagum is a mixture of polyol(s) and or sugars with a chewing gum base. It is available as directly compressible powder, free flowing powder which can be compacted into a gum tablet using conventional tablet press thus enabling rapid and low-cost development of a gum delivery system. It is manufactured under CGMP conditions and complies with Food Chemicals Codex specifications as well as with FDA, so they can be considered as "Generally regarded as safe"(GRAS). Pharmagum is available in three forms namely S, M and C. Pharmagum M has 50% greater gum base compared to Pharmagum S. Pharmagum S consists primarily of gumbase and sorbitol. Pharmagum M contains gumbase, mannitol & Isomalt.[15]

Characterization of gum base [16]

Determination of color

The color of gum was observed visually.

Determination of base softening point of gum

The sufficient quantity of gum base was taken in porcelain dish and heat at the lowest temperature on heating mantle. Softening point was determined by thermometer. At which temperature gum was started to soft be measured.

Determination of acid value of gum base

Accurately weigh, 10 mg of gum base dissolved in 50 ml of mixture of equal volumes of ethanol (95%) and ether previously neutralize with 0.1 M potassium hydroxide to phenolphthalein solution. Warm the flask containing sample to dissolve the gum base. Add 1 ml of phenolphthalein solution and titrate with 0.1 M KOH until the solution remains faintly pink after shaking for 30 minutes. Calculate the acid value from following formula:

$$\text{Acid value} = 5.61\ n / w$$

Were,

n = the no. of ml 0.1M KOH w = the weight in gram of the substance.

Determination of solubility of gum base

For determination of solubility of gum base 1 gram of gum base dissolved in 10 ml of different solvents like diethyl ether, ethanol, chloroform, acetone, pH 6.4 buffer solution and water. Each solvent containing gum base kept in rotary shaker for 24 hours. After 24 hours solvent was filtered and determine the solubility.

Evaluation of MCG

a) Organoleptic properties:

Such as colour, odour, surface texture and appearance were checked out.

b) Stickiness:

The formulated medicated chewing gum base was placed on plain surface A mass of 250 gm was hammered on it up to 10 min. The frequency of hammering was about 30 min. None of the batch stuck to hammer or surface.

c) Plasticity/hardness:

Hardness of chewing gum was determined by Monsanto hardness tester and the average hardness and standard deviation were calculated. [17]

d) Weight variation test:

To find out weight variation, 20 MCG of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

e) Friability:

Tablets tend to cap during handling and transportation which affects the quality, appearance, drug content, coating requirements and hence friability test is carried out. The apparatus used is Roche friabilator, which consists of a rotating disk 12 inch in of diameter rotating at speed 100 rpm. 10 gum units to be evaluated are added into disc and rotated for 100 revolutions at 25 rpm. The difference in weight represents the friability percentage (F%) that can be calculated based on Formula:

$$\mathbf{F\% = (W_{intial} - W_{final}/W_{intial}) \times 100}$$

Note: MCGs pass the friability test if the F% is less than 1%.[18,19]

f) Drug Content:

Chewing gum was manually divided into pieces and transferred into a separating funnel containing 10 ml of Phosphate Buffer. The separating funnel was shaken for 10 - 15 min to disperse the chewing mass. The turbid solution was shaken simultaneously with 50 ml Phosphate Buffer for 15 min for dissolving the drug into it. The separating funnel was kept undisturbed for 15 min for the separation of the two phases. The aqueous phase was collected and filtered through Whatman filter papers. The filtrate was sufficiently diluted and estimated for the drug content by UV spectrophotometer .[20]

g) *In-vitro* drug release: [9]

Principle

The test is used to determine the dissolution rate of active substances in medicated chewing gums. This is done by applying a mechanical kneading procedure to a piece of gum placed in a small chamber designed to simulate the process of chewing.

Apparatus-I

The chewing apparatus consists of:

- 1 chewing chamber,
- 1 vertical piston,
- 2 horizontal pistons with O-rings and sealing rings.

The chewing chamber consists of 4 individual parts:

- 1 central chamber,
- 1 funnel,
- 2 guides with bushes.

