

Caffeine–Clove Oil Medicated Chewing Gum: Formulation Strategies, Current Challenges and Future Perspectives

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Abstract

Medicated Chewing Gum (MCG) is a mobile drug delivery system that is useful for delivery of drugs both locally and systemically via the oral cavity. It has benefits like quick onset of action, enhanced patient compliance, and bypasses first-pass metabolism. Caffeine is a central nervous system stimulant that has been shown to be efficiently used in the formulations of medicated chewing gum because of its rapid absorption into the body via the buccal route and rapid pharmacological action. Clove oil is a highly concentrated source of eugenol and it has potential as an antimicrobial agent, pain reliever and anti-inflammatory agent, especially when used in the mouth cavity. This combination may offer dual therapeutic benefits. While clove oil offers analgesic and antimicrobial action in the oral cavity, caffeine offers an adjuvant analgesic effect and CNS stimulation. Thus, this combination may provide a synergistic activity. Although caffeine and clove oil have therapeutic value, their application as a unit form of medication in a chewing gum has not been widely investigated. The purpose of this review is to discuss the pharmacology, current challenges, manufacturing and release strategies and possible synergistic action of caffeine and clove oil in chewing gum. Adopting new strategies including microencapsulation, emulsification, nano-delivery systems and controlled-release technology offers a good opportunity to improve stability, taste masking and drug release profile from the gum matrix.

Keywords: Medicated chewing gum, Caffeine, Clove oil, Eugenol, Buccal drug delivery, Taste masking, microencapsulation.

1. Introduction

Medicated chewing gum (MCG) is an emerging technology of drug delivery which is a combination of convenience for the patient and controlled drug release characteristics. It is supposed to release active pharmaceutical agents during the act of mastication so that they could be absorbed through the buccal mucosa or produce localised action in the oral cavity^{1,3-5}. This route of delivery possesses numerous advantages over conventional dosage vehicles and it allows higher adherence of patients, rapid response and convenience of administration without having to use water^{4,5,8,9}. Furthermore, MCG can decrease GIT side effects and elevate bioavailability due to its ability to partially enter the systemic circulation, and this decreases the effects of first-pass metabolism^{3-5,9}.

The European Pharmacopoeia describes medicated chewing gums as single-dose solid preparations, predominantly composed of a gum base, and are intended to be chewed but not swallowed to allow a slow and controlled release of the active substance⁶. On the same note, regulatory bodies like the U.S. Food and Drug Administration (FDA) have identified MCGs as a flexible dosage form that can be used to administer the drug to produce local and systemic effects⁷. These characteristics highlight the topicality of MCGs as an effective and easy-to-use substitute in existing pharmaceutical prescriptions, in particular those which require rapid absorption and a particular oral administration^{6,7}.

History

The origin of chewing gum dates back to the Mayans, Aztecs and early Greeks, where natural gum and resins like chicle, mastic and spruce gum were commonly used for oral hygiene, as a thirst quencher and for recreational purposes^{1,2,4}. These practices were the first step towards the development of chewing gum as a useful substance. In the 19th century, steps towards the industrialization started, and chewing gum transforms into a commercially produced product, becoming a popular confectionery product all over the world (1,2). Initially, the formulations were

mostly concerned with flavour and texture; later, sustained developments in science and production methods increased its opportunities for use^{4,8}.

The application of chewing gum as a pharmaceutical dosage form took place in the late 20th century, as a result of advances in the technology of drug delivery^{1,2}. Active pharmaceutical ingredients (APIs) were introduced into the gum bases by researchers, which allowed the regulation of drug release during mastication and absorption by the oral mucosa^{3-5,13-17}; this gave rise to medicated chewing gum (MCG) as a new form of drug delivery system that has local and systemic therapeutic applications^{1-5,9}. Throughout the years, MCG become a patient-friendly dosage form with better therapeutic outcomes, particularly with nicotine MCGs, and increased compliance^{4,5,49-52}.

Advantages of medicated chewing gum

1. Mastication of medicated chewing gum provides enhanced stimulation of salivary flow and improves oral clearance, fights plaque pH and improves enamel remineralisation, preventing the onset of dental caries and improving oral health^{10-12,85-90}.
2. The buccal route enables faster action and increases bioavailability by circumventing first-pass metabolism and improving absorption^{3-5,13-17}.
3. Medicated chewing gum provides a water-free, easy and convenient way to administer the drug. It is very effective in children and frequent travellers and enhances compliance^{1,2,4,5,8,9}.
4. Chewing gum has been associated with alertness, stress relief, and improved concentration, especially formulations containing stimulants like caffeine¹⁸⁻²⁸.
5. Drug administration can be easily terminated by removal of the chewing gum, making it a safer and non-invasive dosage form^{1,4,5,49}.
6. Medicated chewing gum can incorporate various drugs that act locally in oral cavity and also have systemic drug delivery by absorption through the oral mucosa and stomach^{1-5,9,13-17}.
7. Drug release occurs under physiological conditions due to chewing of gum matrix without requiring disintegration or dissolution in the stomach^{1,2,4,5,49-53}.

