Expert Opinion

Medicated chewing gum – a potential drug delivery system

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Importance of the field: Over the years, patient convenience and patient compliance-orientated research in the field of drug delivery has resulted in bringing out potential innovative drug delivery options. Out of which, medicated chewing gum (MCG) offers a highly convenient patient-compliant way of dosing medications, not only for special population groups with swallowing difficulties such as children and the elderly, but also for the general population, including the young generation.
Areas covered in this review: In this review, various formulation ingredients, different manufacturing processes, and assessment of *in vivo* and *in vitro* drug release from MCG are thoroughly discussed along with the therapeutic potential and limitations of MCG.
What the reader will gain: Readers will gain knowledge about the rationale and prominent formulation and performance evaluation strategies behind chewing gum as a drug delivery system.
Take home message: The availability of directly compressible co-processed gum material enables rapid, safe and low-cost development of MCG as a drug delivery option. By MCG formulation, revitalization of old products and reformulation of new patented products is possible, to differentiate them from upcoming generics competition in the market.

Keywords: buccal drug delivery, medicated chewing gum, oral mucosal drug delivery, patient compliance

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1. Introduction

People of every society have chewed varieties of gum and gum-like substances (resins and waxes) for thousands of years. Medicated chewing gum (MCG) is not different from it, but it is the gum base incorporating drug(s) [1]. Medicated chewing gums are defined by the European Pharmacopoeia and the guidelines for pharmaceutical dosage forms issued in 1991 by the Committee for Medicinal Products for Human Use (CPMP) as 'solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not to be swallowed, providing a slow steady release of the medicine contained' [2]. It can be used either for local (mucosal) treatment of mouth disease or for systemic (transmucosal) delivery by direct intraoral absorption through the buccal mucosa.

In 1848, the first commercial chewing gum, 'state of Maine pure spruce gum', was introduced into the US market [3] and the first patent was filed as dentifrice in 1869. The first MCG product 'Aspergum' containing acetylsalicylic acid for headache was launched in 1928 [4]. The success story of nicotine chewing gum in the 1980s has led to more general acceptance of chewing gum as a drug delivery system [5]. Nowadays, MCG is gaining more attention as a very good vehicle to administer active principals in pharmaceuticals and nutraceuticals [6]. Some of the popular marketed MCG products are listed in **Table 1**.

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Article highlights.

- Medicated chewing gum is a gum base intended to be chewed but not to be swallowed, providing a slow steady release of the medicine contained, which can be either used for local (mucosal) treatment of mouth disease or systemic (transmucosal) delivery by direct intraoral absorption through the buccal mucosa.
- Formulation ingredients like elastomers, softeners, bulking agents plays an important role in final product feel & its consistancy; while sweeteners & flavors plays a very essential character in its sensory properties.
- Now days, MCG can be directly compressed on a pharmaceutical in-house tablet compression machine by utililizing directly compressible gum material; which is mixture of synthetic gum base, sugar alcohols & anticaking agents; which enables rapid, safe and low cost development of MCG as a drug delivery system.
- Ion exchange resin complexation, cyclodextrin complexation & microencapsulation techniques are used in MCG for sustaining release of active ingredient or its taste masking.
- "Chew out" study is carried out to asses' *in vivo* drug release from MCG, in which residual amount is extracted from chewed sample; while official modified dissolution apparatus is used for evaluating *in vitro* drug from MCG at sixty chewing strokes per minute.
- Interindividual variation in chewing frequency & chewing intensity is the main factor which affects release of active ingredient from MCG; while salivary dilution and involuntary swallowing are main reasons for variability in absorption site. i.e., either from buccal mucosa or from gatrointestinal tract.

This box summarizes key points contained in the article.

Superior technology and comprehensive knowledge of chewing gum, together with the addition of medicated chewing gum in the European pharmacopoeia in 1998, have contributed to the high acceptance of this recent system of drug delivery [7-10]. These days, MCG meets the same superior quality of standards as tablets as per current good manufacturing practices (cGMP) guidelines [11], and it can be easily formulated to obtain different release rates of active pharmaceuticals [12-14], which enables distinct patient group targeting. Particularly in children, MCG may be a more favored method of drug administration compared with oral liquids or tablets.

2. Advantages and drawbacks of MCG

2.1 Advantages of MCG

Medicated chewing gum offers numerous advantages over other drug delivery systems, among which some important advantages are highlighted in **Figure 1**. At present, there is an increasing trend towards involvement of the patient in drug administration and its handling. MCG is in line with this trend, as it allows trouble-free self-medication, and it does not prevent patients from living an active life during treatment.

2.1.1 *Patient compliance*

MCG makes peroral administration of drugs possible anywhere anytime without simultaneous intake of water, which promotes very high patient compliance. Furthermore, the treatment can be terminated at any time by expelling the chewing gum; and as it is not meant to be swallowed, it increases patient compliance, especially for children or patients with swallowing difficulties such as dysphagia [15]. Moreover, MCG does not draw any attention to the medication, though it is medicated and therefore it does not stigmatize the patient [16].

2.1.2 *High acceptance in children*

Most children have trouble swallowing tablets. To conquer this problem liquid formulations have been developed, but giving liquid formulations to children also may not be easy. MCG is a promising substitute that makes it possible by masking the bitter/bad taste of the active substance, making it an enjoyable experience for children [17]. In contrast to a liquid formulation, MCG has a longer shelf-life because of the absence of the danger of microbial contamination.

2.1.3 *As an oral mucosal drug delivery*

MCG offers the advantages of both mucosal (local) as well as transmucosal (systemic) absorption, as an oral mucosal drug delivery system. MCG offers the higher possibility of releasing drug intended to treat or prevent local diseases of the mouth, in a controlled manner over an extended period for prolonged therapeutic effect. As a systemic delivery option by means of the oral mucosa, it has the potential to overcome the problems of short-lived action, variations in drug release and brief retention times, which are the main disadvantages associated with conventional systemic oral mucosal drug delivery systems [18].

2.1.3.1 *Local action*

For the treatment of oral diseases, high therapeutic levels of active ingredient in the saliva are desirable. To convene this purpose different formulations such as oral gel and mouth rinse have been developed. MCG is a definitive drug delivery system for this treatment area that delivers a high level of active ingredient locally in the oral cavity [19]. Fluoride chewing gum has proved to be effective in preventing dental caries in fluoride-deficient children [20], a high incidence of caries in adults, and in patients suffering from xerostomia (the subjective complaint of dry mouth resulting from lack of saliva) [21]. Lin and Lu have measured the stimulated salivary flow rates generated by fluoride chewing gum. The mean stimulated flow rate for fluoride gum, 2.1 ± 0.7 ml/min, was found to be significantly higher ($p = 0.002$) than that of the control, 1.7 ± 0.6 ml/min [22]. The role of sugar-free chewing gum in re-elevating plaque pH after meals is already proven and hence it is very valuable to dental health. Chewing Orbit® sugar-free gum for 20 min after eating and drinking stimulates the saliva. This stimulated saliva contains bicarbonates that help neutralize the plaque acid much more quickly than if it was unstimulated. Moreover, stimulated saliva contains

Table 1. Marketed MCG for pharmaceuticals and nutraceuticals.

