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FORMULATION AND EVALUATION OF CHEWING GUM FOR RAPID RELIEF FROM MOTION SICKNESS

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INTRODUCTION

1.1 Overview of Motion Sickness

Motion sickness, also known as kinetosis, is a physiological condition that arises when there is a conflict between the visually perceived movement and the vestibular system's sense of motion.[1] This conflict occurs when the brain receives mismatched sensory inputs from different organs responsible for balance and spatial orientation. Typically, this condition manifests during activities that involve passive movement, such as travel in cars, boats, airplanes, or amusement rides, where the sensory systems are exposed to continuous changes in velocity and direction.[2]

The clinical presentation of motion sickness is diverse and usually begins with early signs such as dizziness, nausea, and yawning, which may progress to more pronounced symptoms like vomiting, pallor, cold sweating, salivation, and a general sense of discomfort or malaise.[3] The severity of symptoms may vary considerably among individuals, ranging from mild uneasiness to debilitating sickness that disrupts routine activities. Importantly, these symptoms tend to intensify with prolonged exposure to the causative motion stimuli, and in some cases, may persist for hours even after the motion has ceased.[4]

The underlying pathophysiology is primarily explained by the sensory mismatch theory, which states that motion sickness results from conflicting sensory information being processed by the central nervous system.[5] The brain receives simultaneous input from the visual system (eyes), the vestibular apparatus in the inner ear, and proprioceptive receptors in muscles and joints. For example, while a person is seated in a moving car, the vestibular system detects acceleration and deceleration, but if the eyes are fixed on a stationary interior object, they may signal an absence of motion. This discordance confuses the brain, triggering a cascade of neurological responses often mediated by the vestibular nuclei and vomiting center culminating in the characteristic symptoms of motion sickness.[6]

Epidemiologically, motion sickness affects a substantial portion of the population. Certain demographic groups are more prone to this condition, such as children between the ages of 2 and 12 years, women particularly during menstruation or pregnancy due to hormonal fluctuations and individuals who suffer from migraine disorders, likely because of heightened vestibular sensitivity.[7] Although motion sickness is generally not a lifethreatening disorder, its recurrent episodes can cause significant discomfort, impair daily functioning, and reduce the quality of life, particularly for individuals whose occupations or lifestyles require frequent travel, such as naval personnel, pilots, or longdistance commuters.[8]

Given the acute onset of symptoms and the demand for prompt symptom relief, therapeutic interventions for motion sickness must be designed to act quickly, be easy to administer, and produce minimal adverse effects.[9] While traditional oral medications like antihistamines and anticholinergics are effective, their onset of action may be delayed, and they can be associated with side effects such as drowsiness or dry mouth. Consequently,

alternative drug delivery systems such as medicated chewing gum are increasingly gaining attention. These systems offer advantages like faster onset of action due to buccal absorption, better patient compliance, and convenience of administration without the need for water, making them particularly suitable for travelers.[10]

1.1 Therapeutic Strategies for Motion Sickness

The management of motion sickness primarily focuses on either preventing the onset of symptoms or alleviating them rapidly once they appear. An effective therapeutic approach often requires early intervention, as delaying treatment can allow symptoms to intensify, thereby reducing the efficacy of therapeutic measures. Management strategies are generally divided into two broad categories: nonpharmacological approaches and pharmacological interventions. These strategies aim to restore harmony between the sensory systems visual, vestibular, and proprioceptive while simultaneously reducing central nervous system (CNS) excitability and the resultant autonomic responses that trigger symptoms.[11]

Nonpharmacological methods primarily emphasize behavioral and environmental modifications designed to minimize sensory conflict. These include maintaining a forwardfacing position, focusing on a stable horizon, choosing seating areas with minimal motion (e.g., near the wings in aircraft, midship in boats, or front seats in vehicles), and avoiding activities such as reading that increase visualvestibular discrepancies. Relaxation techniques, controlled breathing, and ensuring adequate ventilation to avoid unpleasant odors can also mitigate symptom onset.

Pharmacological interventions, on the other hand, target the neurochemical pathways implicated in motion sickness, such as cholinergic and histaminergic systems. Agents like antihistamines (dimenhydrinate, meclizine), anticholinergics (scopolamine), and in some cases sympathomimetics are employed to suppress vestibular input or modulate CNS responsiveness. These drugs can be administered via oral, transdermal, or alternative delivery systems, depending on the desired onset speed, duration of effect, and patient compliance.

The integration of both nonpharmacological and pharmacological strategies provides the most comprehensive control over motion sickness, especially for individuals who are highly susceptible or frequently exposed to motion stimuli.[11]

1.1.1 NonPharmacological Measures

Nonpharmacological management of motion sickness emphasizes preventive strategies and supportive interventions that aim to reduce sensory mismatch without the use of drugs. These measures are especially valuable for individuals who experience mild symptoms, those who cannot tolerate medications, or in situations where drug administration is not practical.