Limitations of medicated chewing gum

1. Medicated chewing gum cannot be used with drugs demanding large doses. Only small quantities of API can be incorporated into the gum base without affecting its texture and palatability^{4,5,9,49,50,53,57}.
2. Drug release from MCG is associated with the chewing behaviour of individuals; the frequency, intensity and duration of chewing are variable and inconsistency may result in the treatment of the patient^{1,4,5,9,49-53}.
3. Repeated chewing can lead to jaw fatigue in geriatrics, and over-swallowing of saliva with the drug can lead to gastrointestinal discomfort or irritation of the mouth^{1,4,5,9,11}.
4. Most APIs have a bitter, metallic taste or unpleasant smell; it can be quite challenging in taste masking. Poor taste masking can lower patient compliance, particularly in paediatric groups^{49,50,53-57,63-65,69,70}.
5. Medicated chewing gum can be unsuitable for patients with severe dental problems, temporomandibular joint disorders or chewing difficulty^{1,4,5,9,11}.

Active pharmaceutical ingredients in medicated chewing gum

Caffeine

Caffeine (1,3,7-trimethylxanthine) is a natural alkaloid found in plant species, especially *Coffea arabica* and *Camellia sinensis*, and has long been used globally in drinks like coffee and tea^{18,25}. It is among the most popular psychoactive drugs in the world, and its pharmacological applicability goes far beyond usual usage^{18,21,22}. Caffeine acts by competitive antagonism of adenosine receptors, mainly A1 and A2A receptors^{18,26,27}. Caffeine blocks these receptors and causes neuronal excitation and the release of important neurotransmitters such as dopamine and norepinephrine, which elevate the heart rate and respiratory rate^{19,21-24}. Caffeine has well-documented positive effects on alertness, cognitive performance, mood elevation, and physical endurance, and at the same time, it decreases the perception of fatigue. As a stimulant, it is used in some sporting situations, and caffeine has been used clinically as an adjuvant analgesic to enhance the action of traditional pain relief medications. It is also mentioned in the treatment of migraine and excessive drowsiness^{21,22,25}.

The regulatory advice regarding the safe dosage of caffeine regards any amount up to 400 mg per day as a safe dose for healthy adults. The tolerability of caffeine is variable depending upon age, body weight, and physiological characteristics²³⁻²⁵. Children are suggested to have lower thresholds, as caffeine intake should be treated with more

care in these cases^{23,24}. Caffeine is a good match with medicated chewing gum in terms of delivery. It has a favourable buccal absorption profile with a rapid systemic entry that does not go through hepatic first-pass metabolism, leading to a faster onset of action, increased bioavailability, and enhanced patient compliance as compared to conventional oral dosage forms like tablets or pills^{3-5,20,28}.

Clove oil

Clove oil, extracted from the dried flower buds of *Syzygium aromaticum* (family: Myrtaceae), is a widely known chemical agent with a wide range of uses in traditional and modern medicine^{39,40}. It is native to the Maluku Islands of Indonesia and is extensively grown in tropical areas as a spice^{32,39}. The major components of the essential oil are eugenol, a phenolic compound which forms about 70–85% of its total composition, and some minor components including eugenyl acetate and caryophyllene^{30,32,39-42}. Eugenol is mainly responsible for the typical smell, cooling sensation, and pharmacological effects of clove oil^{29,30,32}. It exhibits strong analgesic, potent antimicrobial, and anti-inflammatory effects and has found great usefulness in oral and dental medicine^{32,33,39-41}. It is also used to treat dental pain, gingivitis, and periodontal diseases^{29,30,33,35,39,40,42}.

Eugenol is said to produce its analgesic effect due to its capacity to suppress the production of prostaglandins through the inhibition of cyclooxygenase (COX) pathways, which suppresses nociceptive signalling^{29,33}. Moreover, eugenol regulates voltage-gated channels, such as sodium and calcium channels, which play an important role in transmitting pain³³. Other mechanisms that reduce the inflammatory effects include the inhibition of inflammatory cytokines like tumour necrosis factor-alpha (TNF-alpha) and interleukins^{31,32,40}. From an antimicrobial perspective, clove oil exhibits broad-spectrum activity against Gram-positive and Gram-negative bacteria, as well as various fungal species^{30,31,35-38,43-45}. The process includes breaking the cell membranes of microbes, making them more permeable, and finally, releasing intracellular components, which results in cell death^{29,31,34-36,48}.

These characteristics play a major role in ensuring its success in keeping the mouth clean and avoiding colonisation by microbes^{31,35,36,43-45}. Moreover, due to the lipophilic properties of clove oil, it is more likely to penetrate the oral mucosa and be used to deliver drugs in the local area. This property, coupled with its strong biological activity, makes clove oil a perfect choice to be incorporated into more sophisticated drug delivery systems like medicated chewing gums, whereby sustained delivery and longer therapeutic performance in the oral cavity is preferable²⁹⁻⁴⁹.

Rationale for combination of caffeine and clove oil (potential synergistic action)

The combination of caffeine and clove oil in a medicated chewing gum represents a unique and strategic approach that may provide complementary pharmacological benefits through both systemic and local mechanisms of drug action^{18-31,33,49-57}. Medicated chewing gum is particularly a very suitable mobile drug delivery system which allows prolonged contact with oral mucosa while simultaneously facilitating rapid buccal absorption of suitable drugs^{3-17,49-57}. Consequently, caffeine may be rapidly absorbed into systemic circulation to provide central nervous system stimulation by increased neuronal activity due to enhanced release of neurotransmitters such as dopamine and norepinephrine¹⁸⁻²⁸. These actions improve alertness, concentration, mood and reduce fatigue¹⁹⁻²⁷. Additionally, caffeine is used as adjuvant analgesic in some pain medications^{21,22,25,26}. In contrast, the chief constituent of clove oil, eugenol, exhibits its effects such as analgesic, anti-inflammatory and broad-spectrum antimicrobial activities in the oral cavity²⁹⁻⁴⁵ by inhibiting cyclooxygenase-mediated prostaglandin synthesis, inhibitory action on voltage-gated sodium and calcium channels involved in pain transmission, suppressing inflammatory cytokines, and disrupting microbial cell membranes^{31-38,40,48}. Thus, the two active ingredients possess distinct yet complementary pharmacological profiles^{18-31,33-49,51-57}.