Marketed MCG	Active ingredient	Indication
Aspergum® [4]	Aspirin (acetyl salicylic acid)	Pain relief
Orbit white® [79] Happydent white® [80] Trident white® [81] Recaldent® [82]	Calcium as a tricalcium phosphate	Dental hygiene and for tooth whitening
Fluogum® [20] Fluorette® [83]	Fluoride as a sodium fluoride	Prevention of dental caries
Travvel gum® [84]	Dimenhydrinate	Motion sickness
Niquitin cq® [85] Nicorette® [86]	Nicotine	Smoking cessation
Hexit® [87] Vitaflo chx® [87] Advanced® [87]	Chlorhexidine	Antibacterial
Stay alert® [88]	Caffeine	CNS stimulant
Endekay® [87]	Vitamin C (ascorbic acid)	Vitamin supplement
Zoft virility gum® [89]	Extracts of Hawthorn Berry, Horny Goat Weed, Damiana Leaf, Muira Puama Root, Ginkgo Biloba Leaf, Ginseng Root, Catuaba Bark Extract, Saw Palmetto Berry	Increases male sexual desire and performance
Chew away gum® [90] Slim n trim® [91]	Extracts of *Hoodia gordonni* – nature's calcium channel blocker	Appetite suppressant for weight loss
Zoft menopause gum® [89]	Extracts of Dong Quai Root, Black Cohosh Root, Damiana Leaf, Mexican Wild Yam Root	Symptomatic relief from post-menopausal syndrome
Zoft stress gum® [89]	Extracts of Ashwagandha, Passion Flower and Jujube Fruit and Calcium carbonate	Reduces the symptoms associated with stress, anxiety and depression

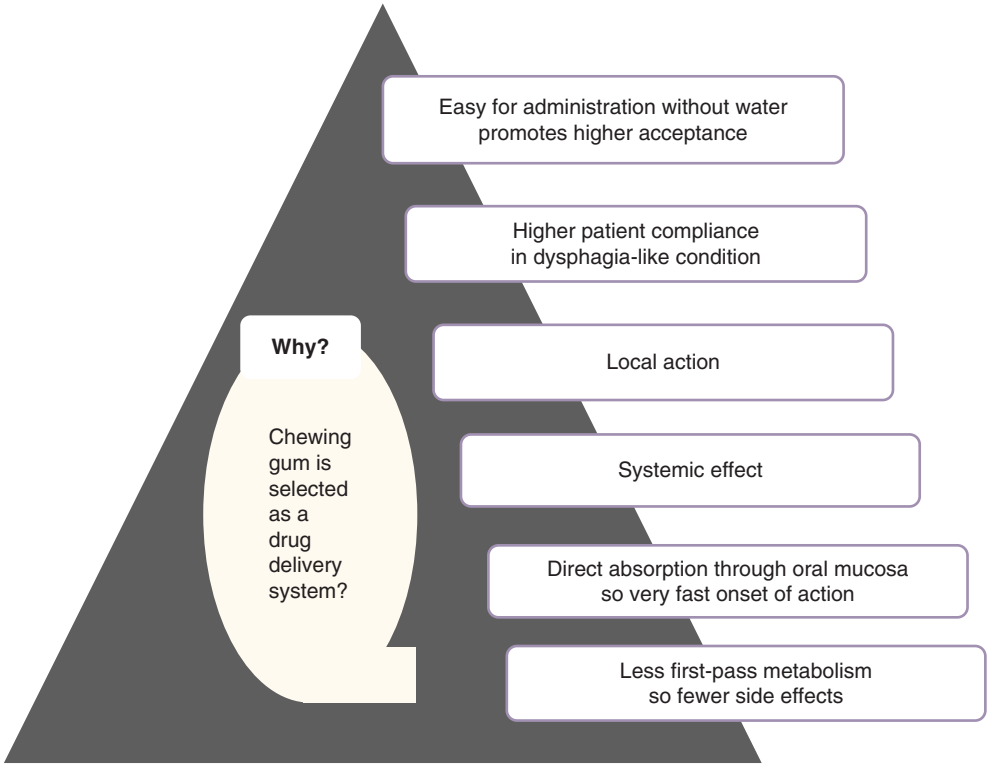

Figure 1. Reasons for selection of MCG as a drug-delivery system.

more calcium and phosphate to replace the minerals lost from the teeth through an acid attack. These special minerals help in repairing of damage caused by early tooth decay. This is called remineralization, which reduces the risk of tooth decay by up to 40% [23].

MCG containing chlorhexidine is used for the treatment of inflammatory conditions such as gingivitis, peridontitis and other oral and pharyngeal infections. Although chlorhexidine is a well-established agent used for the control of supragingival plaque, it has the drawback of tooth staining, which limits its clinical applications to short-term use. A clinical trial was carried out to compare the clinical effectiveness and stain-forming potential of chlorhexidine in MCG with chlorhexidine gluconate mouth rinse [24]. Plaque, gingivitis and stain evaluations were made at 4 and 8 weeks. Stain intensity and stain extent at week 8 were significantly less for the chlorhexidine gum compared with the chlorhexidine mouth rinse.

2.1.3.1.1 *Treatment of dry mouth*

Dry mouth is the major symptom in Sjogren's syndrome (an autoimmune disorder characterized by lymphocytic infiltration of the salivary and lachrymal glands [25]) and it is also a side effect of some tricyclic antidepressants [26]. Chewing gum stimulates salivary secretion and therefore moderately heals this condition; and as the chances of dental caries are greater in a dry mouth, chewing gum may also be beneficial for dental health [27] because it has been proved that long-term activation of the salivary glands by chewing the gum several times a day enhances resting salivary flow rate, especially in those people who have a very low salivary flow rate [28].

2.1.3.2 *Systemic effect with quick onset of action*

As the chewing gum composition is chewed, the medicament is gradually released from the composition and enters the saliva of the oral cavity. During continual chewing, the medicament in the saliva is forced, owing to the pressure created by the chewing action, through the mucosa of the oral cavity into the systemic circulation by means of the buccal or sublingual absorption routes, which proportionally reduces the lag time for the onset of action [29]. Moreover, oral mucosa favors rapid drug absorption because it has a very thin epithelium without stratum corneum and very rich vascularity [30]. Compared with other formulations, in the case of MCG the active ingredient remains in contact with the oral cavity for a longer period of time during chewing and it is forced through the oral mucosa to a larger extent. In doing so, a larger portion of the drug is made available for rapid absorption without a first-pass effect to the general circulation [31].

Kamimoria *et al.* have studied the rate of absorption and relative bioavailability of caffeine administered in chewing gum and capsules to normal healthy volunteers. Observed mean T_{max} for the gum groups ranged from 44.2 to 80.4 min as compared with 84.0 – 120.0 min for the capsule groups. T_{max} for the pooled data was significantly lower ($p < 0.05$) for the gum groups as compared with the capsule groups. No statistical differences were found for C_{max} and $AUC_{0-\infty}$ for comparisons of the gum and capsule formulations at each dose. These findings suggest that there may be an earlier onset of pharmacological effects of caffeine delivered as the gum formulation, which is advantageous in situations where the rapid reversal of alertness and performance deficits resulting from sleep loss is desirable [32].