Funnel and guides are mounted on the central chamber. The O-rings are incorporated in the piston recess with the sealing ring round it; the sealing rings ensure that the chamber is watertight. The horizontal pistons are placed in the chewing chamber through the guides.

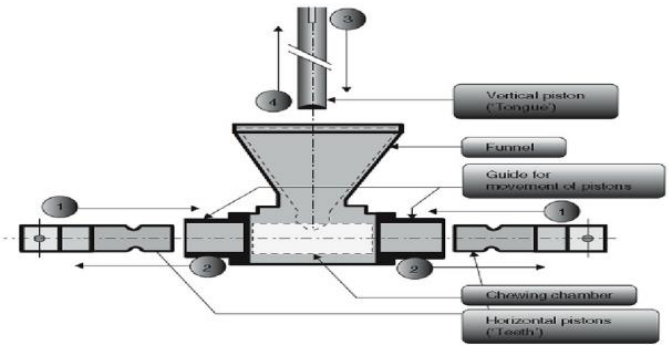

Fig No. 09 Apparatus I

The gum is artificially chewed by the horizontal pistons, and the vertical piston ensures that the gum stays in the right place between chews. Machine speed is controlled to ensure a constant cycle. One cycle (chew) is defined as follows: the horizontal pistons start from their outermost position, move to their innermost position and back to their outermost position.

Within one cycle, the vertical piston moves from its lowest position to its uppermost position and back to its lowest position. Each horizontal piston has a stroke of 25.0 mm. The maximum distance between these 2 pistons is 50 mm. The minimum distance between the 2 horizontal pistons is 0.1 mm to 1.0 mm. The vertical piston has a stroke of 22.0 mm. Horizontal piston movement is controlled, so that the 2 pistons are at their innermost position at the same time. Vertical piston movement is controlled, so it does not conflict with the movement of the horizontal pistons. If necessary, the machine can be constructed so that the horizontal pistons rotate around their own axes in opposite direction to each other by the end of the chew to obtain maximum chewing. All parts of the apparatus that may meet the preparation or the dissolution medium are chemically inert an do not adsorb, react or interfere with the sample.

Apparatus II. Alternative Chewing Gum Apparatus, Noncompendial - Wennergren

One of the no compendial apparatus commercially available was designed by Wennergren. The chewing procedure consists of reciprocations of the lower surface in combination with a shearing (twisting) movement of the upper surface that provides mastication of the chewing gum and at the same time adequate agitation of the test 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°) so that the lower surface functions as a small bowl with a flat bottom. This bowl prevents the chewing gum from sliding during mastication.

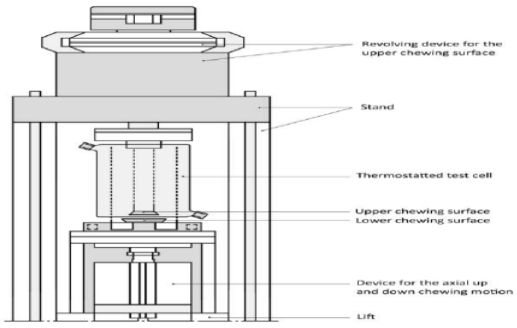

Fig No. 10 Apparatus II

c) Stability studies[21]

An accelerated stability study for developed MCG was carried out as per ICH guidelines with necessary modifications. The MCG was exposed at different temperature conditions of 40±2^{o}

C, 30±2° C and 45±2° C for a period of 45 days. The MCG was tested for consistency, colour, odour, and drug content.

APPLICATIONS OF MEDIATED CHEWING GUM[22]

Some of the major applications of mediated chewing gum are described below:

(A) Local Therapy

The main target of chewing gum formulation is to prevent and treat of oral diseases. From this formulation, the active drug substances release in controlled manner and shows local effects against dental caries. Low plaque pH plays a significant role in the origin of dental caries. Therefore, sugar-free chewing gum is suggested and recommended after meals in caries prevention programmes.

(i) Dental Caries

• To prevent and cure oral disease is the main target place.

• To control the release rate of active substances and to provide a prolonged local effect.

• Lowers intensity and frequency of dental caries by reelevate plaque pH.

• Fluoride chewing gum can be used to prevent dental caries in children.