A potential synergistic advantage of this combination in medicated chewing gum lies in its ability to promote cognitive performance while maintaining oral health^{5,49-57}. The caffeine may enhance mental alertness, athletic activity and reduce fatigue¹⁹⁻²⁴, whereas clove may help alleviate minor oral discomfort, reduce microbial load, and suppress pain and inflammation in the oral cavity. Such dual-action functionality positions it as a suitable formulation for individuals requiring sustained mental performance, including students, healthcare professionals, drivers, military personnel, and night shift workers, who may also benefit from improved oral hygiene during prolonged working hours^{18-28,29-49}.

The medicated chewing gum dosage form may further enhance the therapeutic potential of the combination^{3-17,49-57}. Mastication stimulates salivary secretion, improving the distribution of lipophilic clove oil throughout the oral cavity

and supporting antimicrobial and anti-inflammatory activity with a cooling sensation²⁹⁻³⁶. Simultaneously, buccal absorption of caffeine partially bypasses hepatic first-pass metabolism, allowing faster systemic availability and more rapid onset of stimulant effects compared to conventional oral dosage forms^{3,13-20,28}. Thus, this combination may enhance patient outcomes and treatment adherence^{4,5, 20,49-57, 85-90}.

Potential applications of caffeine-clove oil medicated chewing gum

1. **Mental Alertness and Cognitive Performance Enhancement:** This combination may serve as a rapid cognitive enhancer for improving alertness, vigilance, attention, reaction time and cognitive performance. It may be beneficial for students, shift workers, drivers, pilots, military personnel and healthcare workers¹⁸⁻²⁸.
2. **Athletic Performance Enhancement and Management of Fatigue:** Caffeine also promotes increased heart rate and increased breathing volume, and alters the perception of fatigue, which may be useful for persons in prolonged sporting events, exercise and other exhaustive physical activities¹⁸⁻²⁷.
3. **Oral Health Maintenance:** Clove oil possesses broad-spectrum antimicrobial activity against oral pathogens together with anti-inflammatory properties that may reduce microbial colonization, plaque formation, gingival inflammation and oral discomfort^{29-49, 85-90}.
4. **Relief from Minor Pain and Gingival Discomfort:** Eugenol provides a characteristic cooling sensation, inhibits prostaglandin synthesis and modulates voltage-gated sodium and calcium channels involved in nociceptive (pain) transmission^{29,30,33}. This formulation may provide temporary relief of minor toothache, gingivitis, periodontal irritation or discomfort associated with minor dental procedures^{30,33,35,39,40}.
5. **Travel Convenience:** This combination may be useful during travelling, examinations, field work and outdoor activities, or emergency situations where drinking water is unavailable. Medicated chewing gum offers a portable, mobile, non-invasive dosage form which can be withdrawn at any time without any invasive procedures, making it suitable for on-the-go administration^{1-9, 49-57}.
6. **Functional Pharmaceutical and Nutraceutical Product:** The proposed formulation aligns with current demands for patient-friendly dosage forms that combine therapeutic efficacy with improved convenience^{4, 5, 9, 49-57}.

Marketed Medicated Chewing Products

There are numerous medicated chewing gum (MCG) products that have been commercialized worldwide, and these formulations contain a wide range of active pharmaceutical ingredients^{4,5,8,9,49-57}. The available marketed medicated chewing gums primarily contain only a single active pharmaceutical ingredient intended for either local action or systemic therapy^{4,5,49-57,92,93}. To the best of our knowledge, no commercially marketed medicated chewing gum with the combined benefits of caffeine and clove oil as a dual-action product has been identified in the published literature or currently available commercial products. Representative marketed medicated chewing gum products are summarized in Table 1^{4, 5, 9, 49-57,92,93}.

Table 1. Marketed Medicated Chewing Gum Products

Marketed Product	Active Ingredient	Therapeutic Indication
Aspergum®	Aspirin (Acetylsalicylic acid)	Pain relief, headache, minor musculoskeletal pain
Fluogum®	Sodium fluoride	Prevention of dental caries
Fluorette®	Sodium fluoride	Dental caries prophylaxis
Orbit White®	Xylitol	Oral hygiene, plaque reduction, enamel remineralization
Happydent White®	Xylitol	Oral hygiene and tooth whitening support
Trident White®	Xylitol	Tooth whitening and oral care
Recaldent® gum	CPP-ACP (Casein phosphopeptide-amorphous calcium phosphate)	Enamel remineralization and caries prevention
Travvel Gum®	Dimenhydrinate	Motion sickness and nausea
Nicorette®	Nicotine	Smoking cessation

NiQuitin CQ®	Nicotine	Smoking cessation
Hexit®	Chlorhexidine	Gingivitis and periodontal infections
VitaFlo CHX®	Chlorhexidine	Dental plaque control and oral infections
Advanced®	Chlorhexidine	Oral antimicrobial therapy
Stay Alert®	Caffeine	Alertness and fatigue reduction
Endekay®	Vitamin C	Nutritional supplementation
Zoft Virility Gum®	Herbal actives	Male sexual wellness supplement
Zoft Stress Gum®	Herbal actives	Stress management
Chew Away® Gum	Chromium, Guarana and other weight-management ingredients	Appetite suppression and weight management
Slim N Trim®	Chromium, Caffeine and herbal ingredients	Weight management and energy support

Ingredients in medicated chewing gum:

The medicated chewing gum is a mixture of both water-insoluble and water-soluble components. The gum base forms the insoluble matrix that provides elasticity, chewability and structural integrity, and the water-soluble phase contains ingredients that improve taste, texture, flavour and overall performance of the formulation^{4,5,49,76,82}. In addition, active pharmaceutical ingredients (APIs) and functional excipients are incorporated to the chewing gum to achieve the desired therapeutic effect while maintaining product quality^{49-57,76-83}. The selection and optimisation of these components is critical for ensuring uniform drug distribution, acceptable organoleptic properties and formulation stability. The components of medicated chewing gum are summarised in Table 2^{4, 5, 49-57, 76-83}.