Behavioral Adjustments

Adopting appropriate seating and visual focus can substantially reduce the onset and severity of motion sickness. Sitting in a forwardfacing seat ensures that the body's orientation matches the direction of travel, minimizing vestibular stimulation. For example, in buses or cars, the front seats are generally more stable, while in boats, midship positions experience less pitch and roll. In aircraft, seats over the wings are optimal due to reduced turbulence. Maintaining a steady gaze on the horizon or a distant fixed point allows visual input to align with vestibular cues, thereby reducing sensory conflict. Conversely, activities such as reading or prolonged screen exposure should be avoided during travel, as these can intensify visualvestibular mismatch and exacerbate symptoms.[12]

Dietary Control

The type and timing of food intake before travel significantly influence motion sickness symptoms. Heavy, greasy, or spicy meals can increase gastrointestinal discomfort and enhance nausea during travel. Instead, consuming light, bland snacks such as crackers or toast is recommended. Maintaining adequate hydration is equally important, as dehydration can aggravate dizziness and malaise. Small sips of cool water or clear fluids during the journey can provide symptomatic relief. Caffeine and alcohol should be avoided, as they may contribute to dehydration and exacerbate symptoms.[13]

Controlled Breathing and Relaxation Techniques

Anxiety and anticipatory stress are known to worsen motion sickness by amplifying autonomic nervous system responses. Controlled breathing exercises such as slow, deep inhalation through the nose followed by gradual exhalation through the mouth can help stabilize the physiological stress response. Progressive muscle relaxation and mindfulnessbased techniques can also reduce the emotional and physical discomfort associated with motion sickness, improving overall tolerance to travel.[14]

Acupressure Bands

Acupressure wristbands, commonly worn over the P6 (Neiguan) point on the anterior forearm, are a popular nondrug intervention. Stimulation of this pressure point is believed to modulate vagal activity and reduce nausea and vomiting. These bands are inexpensive, noninvasive, and can be used safely by children, pregnant women, and individuals seeking an alternative to pharmacological treatments. Although clinical evidence is mixed, many users report subjective relief from symptoms.[15]

1.1.2 Pharmacological Interventions

Pharmacological management of motion sickness targets the neurochemical pathways involved in vestibular signal transmission and the emetic reflex. Multiple drug classes are employed, each acting on different neurotransmitter

systems to alleviate symptoms such as nausea, vomiting, vertigo, and dizziness.

Antihistamines (H1 receptor antagonists)
H1 receptor antagonists such as cinnarizine, cyclizine, dimenhydrinate, and meclizine are the most widely used agents in the prevention and treatment of motion sickness. Their primary mechanism involves blocking histamine H1 receptors in the vestibular nuclei and the vomiting center, thereby reducing histaminemediated excitation. In addition to antihistaminic activity, many of these agents possess mild anticholinergic and sedative properties, further contributing to symptom control. Their sedative effect, although sometimes undesirable, can provide comfort to patients during prolonged travel.[16]

Anticholinergics
Scopolamine (hyoscine hydrobromide) is a potent anticholinergic agent that inhibits cholinergic transmission between the vestibular apparatus and the vomiting center. By blocking muscarinic receptors in the central nervous system, it prevents the neural signaling that triggers nausea and vomiting. Scopolamine is particularly effective for longduration travel, and its transdermal patch formulation allows sustained drug release over 72 hours, improving compliance. However, side effects such as dry mouth, blurred vision, and drowsiness may limit its use in some individuals.[17]

Dopamine Antagonists
Dopaminergic pathways play a significant role in mediating nausea and vomiting through the chemoreceptor trigger zone (CTZ). Agents such as metoclopramide and prochlorperazine act as dopamine (D2) receptor antagonists, thereby blocking CTZ activation and reducing emesis. While effective, these agents are generally reserved for severe cases or when other medications are ineffective. Caution is warranted due to the potential for extrapyramidal side effects, especially with prolonged use or higher doses.[18]

Sympathomimetics
Agents such as ephedrine and amphetamines have been studied for motion sickness due to their central nervous system stimulant properties, which may counteract drowsiness and improve alertness. These drugs act by increasing the release of norepinephrine and dopamine, thereby modulating neural activity in the vestibular system. However, due to their side effect profile such as insomnia, hypertension, and potential for abuse sympathomimetics are rarely used as firstline agents in modern practice.[19]

1.1.3 Limitations of Conventional Therapies

Despite the availability of several pharmacological options, conventional oral dosage forms (e.g., tablets, capsules) have notable limitations in the management of motion sickness:

- **Delayed Onset of Action:** Oral medications must undergo gastrointestinal absorption and hepatic firstpass metabolism before reaching therapeutic plasma concentrations, which may delay symptom relief in acute motion sickness.[20]
- **Need for Water:** Oral solid dosage forms require water for swallowing, which may not be practical during active travel, especially in sudden symptom onset.
- **Swallowing Difficulties:** Nausea and vomiting often make swallowing difficult, thereby reducing patient compliance.
- **Poor Palatability or Sedation:** Many antihistamines have a bitter taste and cause sedation, which may be undesirable for individuals needing to remain alert during travel.