2.1.3.2.1 *Less first-pass metabolism and improved bioavailibility*

As a result of direct intraoral absorption of active ingredient in the case of MCG, first-pass metabolism is avoided and thus the bioavailability of the active ingredients increases. Noehr-jensen *et al.* investigated the pharmacokinetics of loratadine and its active metabolite desloratadine after single-dose administration of loratadine as a conventional tablet, orally disintegrating tablet and a chewing gum formulation. The results of this study suggested that there was threefold increase in relative bioavailability of loratadine in MCG as compared to tablets due to approximately 40% absorption of loratadine via direct intra-oral buccal mucosa. Plasma concentrations of desloratadine following the administration of loratadine as chewing gum were very low owing to a bypass of the first-pass metabolism [33].

Moreover, as the gastric mucosa is not directly exposed to high concentrations of the drug in the solid-state, it reduces the risk of intolerance or erosion. Besides, the gastrointestinal tract suffers much less from the unwanted effects of excipients as gum does not reach the stomach.

2.1.4 *Marketing advantages as a business opportunity*

There is a necessity to reformulate existing drug into new drug delivery systems (NDDS) to extend or protect product patents, thereby delaying, reducing or avoiding generic erosion at patent expiry. By formulating the drugs in a MCG composition, revitalization of old products and reformulation of new patented products is possible, to distinguish them from future generics competition in the market.

Danish gum specialist Fertin® Pharma is a leader in the field, with its MedChew® technology attracting interest from several major pharmaceutical players. One of the most advanced of these collaborations is its MetControl® project with US firm Generex Biotechnology, which is focused on developing a gum formulation containing metformin for diabetes treatment. In June 2008, Generex reported clinical data that indicated that MetControl is bioequivalent to traditional tablet formulations in both drug release rate and systemic absorption of metformin [34].

Functional chewing gum containing extract of *Hoodia gordonii* has been the most publicized and marketed natural weight-loss product in the US in the past decade. Hoodia works by releasing a chemical compound (P57) that is similar to glucose, but is up to 100,000 times more powerful, which signals to the hypothalamus that enough food has been consumed, and this, in turn, stunts the appetite [35]. Its direct intraoral absorption during chewing allows the supplement to

be absorbed within seconds and bypasses the solubility and absorption problems.

2.1.5 *Inherent benefits of chewing gum apart from drug delivery*

MCG also benefits from the advantages that are inherent to chewing gum, such as oral care [24], stress relief [36], improved focus and concentration [37] and weight management [38].

2.2 Drawbacks of MCG

MCG has quite a few limitations.

2.2.1 *Influence of rate and pattern of chewing on drug release*

Drug released from MCG is strongly influenced by the manner in which patient chews the MCG formulation, that is, a chewing rate of 1 chew every second gave a significantly higher release of nicotine from Nicorette® chewing gum than a chewing rate of 1 chew every 8 s [39].

2.2.2 *Variability in absorption site owing to salivary dilution and involuntary swallowing*

The main hindrance of any buccal drug delivery is the decline in the drug concentration in the oral cavity as a result of salivary dilution, particularly for transmucosal delivery. Drug released into saliva swiftly disappears from the oral cavity because of involuntary swallowing of saliva with dispersed/dissolved drug, which may reduce the chances of drug absorption from the buccal mucosa. As compared with other conventional systemic oral mucosal drug delivery systems (solutions, orodispersible tablets, fast dissolving tablets and mouth dissolving films), MCG has higher retention and contact time in the oral mucosa and, as it is being chewed, the medicament in it is gradually released from the composition into the saliva. During continual chewing, the medicament in the saliva is then forced, owing to the pressure created by the chewing action, through the mucosa of the oral cavity to a larger extent into the systemic circulation. However, drugs that are released from chewing gum and swallowed involuntarily will be introduced to the gastrointestinal tract in either dissolved or suspended form in saliva and thus will be readily bioavailable [40].

3. Excipients in MCG formulation

MCG is a mixture of natural resins obtained from trees (chicle like rubbery latexes) or the milky juices from plants or synthetic gums (manmade polymers), which is sweetened with natural sugar, corn syrup or artificial sweeteners and may also contain coloring and flavoring agents. Antioxidants may be added to protect the gum base and flavors from oxidation.

The fundamental raw (untreated) material for chewing gum is natural gum chicle, obtained from the sapodilla tree, a member of the family Sapotaceae, which is botanically known as *Manilkara zapota* (L.) van Royen [41]. This product is harvested in Mexico, Belize and Guatemala during the rainy season from July to February [42]. Chemically, chicle is made up of polyterpenes that are composed of thousands of C_5H_8 isoprene (2-methyl-1,3-butadiene) subunits, as depicted in **Figure 2**.

As chicle is very costly and not easy to obtain, other natural gums or synthetic materials such as butadiene-styrene-like basic copolymer, isobutylene-isoprene copolymer (butyl rubber), polyvinyl acetate and identical polymers are used as a chewing gum base. When proper consistency of gum is desired, synthetic elastomers such as butadiene-styrene copolymers, polyisobutylene, isobutyleneisoprene copolymers and polyethylene are very useful. The gum base may include polyvinyl alcohol and polyvinyl acetate of different molecular mass depending on the consistency of gum base desired, which reduces the tendency of the gum to adhere to the teeth (detackifier) and to be divided into pieces during chewing. The gum base determines the basic characteristics of the product, such as texture, softness, hardness, elasticity, crumbliness, stickiness and mouth feel. It also determines the release profile of active ingredients and flavors [43]. Texturizing or filling agents such as talc, magnesium and calcium carbonate, tricalcium phosphate are also included to provide texture and evenhanded size of the gum lump.

Various excipients used in MCG are given in **Table 2**. The major excipients used in MCG are described below.

Bulking agents. Bulking agents are used to produce required bulk of chewing gum when potent drug or low-dose drug is to be incorporated. A low-calorie gum is preferred as a bulking agent, especially for health-conscious and diabetic people. Examples of low-caloric bulking agents are guar gum hydrolysates, indigestible dextrin, polydextrose, inulin, oligofructose and fructooligosaccharides, which also provide a sweet taste [44].

Softening agents. Softening agents are included to provide enormous softness during chewing of the medicated gum for better mouth feel. Commonly used softeners are glycerin, lecithin and fatty acids such as stearic acid, palmitic acid, oleic acid and linoleic acid.

Sweetening agents. Sweetening agents are classified into two categories, aqueous and bulk [45]. Aqueous sweeteners are utilized to retain moisture within the formulation for freshness, and include sorbitol, corn syrups and hydrogenated starch hydrolysates. These may also be used as a softening agent or binding agent in MCG.