Table 2. Major Ingredients of Medicated Chewing Gum and Their Functions

Component	Subcategory	Typical Quantity (% w/w)	Function	Examples
Gum Base (Water-Insoluble Phase)	Elastomers	10–25%	Provide elasticity and resilience, allowing repeated chewing without fragmentation.	Natural rubber (latex), chicle, jelutong, polyisobutylene, isobutylene-isoprene copolymer
	Plasticizers	2–8%	Improve cohesiveness, reduce rigidity, and enhance softness and flexibility.	Glycerol resin esters, pentaerythritol resin esters, terpene resin esters, hydrogenated rosin esters
	Resins	5–15%	Provide structural integrity and chewiness.	Ester gum, terpene resins, polyvinyl acetate, coumarone-indene resins, wood rosin
	Fats and Oils	1–5%	Improve softness, lubrication, and mouthfeel.	Stearic acid, palmitic acid, oleic acid, vegetable oil, cocoa butter
	Fillers/Texturizers	5–25%	Improve texture, bulk, stability, handling, and reduce stickiness.	Talc, calcium carbonate, magnesium carbonate, titanium dioxide, dicalcium phosphate
Water-Soluble Phase	Bulk Sweeteners	20–60%	Improve taste and patient acceptability while providing bulk.	Sucrose, dextrose, sorbitol, mannitol, xylitol

	High-Intensity Sweeteners	0.05–1%	Provide sweetness with minimal caloric contribution.	Aspartame, sucralose, saccharin
	Flavouring Agents	0.5–3%	Enhance taste, freshness, and patient compliance.	Peppermint oil, spearmint oil, citrus oil, clove oil, essential oils
	Softeners	1–5%	Retain moisture and maintain a soft chewing texture.	Glycerine, lecithin, monoglycerides, diglycerides, tallow, lard, fatty acids
	Emulsifiers	0.5–3%	Promote uniform mixing of hydrophilic and lipophilic components and improve formulation stability.	Lecithin, polysorbates, sorbitan esters, glycerol monostearate
	Colourants and Whiteners	0.01–2%	Improve product appearance and brand identity.	FD&C dyes, natural plant extracts, titanium dioxide
	Antioxidants	0.01–0.5%	Protect formulation components from oxidative degradation and extend shelf life.	Butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), tocopherol, ascorbic acid, propyl gallate
	Bulking Agents	5–20%	Increase bulk in sugar-free or low-calorie formulations without significantly increasing caloric value.	Polydextrose, inulin, oligofructose, guar gum hydrolysate, indigestible dextrin
Coating materials	Film/Sugar coating	2-10%	Improve appearance, taste, masking, moisture protection, and stability	Xylitol, sorbitol, shellac, HPMC, waxes
Active Pharmaceutical Ingredient (API)	Therapeutic Agent	0.1–20%*	Provides the intended pharmacological effect. APIs may be incorporated into the gum base, coating, or both.	Nicotine, caffeine, clove oil (eugenol), aspirin, dimenhydrinate

Factors affecting release of drugs

The following factors influence the release of drugs from MCG:

1. Saliva flow rate, volume and flux: Mastication triggers the autonomic nervous system and significantly increases the volume of saliva produced, which has a direct influence on drug dissolution^{10-12,85}. According to the Noyes-Whitney equation, an increase in saliva production is also associated with better diffusion of water-soluble drugs such as caffeine^{20, 49-55, 67}.

2. Chewing parameters (Rate, duration and intensity): The chewing behaviour of an individual also influences the breakdown of the chewing gum base and the release of the drug in the mouth cavity^{1,4,10,11}. The rate of chewing dictates the mechanical stress applied to the gum matrix, and intensive mastication increases the surface area exposure of the gum base to saliva, leading to the diffusion of the drug into the oral cavity^{49-55,81}. The inter-individual differences in chewing behaviour should be considered during the evaluation of MCG release; typically, it requires specialised chewing simulators to standardise these parameters and ensure reproducible release^{1, 4, 10, 11, 49-55, 81}.

3. Oral residence and Mucosal Contact time: The residence time of the formulation within the oral cavity will determine the duration of exposure to the buccal and sublingual mucosa^{3,13-17}. A prolonged time of mucosal contact of the drug in the mouth cavity will influence absorption locally. Generally, a longer time of contact improves the

mucosal permeation of clove oil, which is an antimicrobial, anti-inflammatory and analgesic agent²⁹⁻⁴².

4. Formulation Factors: Drug release is strongly influenced by the composition of the gum base, excipients and their physicochemical properties^{49-57,76-83}. Hydrophilic matrices promote caffeine release by accelerating water penetration into the gum base, rapidly channelling out hydrophilic drugs like caffeine. The lipophilic gum base promotes the release of clove oil via strong hydrophobic interactions with hydrophobic resins within the gum base^{29-42,49-57}. For stabilising volatile ingredients such as clove oil, advanced methods such as cyclodextrin inclusion complexation, microencapsulation, nano-emulsions or complexation can be used to achieve controlled biphasic release⁵⁹⁻⁷⁵.