These limitations underscore the importance of developing alternative delivery systems that bypass firstpass metabolism, provide rapid drug absorption, and enhance patient compliance. Medicated chewing gum is one such innovative dosage form, offering faster onset, ease of administration, and greater patient acceptability in acute situations like motion sickness.[21]

1.2 Role of Cinnarizine in Treatment

Cinnarizine, a firstgeneration H1 antihistamine belonging to the diphenylmethylpiperazine group, is one of the most commonly prescribed agents for motion sickness due to its dual pharmacological properties.[22]

Mechanism of Action: Cinnarizine exerts its therapeutic effects through a combination of H1 receptor antagonism and calcium channel blockade. By blocking histamine H1 receptors in the vestibular nuclei and vomiting center, cinnarizine reduces histaminergic excitation, which is a key contributor to nausea and vertigo. Its calcium channel blocking property stabilizes the membranes of vestibular hair cells, decreasing the abnormal neuronal firing associated with motioninduced imbalance. Collectively, these actions reduce labyrinthine excitability and inhibit the transmission of abnormal sensory signals to the brainstem, thereby alleviating symptoms such as nausea, vomiting, vertigo, and dizziness.[23][24]

Pharmacokinetics and Limitations: Cinnarizine exhibits low aqueous solubility, which can limit its dissolution and absorption from the gastrointestinal tract. Additionally, it undergoes significant firstpass metabolism, resulting in reduced systemic bioavailability. As a consequence, oral administration may produce a delayed onset of action, which is not ideal in acute conditions requiring rapid relief. These pharmacokinetic limitations highlight the potential benefits of alternative formulations such as medicated chewing gum that can improve bioavailability by facilitating buccal absorption, bypassing firstpass metabolism, and providing a faster therapeutic effect.[25]

Moreover, the sedative effects of cinnarizine, while sometimes beneficial in reducing motionrelated anxiety, may also contribute to unwanted drowsiness, particularly when administered in higher doses.[26] Hence, there is a strong justification for exploring novel delivery systems that can offer localized absorption, bypass firstpass metabolism, and provide rapid therapeutic action.[27]

In this context, delivering cinnarizine through a medicated chewing gum offers distinct advantages. The buccal route ensures faster absorption, avoids hepatic metabolism, and allows better control over drug release. Additionally, the act of chewing stimulates salivation and enhances drug dissolution, improving both bioavailability and onset of action. Thus, cinnarizine is an ideal candidate for formulation into a chewing gum for the effective and convenient management of motion sickness.[28]

Table 1.1: Comparison of Commonly Used Drugs for Motion Sickness.

Drug Name	Drug Class	Mechanism of Action	Onset of Action	Duration of Action	Sedation	Route of Administration
Cinnarizine	H1 Antihistamine + Calcium Channel Blocker	Blocks histamine H1 receptors and vestibular calcium channels	Moderate (30–60 min)	4–6 hours	Mild	Oral (tablet), Buccal (gum)
Dimenhydrinate	Antihistamine	Anticholinergic and Antihistamine activity	Rapid (30 min)	4–6 hours	Moderate	Oral, IV
Metoclopramide	Dopamine Antagonist	Blocks D2 receptors in CTZ and GI tract	Moderate (30–60 min)	1–2 hours	Low	Oral, IV
Promethazine	Phenothiazine Antihistamine	H1 receptor blockade with antiemetic effect	Rapid (20–30 min)	4–6 hours	High	Oral, IV

1.3 Chewing Gum as a Drug Delivery System

Medicated chewing gum (MCG) is an innovative oral drug delivery platform designed to release active pharmaceutical ingredients (APIs) in the oral cavity for both local and systemic therapeutic effects. It combines the pharmacokinetic advantages of buccal drug delivery with the convenience and high patient compliance of a chewable dosage form, making it an attractive alternative to traditional oral medications.[29]

Unlike conventional solid dosage forms such as tablets and capsules, MCG does not require water for administration. This feature is particularly beneficial in conditions like motion sickness, where the onset of symptoms may be sudden, and immediate access to water might not be feasible. The convenience of administration at any time and place enhances patient adherence, especially during travel.[30]

The act of chewing serves a dual function in the drug delivery process. First, it increases salivary secretion, which facilitates the dissolution and dispersion of the API. Second, the resulting salivadrug mixture provides a direct pathway for drug absorption across the buccal mucosa. This buccal route allows the drug to bypass hepatic firstpass metabolism, thereby improving systemic bioavailability and leading to a more rapid onset of action compared to gastrointestinal absorption.[31]

The formulation of MCG requires careful selection of excipients to ensure optimal therapeutic and sensory properties. A gum base comprising elastomers, resins, waxes, and softeners serves as the structural matrix. The API is incorporated along with sweeteners, flavoring agents, and fillers to mask unpleasant taste and enhance patient acceptability. The physical characteristics of the gum base, such as softness, elasticity, and chewability, significantly influence drug release kinetics, stability, and patient preference.[32]

MCG has gained increasing acceptance as a pharmaceutical dosage form in recent years. Regulatory bodies such as the European Pharmacopoeia and the United States Pharmacopoeia have included monographs for medicated chewing gum, establishing standards for quality, safety, and efficacy.[33] Successful applications of MCG in therapeutics include nicotine gums for smoking cessation, xylitol gums for dental caries prevention, and formulations for analgesics, antacids, and systemic drugs.[34] In the context of motion sickness management, medicated chewing gum provides unique.