Bulk sweeteners are further classified into nutritive and non-nutritive sweeteners. The amount of bulk sweetener used in chewing gum composition is from 30 to 75%. Sugar and sugar alcohols are each considered nutritive sweeteners. Sugars are mainly sucrose, dextrose, maltose, maltodextrin, fructose and galactose and are used at between 2 and 15%. Sugar alcohols are low-intensity natural sweeteners such as mannitol, sorbitol and xylitol. Sugar alcohols or polyols contain fewer calories (average of 2 kcal/g) than sugar (4 kcal/g) because they are not completely absorbed from the intestine. They also provide a cooling sensation in the mouth. The sweetness of sugar alcohols varies from 25 to 100% as sweet as table sugar (sucrose).

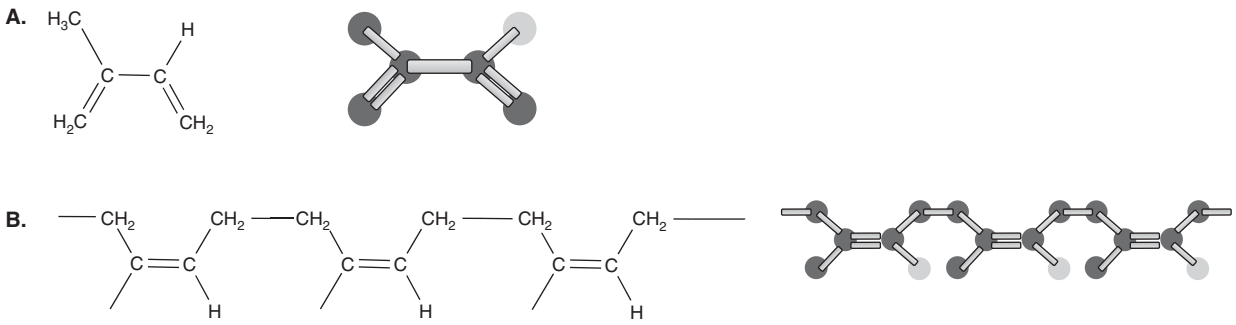

Figure 2. Chemical structure and 'Ball and Stick' models of (A) Isoprene [2-methyl-1, 3-butadiene] unit (B) Polyterpene chain.

Table 2. Excipients used in MCG formulations*.

Category	General range	Few examples
Elastomers and rubbers	15.0 – 45.0%	Natural (chicle, crown gum, nispero) and synthetic (butadiene-styrene copolymers, polyisobutylene, isobutyleneisoprene copolymers)
Elastomer solvents	45.0 – 70.0%	Natural rosin esters such as partially hydrogenated rosin, pentaerythritol esters of rosin or glycerol esters of partially hydrogenated wood or gum rosin and glycerol esters of partially dimerized rosin. Synthetic terpenes (D-limonene, α-pinene, β-pinene)
Bulking agents	Up to sufficient quantity	Guar gum hydrolysates, indigestible dextrin, polydextrose, inulin, oligofructose and fructooligosaccharides
Softening agents	0.5 – 15%	Glycerin, lecithin and fatty acids such as stearic acid, palmitic acid, oleic acid and linoleic acid
Sweetening agents	Up to 60%	Sugars (sucrose, dextrose), sugar alcohols (mannitol, sorbitol), aspartame, neotame
Flavoring agents	0.01 – 1.0%	Natural and artificial volatile essential oils
Coloring agents	0.1%	Various FD&C-approved colors
Opacifiers	0.5 – 2.0%	Titanium dioxide, magnesium oxide
Texturizing or filling agents	Up to 60%	Talc, magnesium and calcium carbonate, tricalcium phosphate, colloidal aluminium silicate (Bentonite) or magnesium aluminium silicate (Atta pulgite)
Antioxidants	0.02% of gum base	Propyl gallate, butylated hydroxy anisole and butylated hydroxy toluene

*Information gathered from various patents [43-47,92,93].

The high-intensity artificial sweeteners such as saccharin, aspartame, neotame, acesulfame potassium and sucralose are considered as non-nutritive sweeteners. These sweeteners are evaluated based on their safety, sensory qualities (e.g., clean sweet taste, no bitterness, odorless) and stability in various pH environments. These are compounds with sweetness that is many times that of sucrose, common table sugar. As a result, much less sweetener is required, and energy contribution is often negligible. The amount of high-intensity sweetener used in chewing gum composition is between 0.001 and 5.0%, most preferably in amounts from 0.05 to 1.00% of the final weight of chewing gum composition. FDA-approved high-intensity artificial sweeteners with sweetness as compared with table sugar (sucrose) and special indications are listed in **Table 3**.

Flavoring agents. Flavoring agents are added to improve the flavor in chewing gum, which can overcome the bitter taste of the drug. There are several natural and artificial flavors that can be generally described to possess similar taste-masking effects, of which some popular flavorants used in pharmaceuticals are listed in **Table 4** [46]. The amount of flavoring agent used in chewing gum composition is normally a matter of preference subject to the set range and such factors as the individual flavor, the type of bulking agent or carriers used, and the strength of flavor desired. The flavors may be supplemented by menthol as appropriate. Menthol is used as a flavoring adjuvant from 0.01 to 1.0%.

Coloring agents. In the US, FD&C numbers (which generally indicate that the FDA has approved the artificial coal tar dye colorant for use in foods, drugs and cosmetics) are given to approved synthetic food dyes that do not exist in nature [47], whereas in the European Union, E numbers are used for all additives, both synthetic and natural, that are approved in food applications. In the US, the following seven coal

Table 3. FDA-approved high-intensity artificial sweeteners.

Approved artificial sweeteners	Times sweeter than sucrose	Description
Saccharin (Sweet'N Low® or Necta Sweet®)	200 – 700×	Sweet bitter profile is concentration dependent; it is sweet at very low concentrations, but bitter at higher concentrations. Approximately 20% of the population are 'saccharin sensitive', that is, they perceive saccharin to be bitter even at low concentrations. On repeated tasting, saccharin becomes less sweet and increasingly bitter
Aspartame (Nutrasweet® or Equal® or Sugar Twin®)	160 – 220×	Chemically aspartyl-phenylalanine methyl ester. No bitter aftertaste. Very stable in dry solid-state, but unstable in liquid-state and hydrolyzed into aspartylphenylalanine and diketopiperazine, with loss in sweetness. In liquid-state it shows greatest stability between pH 3.4 and 5.0 at refrigerated temperatures. In the body, it is metabolized to phenylalanine, so it is not recommended for pheylketoneurics (PKU)
Neotame (a new version of aspartame)	7000 – 13,000×	Chemically dimethylbutyl-aspartyl-phenylalanine methyl ester, related to aspartame. Resistant to hydrolytic degradation; not metabolized into phenylalanine so no danger for individuals with PKU
Acesulfame K (Ace-K® or Sunett®)	200×	Heat-stable synergistic sweetening enhancement with aspartame
Sucralose (Splenda®)	600×	Chemically trichlorogalactosucrose Presence of chlorine is thought to be the most dangerous component of sucralose; stable over a broad pH range, heat stable

Table 4. Flavoring agents for specific taste-masking.