5. Inter-Individual Variability: Drug release can also vary due to the physiological differences between individuals^{10-17,49-55}. The diminished level of salivary flow in older people might slow down the rate of drug absorption; variations in salivary pH and enzymatic activity can also influence absorption^{10-12,85}. Inter-individual variability should be taken into account when designing the formulation and clinical trials to obtain consistent therapeutic results⁴⁹⁻⁵⁵.

6. Drug Solubility in Water: The aqueous (water) solubility of drugs in saliva will influence the time taken for onset of drug action^{20,49-57,67}. Caffeine will be released quickly due to its hydrophilic properties^{20,28}. Clove oil has poor water solubility, and advanced methods such as emulsification and inclusion complexation may be used to stabilise the drug⁵⁹⁻⁷⁵.

Manufacturing methods

Medicated chewing gum can be prepared in a variety of ways, depending on the physicochemical properties of the active ingredients (e.g., caffeine and clove oil), the profile of release required, and the mass scalability requirements.

1. Conventional (Traditional) Method

In the traditional method, the base of the gum is first softened or melted in a high-temperature kettle mixer^{1,2,4,49,53}. This is subsequently succeeded by the incorporation of sweeteners, syrups, flavouring agents, active pharmaceutical ingredients (APIs), and other excipients in a well-monitored sequence⁷⁶⁻⁷⁸. It is then rolled in a series of rollers to form a thin sheet/ribbon of this homogeneous mass. To prevent sticking, a fine coating is applied in the form of powdered sugar or sugar substitutes to make it palatable^{49,53}. The material is conditioned at regulated temperature and humidity (not exceeding 48 hours on average) so that it can set correctly and is then cut in order to get the necessary shapes and sizes⁷⁶⁻⁷⁸.

Advantages:

- Established and simple process that can be used in large-scale production^{1,4,49,53}.
- Disperses caffeine well in the gum^{4,49,53}.
- Can be used with traditional flavour systems such as clove oil^{4,49,53}.

Limitations:

- High processing temperatures could cause volatilization or degradation of clove oil (eugenol)^{49,50,53}.
- Diffusion: Viscous mass, which causes the inability to attain homogeneous distribution of the drug, and hence dose accuracy^{49,50,53}.
- Incompatible with pharmaceutical-grade accuracy and thermolabile actives^{49,50,53}.

2. Cooling, Grinding, and Tableting Process

This technique was invented to settle the shortcomings of thermal processing^{49,50,53}. To render the gum base brittle, it is cooled to very low temperatures (typically -15°C or below)⁷⁶⁻⁷⁸. The solid mass is then milled to fine particles via cryogenic processes with solid carbon dioxide and anti-caking agents such as silicon dioxide to avoid agglomeration^{49,50,53,76-78}. Maltodextrin or phosphates as aids can be utilised to facilitate the process. Mixers (sigma mills or high-shear mixers) are then used to mix the powdered gum with excipients (binders, lubricants, sweeteners, and APIs). Fluidised bed reactors can also be used to create granules and coating. The mixture that is formed is pressed into tablets using traditional tableting machinery^{49,50,53,76-78}.

Advantages:

- Can be used with thermolabile and volatile substances like clove oil^{49,50,53}.
- Provides better control over the dose^{49,50,53}.
- Gives a less crispy texture and better mouthfeel^{49,50}.

Limitations:

- Needs special equipment (cryogenic grinding systems)^{49,50}.
- Strict temperature and humidity control is necessary during processing^{49,50}.
- Certain grinding aids may react incompatibly with certain APIs, e.g., acidic drugs^{49,50}.

3. Direct Compression Method

The direct compression technique makes use of ready-to-use, free-flowing, and co-processed gum bases like Pharmagum® or Health in Gum^{49,50,53}. These contain polyols (e.g. sorbitol, xylitol), gum base, plasticizers, and anti-caking agents. It is made in the same fashion as a tablet-making process where APIs such as caffeine and clove oil (typically already encased) are combined with the compressible base and pressed directly into gum tablets using regular tablet compression presses. This is done in ambient conditions and does not require any heat or complicated pre-processing^{49,76-78}.

Advantages:

- No heat is needed and therefore it can be used well in volatile clove oil and thermosensitive ingredients^{49,50,53}.
- Clean, fast, and inexpensive production process^{49,50,53}.
- Standardised dosage and accelerated drug absorption^{49,50,53}.

Limitations:

- Traditional gums can be softer than the resulting gum, which may be more elastic^{49,50}.
- Lack of chewability or crumbling potential^{49,50,53}.
- Should be optimised to balance texture and drug release^{49,50,53}.

Evaluation of medicated chewing gum (mcg)

1. Weight Variation: The weight of medicated chewing gum is an important parameter to ensure the dose uniformity of the product. The generally acceptable pharmacopeial limit for weight variation in the European Pharmacopoeia and other regulatory guidelines is $\pm 5\%$ variation. The measurements are generally performed in controlled environmental conditions having $25 \pm 2^\circ\text{C}$ and $50 \pm 5\%$ relative humidity using calibrated analytical balances^{6,49,50,76-79}.