advantages

- Rapid onset of therapeutic effect due to buccal absorption.
- Sustained drug release through continuous mastication.
- Improved palatability with effective taste masking of bitter drugs.
- Noninvasive, patientfriendly administration without the need for water.
- Portability and discreet use during travel, enabling convenient symptom management.[35]

These advantages make medicated chewing gum an ideal delivery system for cinnarizine, potentially providing rapid relief from motion sickness while enhancing

patient compliance.[36]

1.4 Rationale of the Research

Motion sickness is an acute and episodic condition that demands prompt therapeutic intervention. While conventional oral dosage forms such as tablets and capsules remain effective in preventing or alleviating symptoms, they pose several practical challenges during realworld use. These include the necessity of water for administration, delayed onset of action due to gastrointestinal absorption and hepatic firstpass metabolism, and poor compliance, particularly in individuals already experiencing nausea or vomiting during travel.[37]

Cinnarizine, a firstgeneration antihistamine widely prescribed for motion sickness, is limited by poor aqueous solubility and low oral bioavailability. Conventional formulations frequently lead to variable absorption rates, delayed therapeutic onset, and inconsistent clinical outcomes. Furthermore, the sedative properties of cinnarizine may limit its usability in situations requiring higher doses or prolonged administration, as they can impair alertness and functional capacity.[38]

To address these limitations, the present research was conceptualized with the goal of developing an alternative delivery system that could:

- Achieve rapid onset of action to control symptoms effectively.
- Bypass firstpass metabolism for improved systemic availability.
- Enhance drug bioavailability and reduce variability in therapeutic outcomes.
- Provide superior patient compliance and convenience during travel or acute episodes.[39]

Medicated chewing gum was identified as the ideal delivery platform for this purpose. Its buccal absorption pathway bypasses hepatic metabolism, enabling a quicker rise in plasma drug levels. In addition, its ease of use without water, pleasant sensory characteristics, and portability make it particularly suitable for travelers. The chewing action also stimulates salivation, aiding in drug dissolution, improving absorption, and delivering faster symptom relief.[40]

The rationale for selecting cinnarizine in an MCG formulation lies in its therapeutic effectiveness for vestibular disorders combined with its pharmacokinetic challenges that can be addressed by buccal delivery. Developing a cinnarizine chewing gum not only aims to enhance drug absorption and onset of action but also responds to practical needs for a patientfriendly, effective solution for motion sickness. By optimizing this novel dosage form, the present research aspires to contribute a clinically valuable advancement in the management of kinetosis.[41]

1.5 Objectives of the Study

The primary aim of this research was to develop and evaluate a novel medicated chewing gum formulation containing cinnarizine for the effective and patientfriendly management of motion sickness. The formulation was intended to provide a rapid onset of action, improved bioavailability, and enhanced compliance, especially in travel situations where conventional dosage forms may be inconvenient.[42]

To achieve this goal, the following specific objectives were set:

1. To perform preformulation studies of cinnarizine, including the evaluation of physicochemical properties, drugexcipient compatibility using techniques such as FTIR or DSC, and solubility analysis to guide formulation development.
2. To design and formulate cinnarizine chewing gum using a suitable gum base, plasticizers, sweeteners, and flavoring agents by optimizing the process parameters to achieve a stable and palatable product.
3. To evaluate the prepared formulations for physical parameters such as weight variation, hardness, thickness, elasticity, and stickiness to ensure uniformity and mechanical stability during handling and use.
4. To determine the drug content and in vitro drug release profile from the chewing gum formulations and analyze the release kinetics to understand the mechanism of drug release.
5. To assess chewability, taste masking, and palatability of the chewing gum through sensory evaluation with a human volunteer panel to ensure acceptable organoleptic properties.
6. To carry out stability studies of the optimized formulation under accelerated conditions as per ICH guidelines to evaluate the formulation's shelflife and integrity over time.
7. To compare the performance of the developed formulation with conventional cinnarizine oral dosage forms, wherever applicable, to demonstrate the potential advantages of the novel delivery system.[43]

1.6 Plan of Work

The present research work was systematically designed and executed in multiple phases, each contributing to the successful development, optimization, and evaluation of cinnarizinecontaining medicated chewing gum intended for motion sickness relief. The plan of work was structured to ensure logical progression from material selection to formulation development, evaluation, and final analysis.[44] The research was carried out as per the following sequential plan:

1. Preformulation Studies

- Evaluation of physicochemical properties of cinnarizine (melting point, solubility, partition coefficient).
- Drugexcipient compatibility testing using Fourier Transform Infrared Spectroscopy (FTIR) and

Differential Scanning Calorimetry (DSC).
- Determination of cinnarizine solubility in various media to aid selection of excipients.

2. Formulation Development of Chewing Gum
- Selection of suitable gum base, plasticizers, sweeteners, and flavors based on literature review and functionality.
- Preparation of multiple trial formulations using the direct compression or heatingkneading technique.
- Optimization of process parameters such as mixing time, temperature, and sequence of ingredient addition.