Taste of drug	Flavors used for taste-masking
Sweet	Fruit and berry, honey, vanilla, bubble gum
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, Guyana
Salty	Butterscotch, maple, apricot, peach, melon, vanilla, wintergreen, mint

tar dyes are permitted as of 2007 [47]: FD&C Blue No. 1 – Brilliant Blue FCF, E133 (blue); FD&C Blue No. 2 – Indigotine, E132 (dark blue shade); FD&C Green No. 3 – Fast Green FCF, E143 (bluish green); FD&C Red No. 40 – Allura Red AC, E129 (red); FD&C Red No. 3 – Erythrosine, E127 (pink); FD&C Yellow No. 5 – Tartrazine, E102 (yellow); and FD&C Yellow No. 6 – Sunset Yellow FCF, E110 (orange). But, as FD&C Yellow No. 5 (Tartarazine) causes hives in < 0.0001% of those exposed to it and provokes asthma attacks in aspirin-intolerant individuals, most pharmaceutical companies have eliminated the use of this colorant in their products.

Owing to safety concerns of artificial dyes, natural colorants obtained from plant and animal sources have become more popular. Plant extracts such as chlorophyll-green, annatto-yellow, curcumin-yellow, saffron yellow and animal extracts such as cochineal red are incorporated to enhance a pleasing appearance or hide the colors of drugs or excipient in the final product. Opacifiers such as titanium dioxide and magnesium oxide are also included to provide whiteness to the final product.

3.1 Directly compressible gum material and flow regulators

Directly compressible gum material, a mixture of polyols (sorbitol/xylitol/mannitol) and of sugar with gum, plasticizers and anticaking agents is also available these days. It enables rapid development of gum delivery system at low cost using a pharmaceutical in-house tablet compression machine. For regulating flow of powdered blend during compression, glidant, antiadherant and lubricants such as flow promoters are added in the formulation [48].

Glidants. improve the flow property of material from hopper to the die cavity by reducing interparticulate friction. Colloidal silica, that is, syloid, pyrogenic silica (0.25%), hydrated sodium silicoaluminate (0.75%) and corn starch (3 – 10%) are used successfully as glidant to induce flow. *Antiadherents* avoid sticking of material to die walls and picking of material by punches. These materials themselves undergo deformation easily on compression. Talc (1 – 5%) and corn starch (3 – 10%) are very good examples of antiadherants. Lubricants are added to reduce the friction between the cylindrical surface of the compressed dosage form and the die wall during compression and ejection. Metallic stearates (0.25 – 1%) (magnesium and calcium stearate) and high-molecular-mass polyethyleneglycol (PEG 4000 and PEG 6000) are commonly used as water-insoluble *lubricants.* Boric acid (1%), DL-leucine (3 – 10%), sodium benzoate (5%), sodium acetate (5%) and sodium lauryl sulfate (1 – 5%) are successful examples of water-soluble lubricants.

4. Possible therapeutic areas

Active pharmaceutical ingredients (APIs) of small molecular mass that are non-ionized, lipophilic (hydrophobic) and stable to salivary enzymes are likely to be absorbed more easily from oral mucosa. For easy release of API from MCG, API should be freely soluble in salivary fluid, whereas for easy absorption through oral mucosa, API should be sufficiently lipid soluble.

As many APIs are lipophilic they will adhere to the gum base and may therefore be released slowly and incompletely. Methods to increase the rate and extent of release of APIs include the addition of buffering agents or solubilizing agents and coating/encapsulating the API. Release of folic acid from chewing gum containing sodium bicarbonate and sodium carbonate as a buffering agent was significantly higher than its chewing gum without buffering agent [49]. However, Witzel and Mackay have described the method of increasing drug (nystatin) release from 4 to 24% by coating with hydrophilic gum base (arabic gum). By contrast, hydrophilic APIs are rapidly released and it may therefore be necessary to slow down the release rate by means of various methods, such as increasing the amount of gum base or encapsulating the active substances. The water content of gum base is very low and the gum binds lipophilic substances very firmly. To obtain the optimal formulation it is possible to decrease the release rate of highly hydrophilic substances and increase the release rate of lipophilic substances [50].

Antihistamines (chlorpheniramine maleate, cetirizine HCl), appetite suppressants (phenylpropanolamine HCl or caffeine), expectorants (guifensin hydrochloride), antitussives (dextromethorphan, noscapine), opioids (codeine phosphate, codeine sulfate), nasal decongestants (phenylephrine HCl, pseudoephedrine, ephedrine HCl), analgesics and anti-pyretics (aspirin or acetaminophen), anti-inflammatories (ibuprofen, ketoprofen, naproxen), electrolyte and mineral supplements, antacids, laxatives, vitamins, ion exchange resins (cholestyramine), and anti-cholesterolamics such as most prescribed therapeutic categories can be potential possible targets for delivery in the form of MCG owing to its higher patient compliance and quick onset of action [51,52].

5. Manufacturing of MCG

5.1 Traditional method

In the conventional method, first slashes are cut into the bark of the sapodilla tree to collect chicle, which is then boiled over an open fire to evaporate the excess water. Once it is chunky and taffy-looking, then it is packed into wooded forms to make blocks that are then dried in currents of hot air and then softened by melting. It is then placed in a kettle mixer to which corn syrup, active ingredients and other excipients such as fillers, sweeteners (powdered sugar) and fruity flavors are added at a definite time in sequence [42]. The gum is then rolled to form a thin, wide ribbon. During this course of action, a slight coating of finely powdered sugar is added to keep the gum from sticking. Then the gum is cooled for 2 days, which allows the gum to set properly. Finally, the gum is cut to the desired size [53].

Boundaries of the conventional manufacturing method are as follows:

1) Exact texture, shape, or weight of MCG cannot be obtained.
2) Incorporation of thermosensitive drugs cannot be possible because of the high temperature used during melting of the gum.
3) Accuracy in uniformity of content cannot be achieved during melting and mixing of the extremely viscous gum mass.

5.2 Latest technology

As technology advances, several limitations of the conventional method such as lack of exact texture, shape or weight and inaccuracy in uniformity of content can be overcome by sophisticated automatic instruments (e.g., Korea Association of Machinery Industry [KOAMI®] [54]). A schematic representation of the various processing steps involved in manufacturing MCG by the latest technology is given in **Figure 3**.

5.3 Direct compression

Despite the above-mentioned benefits, the potential of medicated chewing gums has not yet been fully exploited because the manufacturing of chewing gum requires different technology from that used in pharmaceutical production. Standard chewing gum manufacturing requires specific equipment and facilities involving hot-melt processes, which are usually rare in the pharma industry.

Recently, free flowing directly compressible co-processed gum materials such as Pharmagum®, developed by SPI Pharma [55], and Health in gum®, developed by CAFOSA [56], have become available in the market. Chemically, it is a mixture of polyols (sorbitol/xylitol/mannitol) and of sugar with gum, plasticizers and anticaking agents. These gums are manufactured under cGMP conditions and comply with food chemical specifications and are 'generally regarded as safe' (GRAS), regulated by FDA title 21 C.F.R Section 172.615. Chewing gum made by this gum material can be directly compressed on a pharmaceutical in-house tablet compression machine, which enables rapid and low-cost development of MCG. As it does not require high temperature, thermosensitive APIs can also be processed. This method is also ideal for water-sensitive APIs. Formulations made with Pharmagum M® and Health in gum® are similar to the tablet in appearance. Gum formed using a compressible formulation is many times harder and crumbles, and when pressure is applied it gives faster release of drugs than conventional methods owing to lower bonding of drug with gum material [56].