2. Hardness: The mechanical strength of the medicated chewing gum must be optimum for proper handling during processing and patient acceptability. Hardness is commonly evaluated by using a Monsanto hardness tester. This evaluation ensures a balance between structural integrity and chewability of the gum. Thus, appropriate and consistent hardness of the product ensures a good user experience^{49,50,53,76-78}.

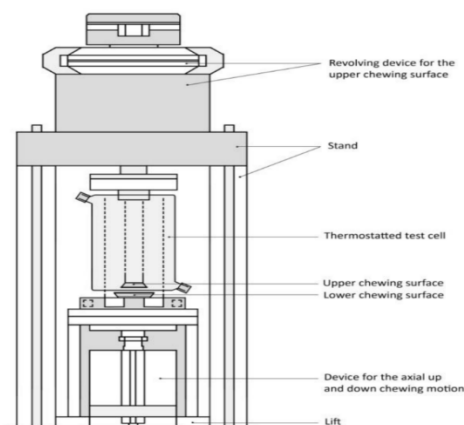
3. Adhesion test: The adhesion or stickiness is usually assessed by repeated impacting of the gum base on a smooth surface with a Teflon-coated hammer under controlled environmental conditions (25°C and $50\% \text{ RH}$). The extent of material adhering to the hammer will be measured after a defined time period. In general, reduced adhesiveness of the gum is preferred, which indicates good compatibility between the gum base and excipients. Reduced stickiness improves patient compliance and handling during manufacturing^{49,50,53}.

4. Organoleptic evaluation: The organoleptic evaluation is particularly important for medicated chewing gums, as these properties strongly influence patient compliance. The sensory evaluation is conducted for colour, odour, taste, texture and overall appearance of the product. This test is often performed by human volunteers. The softness, elasticity and cohesiveness of the product are rated by individuals. Overall, a well-formulated chewing gum ensures good organoleptic characteristics^{4,49,50,53-55}.

5. Elasticity: It is a key mechanical property that influences chewability and drug release behaviour. It is commonly evaluated using a texture analyser (e.g., CT3 Texture Analyzer) under controlled conditions. The gum samples are subjected to tensile stress until breakage, and elongation and break force are recorded^{49,50,53,54,55}.

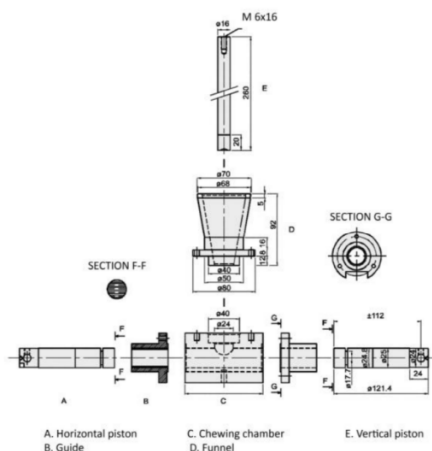
6. Content Uniformity: Content uniformity ensures that each unit of the product will deliver a consistent and accurate dose of the drug. Analytical techniques such as UV-Visible spectroscopy (e.g., λ_{max} at 273 nm for caffeine) are commonly used with appropriate sample preparation in a suitable buffer like pH 6.8 phosphate buffer. The pharmacopeial limit for variation is generally within the range of 85-115%. Low variability in drug content indicates homogeneous distribution of the drug within the gum matrix^{28,49,50,76-79}.

7. In-Vitro drug release studies: These studies are conducted using a specialized chewing apparatus as described in the European Pharmacopoeia (Ph. Eur. 2.9.25). The experimental conditions are a temperature of $37^{\circ} \pm 0.5^{\circ}\text{C}$, 20-50 mL of phosphate buffer at pH 6.8 in a chewing chamber at a kinetic torsion angle (180° twist) and a controlled chewing frequency of 60 strokes per minute for simulating physiological conditions. Thus, in vitro drug release studies are the only official test mentioned in the European Pharmacopoeia for the characterisation of the release profile of active ingredients from medicated chewing gums^{6,49-53,81}.



(Figure no. 1)

(Figure no. 1. Schematic diagram of chewing apparatus)



(Figure no. 2)

(Figure no. 2. Schematic diagram of single-module chewing gum apparatus for in-vitro drug release studies.)

8. Microbial Inhibition Studies: The antimicrobial potential of medicated chewing gum is evaluated by using standard microbial techniques such as agar diffusion assays. Test organisms such as *Streptococcus mutans*, relevant to oral health, will be employed. Studies are conducted in controlled conditions ($37 \pm 1^{\circ}\text{C}$, neutral pH) and the zone of microbial inhibition will be observed; this will be attributed to the presence of clove oil (eugenol) in the formulation^{30-48,58}.

9. Stability Studies: The stability studies are performed in accordance with the ICH guidelines. The samples are stored in a stability chamber under controlled conditions (e.g., $30 \pm 2^{\circ}\text{C}$ and $65 \pm 5\% \text{RH}$) and assessed at defined time intervals (e.g., 7, 15, 30 days, and up to 3 months). Parameters such as colour, taste, drug content, microbial load and drug release are monitored. A formulation demonstrating minimal changes in physiological properties under recommended storage conditions indicates a well-optimised formulation^{49,50,76-80}.

Current challenges in formulation of mcg

Developing a medicated chewing gum (MCG) containing both caffeine and clove oil appears to be a simple delivery system, but it presents significant formulation challenges⁴⁹⁻⁵³. This chewing gum involves combining actives with contrasting physicochemical properties. Caffeine is hydrophilic, chemically stable, and predictable in behaviour^{20,28}, whereas clove oil, rich in eugenol, is lipophilic, volatile, and possesses a strong aroma and taste^{30,32,39-42}. Achieving compatibility between these components while maintaining stability, efficacy, and patient acceptability requires well-designed formulation strategies and controlled manufacturing processes^{49-53,59-75,76-83}.