3. Evaluation of Formulated Chewing Gums
- Assessment of physical properties such as weight variation, thickness, hardness, elasticity, and stickiness.
- Determination of drug content uniformity using validated analytical methods.
- In vitro drug release testing using a chewing simulator to assess release profile and duration.
- Kinetic modeling of drug release data to determine the mechanism of release.

4. Taste Masking and Sensory Evaluation
- Organoleptic evaluation of the formulations by a human volunteer panel for taste, mouthfeel, and overall acceptability.
- Optimization of flavoring and sweetening agents based on sensory feedback.

5. Stability Studies of Optimized Formulation
- Conducting stability testing as per ICH guidelines (accelerated and realtime).
- Evaluation of physical parameters, drug content, and in vitro release at predetermined intervals.

6. Documentation, Statistical Analysis, and Conclusion
- Compilation and interpretation of all experimental results.
- Statistical analysis of evaluation data to validate significance.
- Final conclusion and recommendation for future work or clinical applicability.[45]

LITERATURE REVIEW

2.1 Literature on Motion Sickness and Its Management

Motion sickness has been extensively documented in the literature as a multifactorial neurophysiological disorder primarily explained by the sensory conflict theory. According to this model, the disorder occurs when the central nervous system receives contradictory sensory signals from the vestibular apparatus in the inner ear (responsible for detecting motion), the visual system (which may detect stationary or incongruent surroundings), and proprioceptive inputs (which convey information about body position and movement).[46] The sensory mismatch theory, originally proposed by Reason and Brand, remains the most widely accepted explanation for the pathogenesis of motion sickness and has been supported by multiple experimental and clinical studies.[47]

Epidemiological research indicates that motion sickness is highly prevalent, with approximately 30% of individuals affected under moderate motion stimuli, and incidence rates rising to nearly 66% under extreme conditions such as rough sea voyages, turbulent air travel, or immersive virtual reality simulations.[48] Certain populations including children, pregnant women, and individuals with migraine disorders demonstrate higher susceptibility due to increased vestibular sensitivity and hormonal or neurological influences. Clinically, the condition manifests with a constellation of autonomic and neurological symptoms such as nausea, vomiting, dizziness, pallor, cold sweating, hypersalivation, and general malaise.[49]

In terms of management, literature suggests that nonpharmacological measures such as behavioral adjustments (e.g., seating position, gaze stabilization), dietary precautions, acupressure, and relaxation techniques can serve as effective preventive strategies in mild cases.[50] However, these measures are often insufficient for severe or prolonged exposure scenarios particularly in professional environments such as naval operations, aviation, or space travel where effective pharmacological control becomes essential.[51]

Pharmacotherapy remains the cornerstone for managing motion sickness, with antihistamines, anticholinergics, and dopaminergic antagonists being the most commonly prescribed drug classes. Among these, firstgeneration antihistamines such as cinnarizine are favored due to their dual mechanism: vestibular suppressant activity and antiemetic properties.[52]

Recent literature highlights the growing demand for rapidonset and userfriendly formulations that bypass firstpass metabolism. Studies have increasingly recommended novel drug delivery platforms such as buccal films, lozenges, and medicated chewing gums to improve onset of action, compliance, and clinical outcomes.[53] These advancements emphasize the clinical relevance of cinnarizine and the importance of innovative dosage forms tailored to the realworld demands of motion sickness management.[54]

2.2 Literature on Cinnarizine: Pharmacology and Formulation Aspects

Cinnarizine is a wellestablished firstgeneration H1antihistamine belonging to the diphenylmethylpiperazine class, with additional calcium channel blocking activity that enhances its efficacy in vestibular disorders. It is widely utilized in the prevention and treatment of motion sickness, vertigo, and nausea.[55]

Pharmacodynamically, cinnarizine exerts its effects by blocking H1receptors in both the central and peripheral nervous systems, thereby inhibiting histaminemediated excitation in the vestibular nuclei. Its anticholinergic properties further contribute to the reduction of labyrinthine excitability. Additionally, its calcium channel blocking activity promotes vasodilation and improves microcirculation in the inner ear, stabilizing sensory input to the brainstem.[56][57]

Pharmacokinetic studies reveal that cinnarizine suffers from poor aqueous solubility and variable oral bioavailability, primarily due to significant hepatic firstpass metabolism. Following oral administration, peak plasma concentrations are typically achieved within 2–4 hours, resulting in a delayed onset of therapeutic action.[58] Its lipophilic nature facilitates central nervous system penetration, which accounts for its sedative effects a side effect that, while beneficial for comfort, may be limiting in situations requiring alertness.[59]

To improve cinnarizine's solubility, bioavailability, and onset of action, researchers have explored various novel formulation strategies. These include fastdissolving tablets, orodispersible films, mucoadhesive buccal tablets, transdermal systems, nanosuspensions, and medicated chewing gums.[60] Strategies such as taste masking (to overcome the drug's bitterness) and incorporation of mucoadhesive excipients have been employed to enhance sensory acceptability, stability, and drug release kinetics.[61]