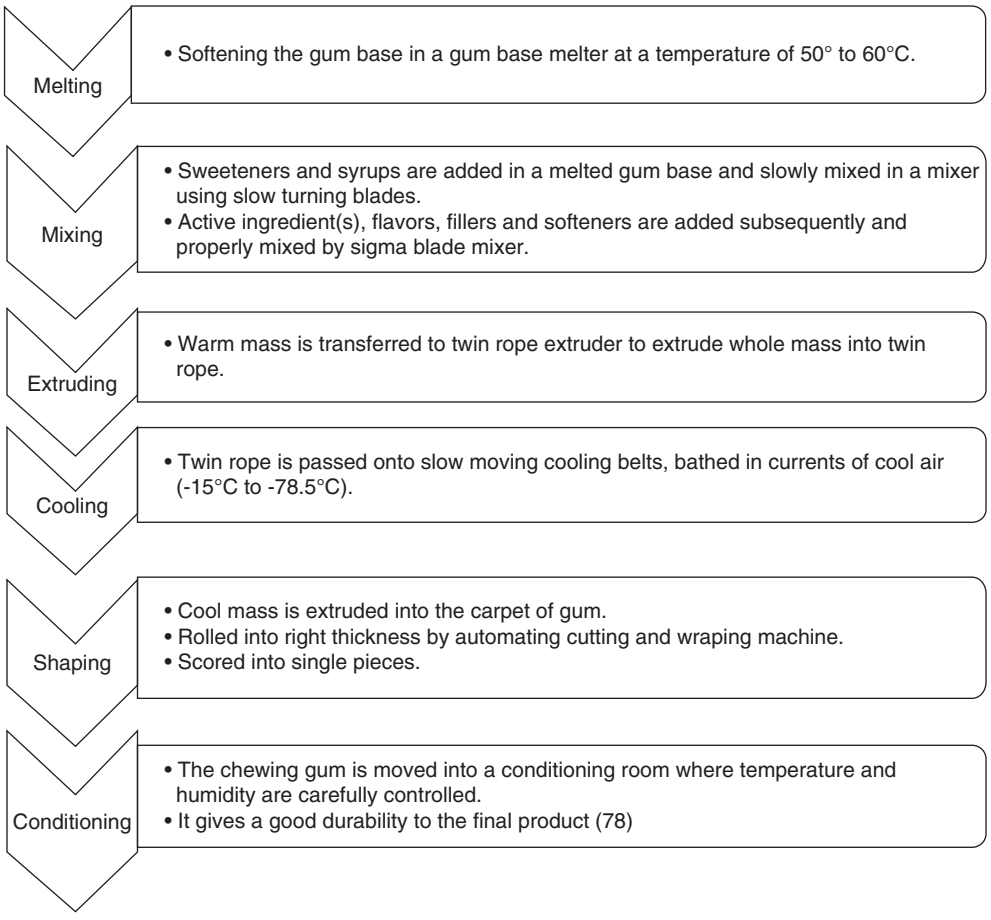

Figure 3. A schematic representation of the various processing steps involved in manufacturing of MCG by the latest technology.

6. Important formulation aspects for MCG

6.1 Ion exchange resin complexation

Complexation of lipophilic active ingredients to ion exchange resins such as polacrillin potassium provides sustained drug delivery. Also, this approach is useful to mask the taste of bitter drugs [57]. As most drugs possess ionic sites in their molecule, the resin's charge provides a means to bind such drugs loosely, and this complex prevents drug release in the saliva, thus masking the taste. For the purpose of masking the taste, weak cation exchange or weak anion exchange resins are used, depending on the nature of the drug. The nature of the drug resin complex (resinate) formed is such that the average pH of 6.7 and cation concentration of ~ 40 meq/l in the saliva are not able to break the drug resin complex, but it is weak enough to be broken down by hydrochloric acid present in the stomach. Thus, the drug resin complex is absolutely tasteless and with no aftertaste; but, the rationale of buccal absorption of drug released from MCG cannot be solved, because drug resinate complex will be dissociated only at acidic pH within the gastric lumen [57].

Very few methods have been documented in the literature that sustain or reduce the release rate of drugs from MCG. When nicotine is incorporated into ordinary gum compositions its release occurs rapidly. Such a release profile is undesirable for clinical use because release of nicotine from a nicotine chewing gum formulated as a smoking substitute should be uniform and last for at least 20 min. In addition, the released nicotine should produce a 'feeling of smoking' not only following absorption but also in the mouth and throat. To solve this purpose Nicorette chewing gum was developed, in which nicotine is formulated as a complex (polacrilex) bound to a cation exchange resin – a weak acidic methacrylic acid polymer (polacrilex resin, Amberlite IRP 64). If nicotine is liberated as the nicotine cation, the absorption does not take place so quickly, thus allowing some of the nicotine to reach other parts of the buccal cavity, including the throat, whereby some of the sensations of smoking are obtained, including a light burning sensation, which the smoker generally estimates in a positive way [58].

6.2 Cyclodextrin complexation

Cyclodextrin complexes have been used to increase the solubility, stability and bioavailability of a variety of active ingredients in formulations, and also explored for masking the taste of certain active ingredients [59].

Cyclodextrins are basically cyclic oligosaccharide molecules having a toroidal shape, with a hydrophobic central cavity and a relatively hydrophilic outer surface. This structure enables cyclodextrins to bind appropriately sized nonpolar guest molecules or moieties of guest molecules within the hydrophobic central cavity, to form clathrate complexes. As the exterior of cyclodextrin is relatively hydrophilic, the formation of such complexes may therefore be used to increase the solubility of otherwise poorly soluble molecules. The naturally occurring cyclodextrins are α, β and γ types containing six, seven and eight glucopyranose units, respectively. They have limited aqueous solubility owing to the strong intermolecular hydrogen bonding in the crystal state. Substitution of any of the hydrogen bonds forming a hydroxyl –OH group or even by a lipophilic methoxy $-OCH_3$ functional group results in a dramatic improvement in their aqueous solubility. Water-soluble cyclodextrin derivatives of commercial interest include the hydroxypropyl derivatives of βCD, randomly methylated β-cyclodextrin (RMβCD) and sulfobutylether β-cyclodextrin sodium salt (SBEβCD). Hydrophilic cyclodextrin derivative such as 2-hydroxypropyl β-cyclodextrin (HPβCD) are considered non-toxic at low to moderate oral dosages and so it is used to increase aqueous solubility of poorly water-soluble drugs. Lipophilic cyclodextrin derivatives, such as the methylated cyclodextrins and sulfobutylether cyclodextrin, are to some extent absorbed from the gastrointestinal tract into the systemic circulation, but oral administration of it is limited by its potential toxicity [60].