1. Thermal sensitivity and volatilisation of clove oil: A primary obstacle during industrial production is the thermal mismatch between various components of the formulation⁴⁹⁻⁵³. Conventional manufacturing utilises high-shear hot-melt extrusion or compounding, which requires elevated temperatures typically between 60°C – 80°C for softening the synthetic elastomers and resins of the gum base⁷⁶⁻⁷⁸. While caffeine remains entirely stable at these temperatures, clove oil and its chemical constituents like sesquiterpenes (beta-caryophyllene) exhibit low boiling points and high vapour pressures. This may lead to significant API loss via evaporation during the blending phase^{39-42,49-53}. So, in order to mitigate this, the formulation must employ strict temperature-controlled cooling steps, post-extrusion dosing, alternative approaches, and the use of organic oil-fat based solvents & emulsifiers which stabilise the clove oil^{59-75,82,83}.

2. Rheological inhomogeneity and phase dispersion: Achieving a homogenous molecular dispersion of a solid hydrophilic drug (caffeine) and a liquid lipophilic drug (clove oil) within a viscoelastic polymeric matrix can be difficult⁴⁹⁻

^{53,76-83}. Without optimal surfactant addition or particle size reduction, it may lead to localised crystalline agglomerates within the matrix, leading to phase separation. The clove oil acts as an unintentional plasticiser; it penetrates the rubbery gum base and alters its glass transition temperature, reducing elasticity and making the matrix excessively soft or sticky during processing^{49-53,59-75,76-83}.

3. Impurities and regulatory compliance hurdles: Organic solvents may be used for incorporating poorly water-soluble components in the formulation, which represents further concerns (⁵⁹⁻⁷⁵). Such solvents may improve drug dispersion, but their removal is difficult and poses a safety and regulatory risk (^{49-53,76-83}).

4. Moisture control: It is also a critical parameter which may influence the mechanical properties of gum, and excess moisture increases stickiness and complicates handling and manufacturing^{49,50,53,76-83}. Residual water or excessive moisture within the formulation may alter the mechanical properties of the elastomer base and accelerate plasticization, leading to extreme adhesion along the walls of the hopper and tableting punches^{49,50,53,64}. So, an optimal moisture level is recommended to improve grinding and reduce adhesion. Generally, to maintain the structural integrity of the gum matrix, the total moisture level must be strictly controlled and kept below 2%. Maintaining this threshold is vital for cryogenic grinding or milling processes, as it prevents material deformation and facilitates smooth particle size reduction without clogging the processing machinery (^{49, 50, 53, 64, 76-83}).

Formulation strategies for caffeine-clove oil mcg

There are several strategies for the incorporation of two APIs with contrasting properties^{49-53, 59-75, 76-83}. Some of these are discussed below.

1. Thermal Fusion (Melting) Method: In this approach, the gum base is melted and blended with excipients and the drug. Caffeine can be added at an earlier stage due to its thermal stability^{20,28}, whereas clove oil is preferably added at a lower temperature in the final stages to minimize the loss of drug due to thermal degradation^{32,39-42}. This method requires precise temperature control to facilitate uniform dispersion and prevent flash-volatilization of eugenol^{49-53, 76-78}.

2. Polymeric Microencapsulation and Coacervation of Clove Oil: This technique may use polymer coating, spray drying, or coacervation to protect the clove oil from evaporation and degradation by forming a protective polymeric shell within the matrix and isolating the volatile clove oil^{42,63-66,71}. This micro-casing approach enhances stability, masks the pungent taste of eugenol, and enables controlled release by creating a physical barrier that drastically drops the vapour pressure of the essential oil, eliminating evaporation during processing and storage^{63-66,71}. Further, it prevents direct contact between the pungent eugenol and oral taste buds, providing a taste-masking effect, which makes it particularly suitable for dual-drug formulations^{42, 65, 71, 49-53}.

3. Emulsification and Nano-emulsion Carrier Systems: The incorporation of clove oil into a lipid-based nano-emulsion or self-emulsifying drug delivery system (SEDDS) by using biocompatible surfactants such as polysorbate-80 and transcutool may improve its dispersion within the gum matrix^{59-61,66}. It also increases the surface area, mucosal wetting, release profile, membrane permeability, bioavailability, and antimicrobial activity of the chewing gum against oral pathogens. This strategy is advantageous for targeted delivery systems^{66, 68, 71-75}.

4. Solid-State Adsorption onto Micro-Porous Carriers: Liquid clove oil can be adsorbed into a processable solid-state matrix of high surface area micro-porous adsorbent carriers such as synthetic amorphous silica (e.g., Aeroperl®, Syloid®), microcrystalline cellulose, or dibasic calcium phosphate, which preserves the oil in a free-flowing state^{49,50,53,76-83}. This stabilizes the liquid phase and prevents oil bleeding under mechanical stress to improve handling and facilitate incorporation into direct-compression based systems at room temperature without the risk of thermal degradation^{49, 50, 53, 76-83}.

5. Layered or Dual-Phase Design: This potential formulation strategy allows separation of various APIs into different layers within the gum matrix⁴⁹⁻⁵³. Caffeine may be positioned in an outer, rapidly dissolving hydrophilic sugar/polyol coat for achieving rapid saliva-driven release of the stimulant into the buccal systemic circulation^{20,28,67}. While the thermally sensitive clove oil may be locked in an internal, hydrophobic elastomer-resin gum core to provide a secure environment and sustained local action, thereby providing an overall effective therapeutic outcome for the patient^{59,60,76-78}.