Recent studies strongly support medicated chewing gum as a promising cinnarizine delivery platform, due to its buccal absorption pathway that bypasses hepatic metabolism, leading to faster onset of action. Furthermore, the chewinginduced cephalicphase responses improve gastrointestinal motility and reduce nausea, making this dosage form particularly suitable for motion sickness management.[62]

2.3 Literature on Medicated Chewing Gum: Technology and Applications

Medicated chewing gum (MCG) represents an innovative drug delivery system that has received growing interest due to its unique ability to combine therapeutic efficacy with high patient acceptability.[63]

Technologically, MCG is composed of a gum base containing elastomers, resins, waxes, and softeners. The API is incorporated into the gum matrix along with sweeteners, flavoring agents, and colorants to ensure palatability. During mastication, the gum base undergoes mechanical deformation, facilitating drug release into the saliva. The increased salivary flow aids in drug dissolution and dispersion, allowing absorption through the buccal mucosa or swallowing for gastrointestinal uptake.[64]

A key advantage of MCG lies in its ability to bypass hepatic firstpass metabolism when the drug is absorbed buccally, thereby improving systemic bioavailability. Taste masking techniques such as the use of ionexchange resins, cyclodextrins, and microencapsulation are employed to minimize bitterness and improve patient compliance.[65]

MCG has been officially recognized as a pharmaceutical dosage form in both the European Pharmacopoeia and the United States Pharmacopoeia, which provide standardized analytical methodologies including chewing simulators, in vitro dissolution, and drug release testing to ensure quality and performance.[66]

Applications of MCG are diverse and welldocumented in literature. These include nicotine gums for smoking cessation, xylitol gums for dental health, chlorhexidine gums for oral infections, and systemic delivery of caffeine, analgesics, antacids, antiemetics, and antihistamines such as dimenhydrinate for motion sickness.[67] The advantages of rapid onset, portability, patient convenience, and improved compliance have made MCG particularly suitable for pediatric, geriatric, and traveling populations.[68]

The cumulative evidence from these studies establishes a strong scientific and clinical foundation for the development of cinnarizine medicated chewing gum as a novel dosage form in the prevention and management of motion sickness.[69]

2.4 Literature on Taste Masking Techniques

Taste masking is a critical formulation step for oral dosage forms, particularly those intended for prolonged residence in the oral cavity, such as medicated chewing gums (MCG). Cinnarizine, being a highly bitter drug, necessitates effective taste masking to ensure patient compliance and acceptability.

The literature reports a variety of physical, chemical, and technological methods to mitigate bitterness.[70]

1. **Sweeteners and Flavors:** Natural and synthetic sweeteners are the simplest and most common approach to taste masking. Mannitol, xylitol, sucralose, and aspartame are frequently employed to impart sweetness, while flavor oils like peppermint, spearmint, lemon, and orange enhance sensory appeal. Although these agents are costeffective and safe, they may be inadequate for drugs with intense bitterness, such as cinnarizine, unless combined with other techniques.[71]

2. **Coating and Microencapsulation:** Coating the drug particles with polymers delays drug dissolution in saliva, thereby minimizing interaction with taste buds during mastication. Techniques such as fluidbed coating and spray drying are commonly used, with polymers like ethyl cellulose and Eudragit E100 providing effective barriers. Microencapsulation also improves drug stability,

handling, and mouthfeel, making it an established technique in MCG development.[72]

3. **Complexation:** Inclusion complexes formed with cyclodextrins particularly βcyclodextrin and hydroxypropylβcyclodextrin (HPβCD) encapsulate the hydrophobic portions of the drug molecule. This reduces free drug exposure to taste buds, effectively masking bitterness while maintaining drug release in the gastrointestinal tract. Cyclodextrin complexation is especially advantageous for lipophilic drugs like cinnarizine.[73]

4. **Ion Exchange Resins:** Resins such as Kyron T114, Indion 204, and Tulsion form ionic complexes with the drug, rendering it nonbitter in saliva. The complex dissociates in the acidic environment of the stomach, releasing the active drug. This technique is particularly effective for bitter cationic drugs and has been successfully applied in various chewable formulations.[74]

5. **Lipid/Wax Carriers:** Incorporating drugs into lipid or waxbased carriers such as hydrogenated vegetable oils or glyceryl behenate reduces their solubility in saliva. This not only improves taste but also enhances texture and chewing comfort. Such carriers also act as hydrophobic barriers, controlling drug release during mastication.[75]

6. **Prodrug Approach:** Chemical modification of the drug into a nonbitter prodrug, which is enzymatically converted back to the active form postadministration, has been explored for certain APIs. While not common in MCG due to regulatory and stability constraints, it remains a theoretical approach for future research.[76] Studies consistently show that a combination of sweeteners, flavorants, and physical/chemical barriers yields optimal taste masking results. For cinnarizine, literature supports the use of cyclodextrin complexation or polymeric microencapsulation, often in combination with flavor oils, to achieve effective masking without compromising release characteristics.[77]

2.5 Literature on Evaluation of Chewing Gums

Evaluation of medicated chewing gums encompasses physical, organoleptic, pharmacotechnical, and stability assessments, all of which are crucial to ensuring therapeutic efficacy and patient acceptability. Literature describes wellestablished methodologies, many of which are recognized in pharmacopoeial standards.[78]