6.3 Microencapsulation

Microencapsulation by water-soluble or water-insoluble polymer is one of the successful methods for sustaining the release of active ingredient sweetener or flavorant from MCG [61]. A commonly noted deficiency in chewing gums has been the relatively rapid exhaustion of the flavor and sweetness sensation during chewing. This loss frequently occurs within the first 3 – 5 min of chewing. A further consideration when manufacturing a MCG is the particle size of any solid substance suspended in the chewing gum. To avoid an unpleasant gritty feeling during chewing or the risk of damaging the enamel of the teeth, the particle size should be kept below ~ 100 µm. Both of these can be solved by microencapsulation. Yang has patented an encapsulation composition including high-molecular-mass polyvinyl acetate blended with a hydrophobic plasticizer to form a film in which aspartame is blended by melt blending, which was cooled to a solid and ground into particulate for incorporating within chewing gum for highly controlled release of active agent [61].

7. Product performance test

7.1 *In vivo* 'chew-out' studies

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

In a chew-out study, each person chews one sample of the MCG for different time periods (i.e., 5, 10, 15, 20 min). Then the chewed gum is removed and analyzed for the 'residual drug content' [62]. The 'amount of drug released during mastication' is calculated by subtracting the 'amount of the residual active ingredient' present in the gum after chewing from 'the total content', whereas pharmacokinetics can be determined from withdrawn blood samples at specific time intervals. The prerequisites of human volunteers, person-to-person variability in the chewing pattern, chewing frequencies, composition of individual salivary fluid and flow rate of saliva are a few limitations of chew-out studies.

7.2 *In vitro* drug release from MCG

7.2.1 *Unofficial single-module chewing apparatus*

One of the unofficial apparatus for carrying out dissolution studies of MCG was designed by Wennergren. This apparatus consists of a two-piston and temperature-controlled reservoir for dissolution medium, as shown in a schematic representation in **Figure 4**. The upper jaw has a flat surface that is parallel to the central part of the lower surface. The small brim of the lower surface is angled upwards (45 degrees) so that the lower surface functions as a small bowl with a flat bottom. This bowl prevents the chewing gum from sliding during mastication [63].

Throughout one cycle of chewing, one piston on each side shift towards each other. When they get together, they press the MCG between them and then make a twisting association before returning to the preliminary point. To carry out a drug release test, a known quantity of chewing gum is placed in the 20 ml volume of dissolution medium, which is equilibrated to a temperature of 37°C. The pressing and twisting forces are transmitted to the gum through the pistons at a chewing rate of 60 strokes a minute. At specified time intervals, that is, 3, 5 and 10 min, samples are collected and analyzed to evaluate percentage drug release [63].

7.2.2 *Official MCG chewing apparatus*

The official modified dissolution apparatus for assessing drug release from MCG, as per European Pharmacopoeia, is depicted in **Figure 5**. In this apparatus, in addition to the pair of horizontal pistons ('teeth'), the chewing chamber is supplied with a vertical piston ('tongue') working alternate to the horizontal pistons, which ensures that the gum is always positioned in the correct place during the mastication process [64]. If required, it is possible to construct the machine so that at the end of the chew the horizontal pistons rotate in opposite directions around their own axis to each other to attain maximum mastication.

The temperature of the chamber can be maintained at 37 ± 0.5°C and the chew rate can be varied. Other adjustable

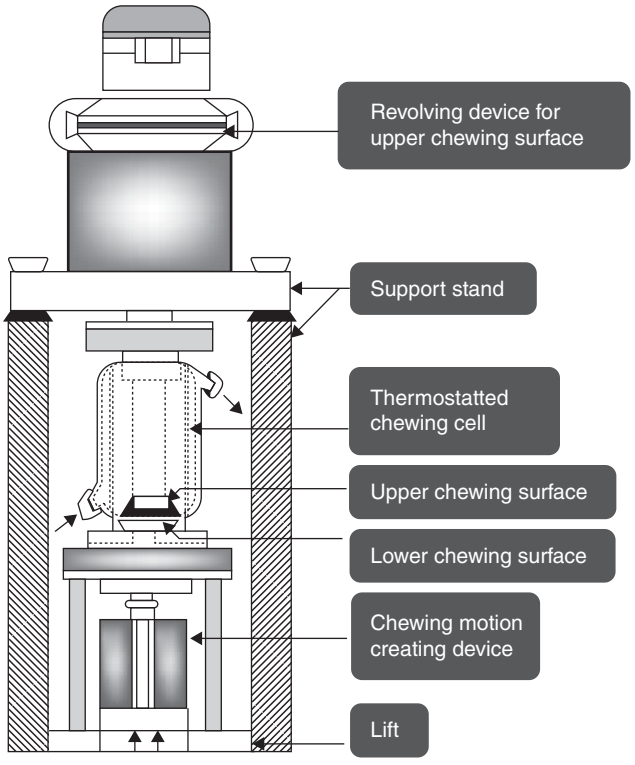

Figure 4. Schematic representation of unofficial single module chewing apparatus.

settings include the volume of the medium, the distance between the jaws and the twisting movement. The European Pharmacopoeia recommends 20 ml of unspecified buffer (with a pH close to 6) in a chewing chamber of 40 ml and a chew rate of 60 strokes a minute [65]. This most recent device seems promising, competent and uncomplicated to operate. Several studies [66-68] have been carried out using the European Pharmacopoeia apparatus, and the results indicate the methodology is rugged and reproducible.

8. Factors affecting release of active ingredient from MCG

8.1 Person-to-person variability

One of the reasons why MCG has not yet been fully exploited is because of the therapeutic uncertainty related to the drug delivery method – that is, a patient's mechanical chewing action. The gum's therapeutic effect depends on chewing and as each person has his/her own chewing force, frequency and chewing time, the results can vary. Barabolak *et al.* used a self-reporting questionnaire technique to determine the length of chewing time (in minutes). The mean chewing time per piece of gum was 36 min, so they suggested that when designing a clinical trial, a chewing time of 30 min should be used if the results were to be extrapolated to ordinary use of chewing gum [69].

The rate at which the subject chews gum also affects the amount of drug released. The average chewing rate is ~ 60 chews every minute. For this purpose, the release of nicotine from Nicorette chewed at different rates has been investigated. In that study it was found that a chewing rate of 1 chew every second gave a significantly ($p < 0.05$) higher release than a chewing rate of 1 chew every 8 s. An *in vitro* study prescribed by European Pharmacopoeia suggests 60 strokes a minute are sufficient for proper release of active ingredient [39].

8.2 Physicochemical properties of drug

The physicochemical properties of the active ingredient such as its molecular mass, ionized or non-ionized form, lipophilicity or hydrophilicity, stability to salivary enzymes (amylase) and its solubility in salivary fluid play very important roles in the release of drug from MCG and absorption of drug through oral mucosa. For example, the saliva-soluble ingredients will be immediately released within a few minutes, whereas lipid-soluble drugs are released first into the gum base and then slowly into salivary fluid.

Aqueous solubility of API plays an important role in the release from chewing gum composition, that is, release of water-soluble drug (aqueous solubility > 1:10) is, in general, ~ 75% or more during 5 min of chewing and 90% or more during 15 min of chewing at a rate of 60 chews a minute. Drugs with aqueous solubility between 1:10 and 1:300 demonstrate up to 60% release during 10 min of chewing and between 50 and 90% release after 15 min of chewing. The release of only slightly water-soluble (1:1000) drug was found to be < 5%, even if the gum was chewed for 30 min [70].