6. Use of Hydrophilic and Lipophilic Release Modifiers: The release rate of both components can be tuned by the addition of suitable release modifiers. Incorporation of hydrophilic polymers such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) into the matrix creates microscopic aqueous channels upon hydration in the oral cavity; this rapidly accelerates water influx, speeding up the process of dissolution and release kinetics of caffeine^{67,69,70}. Similarly, adding hydrophobic excipients or high-molecular-weight waxes and resins (carnauba wax, glyceryl behenate)

helps localise the lipophilic diffusion of clove oil in the oral cavity. This enables the scope of linear, sustained local release with modulation of drug release kinetics in accordance with therapeutic requirements^{49-53,67,69-75,76-83}.

7. Taste Masking Strategies: Caffeine exhibits a lingering bitterness, while eugenol presents a sharp, pungent, and burning gustatory profile^{25,32,39-42}. To ensure palatability and compliance, the formulation must integrate non-cariogenic polyol bulk sweeteners such as xylitol and sorbitol with suitable flavouring agents to mask the bitter caffeine and pungent clove oil^{65,82}. Xylitol undergoes endothermic dissolution, generating a distinct cooling sensation that works synergistically with the natural numbing effect of eugenol. This resulting sensory effect successfully desensitises local gustatory receptors and effectively masks any unintended residual bitterness. This will significantly enhance palatability and compliance^{39-42, 69-71, 84-90}.

TABLE 3. The following table categorizes the specialized formulation approaches required to address the distinct biopharmaceutical limitations of the dual-API system:

Advanced Strategy	Target Phenomenon / Objective	Physicochemical and Biopharmaceutical Mechanism
Cyclodextrin Inclusion Complexation	Taste Masking + Molecular Stabilization	Encapsulates hydrophobic eugenol molecules within a hydrophilic cavity; suppresses volatility and masks sharp gustatory notes.
Polymeric Microencapsulation	Volatility Mitigation & Taste Abatement	Creates physical core-shell microstructures; shields volatile terpenes from ambient oxidation and thermal processing degradation.
Nano-Emulsion Matrices	Uniform Phase Homogeneity	Breaks down the liquid oil phase into sub-micron droplets; maximizes intraoral surface area and boosts local tissue penetration.
Micro-Porous Adsorbent Carriers	Solid-State Oil Stabilization	Capillary retention of liquid oils within inert solid frameworks; converts liquids into compressible powders to prevent matrix bleeding.
Solid Lipid Microparticles (SLMs)	Linearized Sustained Local Release	Disperses the API within a solid lipid crystalline core; controls erosion and diffusion kinetics during extended mastication.

Future prospects of caffeine–clove oil medicated chewing gum

Caffeine–clove oil medicated chewing gum (MCG) represents a promising dual-drug delivery system capable of delivering both local and systemic therapeutic effects^{4,5}. The rapid buccal absorption of caffeine, together with the analgesic and anti-inflammatory properties of clove oil, provides a strong scientific rationale for combining these agents in a single dosage form²⁰⁻³³. This dual drug delivery system approach may offer synergistic therapeutic benefits by providing rapid CNS stimulation and adjuvant analgesia from caffeine combined with the prolonged therapeutic action of clove oil⁴⁹⁻⁵⁸.

Despite this potential, the development and its broader application depend on challenges related to stability, volatility and controlled release^{49-53,59-75}. The variability in individual chewing behaviour, salivary flow and physiological differences complicates the performance of such a product^{10-17,85}. Current advancements in formulation technology provide solutions to address existing limitations. Approaches such as microencapsulation, nano-emulsions and complexation systems have shown potential in enhancing taste and stability and enable controlled release of drugs⁵⁹⁻⁷⁵. The design of biphasic delivery systems facilitates rapid release of caffeine followed by sustained release of clove oil, offering a strategic advantage in the achievement of both immediate and prolonged therapeutic effects⁴⁹⁻⁷⁵.

Since this novel combination has not been extensively investigated, at present, the limited availability of clinical data highlights the need for the development of parameters for a systematic investigation⁴⁹⁻⁵⁸. Future research should focus on optimizing formulation parameters, establishing standard evaluation methods and conducting *in-vitro* studies, *in-vivo* studies and well-designed trials and clinical studies to confirm the safety, efficacy and reproducibility^{6, 49-80}.

Further progress can be expected through the development of controlled-release systems and nanocarrier-based systems to refine the release kinetics and bioavailability of drugs^{2,8}. The use of biodegradable gum bases, sugar-free gum bases and compatible excipients may also improve patient acceptability and compliance^{2,8,49-57,59-80}. Additionally, personalised dosing therapies may also enhance treatment outcomes, supporting the future clinical potential and commercialisation of this delivery system⁴⁹⁻⁸⁰.

Conclusion

Thus, it can be concluded that the medicated chewing gum is a patient-friendly, mobile drug delivery platform that can be used to deliver both local and systemic therapeutic agents. This dual drug delivery system may be used to deliver a quick-acting CNS stimulant such as caffeine along with clove oil, which acts as an analgesic and antimicrobial agent in the oral cavity. This complementary pharmacological profile highlights the potential for a variety of uses, such as cognitive improvement and oral care. It is a great alternative compared to conventional dosage forms and makes it a valuable innovation in pharmaceutical and nutraceutical applications.

Conflict of interest:

The authors declare that they have no conflict of interest.

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