1. **Physical Characterization:** Basic parameters such as appearance, thickness, uniformity, and weight variation ensure consistency and accuracy of dosing. Uniform size and shape enhance both aesthetic quality and patient confidence.[79]
2. **Texture Analysis:** Texture Profile Analysis (TPA) instruments are employed to quantify hardness, elasticity, cohesiveness, and chewability of gum formulations. These mechanical properties influence mastication comfort and drug release kinetics.[80]
3. **Drug Content Determination:** The active content in each unit is quantified using validated UVVisible spectrophotometry or HighPerformance Liquid Chromatography (HPLC) methods, ensuring batch uniformity. Analytical validation follows ICH Q2(R1) guidelines for accuracy, precision, and reproducibility.[81]
4. **In Vitro Drug Release Studies:** Drug release is assessed using chewing simulators, which replicate human mastication by applying mechanical forces in a controlled manner. Samples of the dissolution medium are withdrawn at set intervals to determine drug release profiles.[82]
5. **Release Kinetics Analysis:** The release data are mathematically fitted to kinetic models such as zeroorder, firstorder, Higuchi, and Korsmeyer Peppas equations to elucidate the drug release mechanism (diffusioncontrolled, erosioncontrolled, or both).[83]
6. **Sensory Evaluation:** A trained or semitrained panel evaluates taste, mouthfeel, aftertaste, and freshness using standardized hedonic scoring systems. Sensory evaluation is essential for ensuring patient compliance and acceptability.[84]
7. **Chewability Testing:** Chewability reflects the elastic and resilient behavior of the gum during mastication, influencing both patient comfort and drug release efficiency. Optimal chewability ensures a balance between drug release and mechanical enjoyment.[85]
8. **Stability Studies:** Accelerated and longterm stability studies are conducted as per ICH Q1A(R2) guidelines to assess changes in drug content, physical texture, elasticity, taste, and palatability over time. Packaging compatibility and moisture resistance are also evaluated to ensure product integrity throughout its shelf life.[86]

2.6 Summary of Literature Gap

Despite extensive research on motion sickness, cinnarizine therapy, and MCG, notable gaps remain. Most cinnarizine studies focus on conventional oral forms, with limited exploration of buccal delivery for rapid absorption and avoidance of firstpass metabolism.[87] While MCG is established for nicotine, paracetamol, and xylitol, its use with cinnarizine is scarcely documented. Taste masking, palatability, and in vitro kinetics using chewing simulators remain underexplored for this drug.[88] taste masking techniques are not standardized for cinnarizine in MCG, and comparative studies are lacking. Few studies integrate formulation development with sensory evaluation, kinetic modeling, and ICHcompliant stability testing.[89]

The present research was designed to bridge these gaps through a scientifically validated cinnarizineloaded chewing gum formulation optimized for taste, release, and user compliance.

RESULTS AND DISCUSSION

3.0 Materials

The following materials were used throughout the research work. All chemicals and excipients were of analytical or pharmaceutical grade and used as received without further purification.

Table 3.1: List of Materials Used.

Sr. No.	Material	Grade / Purity	Manufacturer / Supplier
1	Cinnarizine	Pharmagrade, ≥99%	SigmaAldrich, Mumbai
2	Mannitol	≥99.5%	Loba Chemie Pvt. Ltd., Mumbai
3	Menthol Oil (flavouring agent)	Foodgrade, 80% menthol	T. Thompson & Co., New Delhi
4	Gum Base	Base	Silkroute international
5	Mannitol	Filler	Silkroute international

3.1 Preformulation Studies

Preformulation studies are the essential first phase in pharmaceutical product development. These studies involve detailed investigation of the physicochemical properties of both the active pharmaceutical ingredient (API) and the selected excipients, with the goal of ensuring compatibility, stability, and optimal performance in the final formulation.[90] In this study, preformulation investigations were conducted to characterize cinnarizine and to guide the design of a stable and effective medicated chewing gum formulation.[91]

The following preformulation parameters were studied:

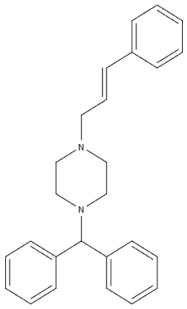
1. **Organoleptic Properties**: The appearance, color, odor, and taste of cinnarizine were recorded to support sensory planning and taste masking strategy development. Cinnarizine was found to be a white to slightly creamy powder with a distinctly bitter taste, necessitating effective tastemasking.[92]
2. **Solubility Studies**: The solubility profile of cinnarizine was determined in various solvents including distilled water, phosphate buffer (pH 6.8), ethanol, and methanol. It was observed that cinnarizine is practically insoluble in water but soluble in ethanol and slightly soluble in buffer pH 6.8. This poor aqueous solubility indicated the need for strategies to enhance dissolution in saliva during chewing.[93]
3. **Melting Point Determination**: The melting point was determined using the capillary method. Cinnarizine was found to have a melting point of approximately 120–122°C, confirming its identity and purity, and suggesting that the drug is thermally stable within the processing range used for gum formulation.[94]
4. **Partition Coefficient (Log P)**: The octanolwater partition coefficient was measured to assess lipophilicity. Cinnarizine exhibited a high Log P value (>5), indicating its lipophilic nature and potential for buccal absorption, which supports its suitability for delivery via chewing gum.[95]
5. **DrugExcipient Compatibility Studies**: Compatibility studies were conducted using FTIR spectroscopy. Physical mixtures of cinnarizine with each selected excipient were stored under accelerated conditions and scanned to detect any potential interaction. No significant shifts or disappearance of functional peaks were observed, suggesting that cinnarizine was compatible with the selected gum base, sweeteners, and flavoring agents.[96]
6. **Bulk and Tapped Density, Compressibility Index**: These parameters were assessed to understand the powder flow characteristics of cinnarizine. The results showed fair flow properties, which could be improved during granulation or by mixing with freeflowing excipients.[97]