8.3 Formulation factors

Composition and amount and type of gum base, solubilizing agents and softening agents may affect the rate of release of the active ingredient from MCG [71]. For example, the release of miconazole is poor when incorporated directly into chewing gum. *In vitro* release studies using the chewing machine and *in vivo* studies using healthy adult volunteers showed that solid dispersions of miconazole-PEG 6000 (1:4) in chewing gum formulation produced a higher release rate than pure miconazole. This happened because PEG 6000 increases the solubility of miconazole in water. When lecithin was added to the miconazole-PEG chewing gum formulation both the release rate and the time of release of miconazole increased markedly *in vitro* and *in vivo* [71]. In one study, the effect of gum base mass on drug release was investigated using salicylamide as a representative. When salicylamide was incorporated into a chewing gum containing a relatively large percentage of gum base, the release of gum base was significantly lower, at 25.6%, compared with a chewing gum in which less gum base was present, that is, 52.0% [72].

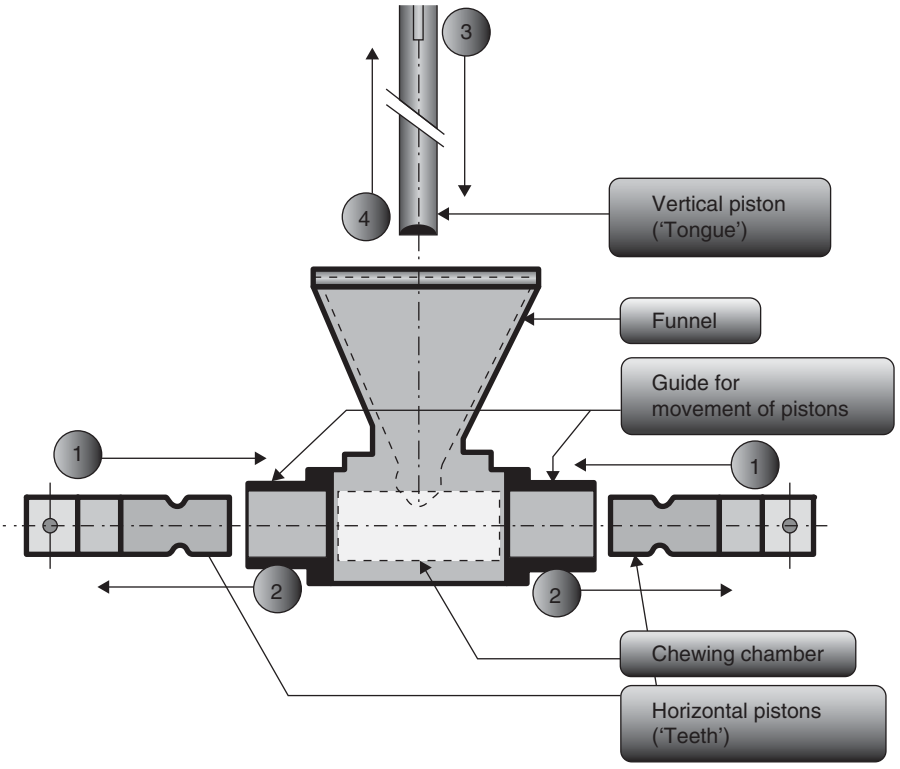

Figure 5. Schematic representation of modified dissolution apparatus as per European Pharmacopoeia, where numbered arrows indicate sequence of motion.

9. Possible absorption pathways

Drug released from the chewing of medicated gum will be either absorbed from the buccal mucosa or, if swallowed, absorbed from the gastrointestinal tract [73].

(1) *Through buccal mucosa.* As the chewing gum composition is chewed, the medicament is gradually released from the composition and enters the saliva of the oral cavity. During continual chewing, the medicament in the saliva is forced, owing to the pressure created by the chewing action, through the mucosa of the oral cavity into the systemic circulation by means of buccal or sublingual absorption routes. Also, oral mucosa favors rapid drug absorption because it has a very thin leaky epithelium owing to the absence of a stratum corneum-like permeation barrier and rich vascularity. In contrast to a typically orally ingested drug wherein the drug solution is too briefly in contact with the oral mucosa for appreciable absorption, in the case of MCG the active agent remains in contact with the oral cavity for a longer period of time during chewing and then it is forced through the oral mucosa to a larger extent. In doing so, a larger portion of the drug will be available for rapid absorption without a first-pass effect to the general circulation [74].

(2) *Through the gastrointestinal tract.* Drugs that are released from chewing gum and involuntarily swallowed will be introduced to the gastrointestinal tract in dissolved, diluted, or suspended form in saliva and so will be very easily bioavailable with a consequent fast onset of action as compared with solid oral dosage forms [29].

10. *In vitro–in vivo* correlation

In one study, MCG containing 30 mg of urea was chewed for different periods of time up to 30 min. A chewing method similar to that mentioned in European Pharmacopoeia (60 strokes a minute) was used for *in vitro* drug release testing, in which volunteers chewed the gums and then the residual amount of urea in the gum was analyzed to determine the *in vivo* release profile. A linear *in vitro–in vivo* correlationship (IVIVC) was obtained with correlation coefficient (R^2) = 0.9992 [75]. The *in vivo–in vitro* release profile of ascorbic acid, which is water soluble, from four different formulations has been reported to be linear for first 15 min, as per a study method described above [76]. In another study, the *in vitro* release profile of noscapine from chewing gum at 60 chewing cycles a minute was similar to its *in vivo* release profile in healthy volunteers [77].

11. Expert opinion

Chewing gum is a viable alternative to traditional dosage forms for drugs intended to cure or relieve diseases in the

oral cavity. Local delivery to tissues of the oral cavity has several applications, including the treatment of toothache, periodontal disease, bacterial and fungal infections, aphthous and dental stomatitis, which require a long period of drug release to the oral cavity.

It can be utilized for systemic drug delivery where a rapid onset of action is needed, such as motion sickness, nausea, pain, allergy and infection and hypertension (provided the drug is easily absorbed through the oral mucosa). As chewing gum is intended to be retained in the mouth for a long time, the issue of taste-masking remains an important factor in product development, as does the control of drug release from the gum base. The convenience and acceptability of chewing gums, combined with effective sweetening and taste-masking, may lead to improved compliance. In the future, the concept of chewing gum as a drug delivery system may be used more often in preference to other oral mucosal drug delivery systems for the local and systemic delivery of most prescribed drugs owing to higher patient acceptance and compliance. Moreover, MCG also benefits from the rewards that are inherent to chewing gum such as oral care, stress relief, improved concentration and weight management.

Nevertheless, by formulating MCG composition, revitalization of old products and reformulation of new patented products to distinguish from upcoming generics competition in the market is possible, which provides supplementary patient benefits and ultimately leads to revenue conservation. Thus, the potential of MCG for direct systemic delivery with higher patient compliance, its fast onset of action and the opportunity for product-line extension make it an attractive innovative drug delivery option.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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