• Chlorhexidine chewing gum can be used to treat various infections (gingivitis, periodontitis, oral and pharyngeal infections) and cause less staining of the teeth.

• To mask the bitter taste of various drugs such as Chlorhexidine. Kolahi and Abrishami (2013) formulated mutanase-containing chewing gum for prevention of dental caries and plaque formation in rats.

(B) Systemic Therapy

MCG formulations provide better absorption through the buccal mucosa after systemic drug delivery. Systemic therapy of MCGs offers the treatment of adults, children, and adolescents due to its various advantages such as quick and critical treatment, easy, no need for water, easy administration, reduced risk of git side effects, and no attention drawn to the condition requiring medication MCGs could be advantageous to a number of indications such as:

(i) Pain

• Chewing gum formulation containing NSAIDS has been clinically treated of minor pains, headache, and muscular aches.

• The oldest medical chewing gum available is Aspergum®, a chewing gum containing ASA (aspirin or acetylsalicylic acid).

(ii) Smoking Cessation

• Nicotine, silver acetate and lobeline-containing formulations have been clinically tested as assistances to smoking termination. Aslani and Rafiei (2012) formulated nicotine containing chewing gum by direct compression technique to assist smokers quit smoking. The result showed that the final formulation had optimal chewing hardness, adhering to teeth, and plumpness characteristics, as well as the most pleasant taste and highest acceptability to smokers.

• Nicotine chewing gum can be regarded as a convenient formulation for breaking an "oral habit" like smoking.

(iii) Obesity

• Active substances like chromium, Guarana and caffeine containing formulations are proved to be efficient in treating obesity.

• Caffeine and Guarana have demonstrated to increase the metabolic rate and stimulate lipolysis and reduce the feeling of hunger. Aslani and Jalilian (2012) prepared caffeine containing chewing gum to increase the alertness and decrease the fatigue.

• Chromium reduces the obesity due to an improved blood glucose balance.

(iv) Other indications

• Beneficial in various other diseases such as xerostomia, allergy, motion sickness, acidity, cold, cough, diabetes, anxiety etc.

• Chewing gum is known to be a potent stimulant of salivary secretion.

• Pilocarpine incorporated formulations increased in salivary secretion.

• Stimulated saliva has a buffering capacity and may therefore help reduce acidity of gastric fluid.

• Antacids containing formulations reduces the postprandial reflux.

• Caffeine containing chewing gum produces positive stimulating effect on memory.

• Active substances such as Dimenhydrinate, scopolamine and dolostone containing formulations are used for the prevention and treatment of diarrhoea and nausea.

Table no: 03 Marketed MCG for pharmaceuticals and nutraceuticals[23]

Marketed MCG	Active ingredients	Indication
Aspergum	Aspirin	Pain relief
Orbit white	Calcium as tricalcium phosphate	Dental hygiene and for tooth whitening
Happydent white		
Trident white		
Recaldent		
Fluogum	Fluoride as a sodium fluoride	Prevention of dental caries
Fluorette		
Travel gum	Dimenhydrinate	Motion sickness
Niquitin cq	Nicotine	Smoking cessation
Nicorette		
Hexit	Chlorhexidine	antibacterial
Vitaflo ch		
Advanced		
Stay alert	Caffeine	CNS stimulant
Endekay	Vitamin C(ascorbic acid)	Vitamin supplement
Zoft vinility gum	Extracts of hawthorn berry,horny goat weed,damiana leaf,muira puarna root,gingo biloba leaf, ginseng root	Increase male sexual desire and performance.
Chew away gum	Extracts of hoodia gordonni –nature's calcium channel blockers	Appetite suppressant for weight loss
Zoft menopause gum	Extracts of damiana leaf,Mexican wild yam root,black cohosh root	Symptomatic relief from post-menopausal syndrome
Zoft stress gum	Extract of ashwagandha, Passion flower and jujube fruit.	Reduces the symptoms associated with stress, anxiety, and depression.

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. Chewing gum can be used as a carrier for vast categories of drugs where extended release and the local action are desired. Medicated chewing gum 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. MCG is assumed to evident its situation as it encounters the high-quality standards of pharm industry and can be formulated to obtain different release profiles of active ingredients.

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