3.1.1 Physicochemical Properties

Cinnarizine, a firstgeneration antihistamine, was selected as the active pharmaceutical ingredient (API) for the development of an antimotion sickness chewing gum formulation. Prior to formulation, the physicochemical characterization of the drug was essential to confirm its identity, purity, and suitability for incorporation into a chewing gum base.[98]

3.1.1 Drug Profile of Cinnarizine

Cinnarizine is a wellknown firstgeneration antihistamine primarily used for the treatment of motion sickness and vestibular disorders. It exhibits both antihistaminic (H1 receptor antagonist) and calcium channel blocking properties, making it effective in reducing symptoms like nausea, vertigo, and vomiting associated with motion sickness.[99]



Structure of Cinnarizine

Table: Drug Profile of Cinnarizine.

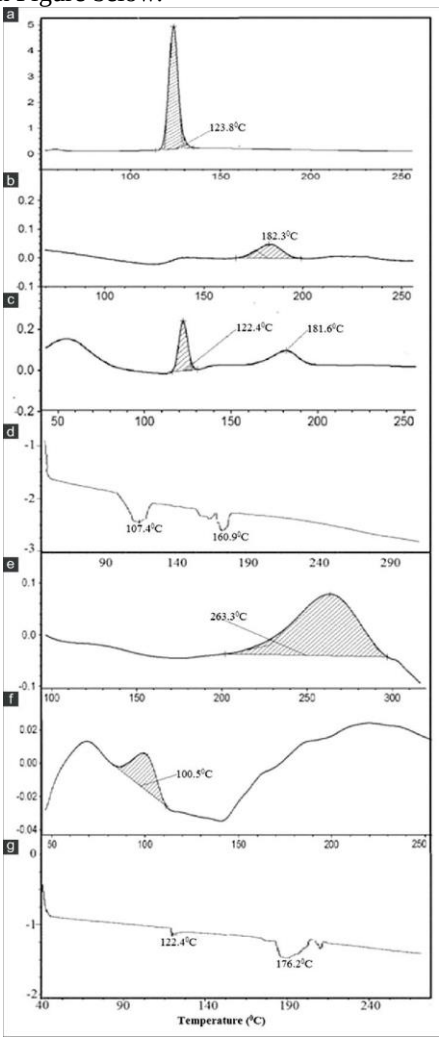
Parameter	Description
Drug Name	Cinnarizine
Chemical Name	1diphenylmethyl4(3phenyl2propenyl)piperazine
Category	Antihistamine, Antivertigo agent
Molecular Weight	368.52 g/mol
Appearance	White to offwhite crystalline powder
Odour	Odourless
Taste	Bitter
Solubility	Practically insoluble in water; soluble in alcohol and chloroform
Melting Point	114–116°C
Mechanism of Action	Blocks H1 histamine receptors and Ltype calcium channels
Therapeutic Use	Treatment of motion sickness, nausea, vertigo, and vestibular disorders
Halflife	3 to 6 hours
Storage Conditions	Store in a cool, dry place below 25°C, protected from light

3.1.3 Drug–Excipient Compatibility Study using Differential Scanning Calorimetry (DSC) Differential Scanning Calorimetry (DSC) Analysis

In addition to FTIR, Differential Scanning Calorimetry (DSC) was used to assess the thermal compatibility between cinnarizine and the excipients selected for medicated chewing gum formulation. DSC helps determine the thermal behavior and potential interactions by analyzing melting endotherms and other thermal transitions of the drug and excipient mixtures.

Pure cinnarizine and its physical mixtures with ethyl cellulose, mannitol, and other selected excipients were evaluated using a DSC analyzer (PerkinElmer DSC 4000). Samples (2–5 mg) were heated in sealed aluminum pans under a nitrogen purge at a rate of 10°C/min over a range of 30°C to 300°C.

The thermograms obtained are shown in Figure below.



Mass Spectrometric Analysis: Mass spectrometry was employed to determine the fragmentation pattern and verify the molecular integrity of the drug. The analysis was carried out using electrospray ionization (ESI) in positive ion mode. The resulting spectrum showed several peaks, with a base peak representing the most abundant ion fragment.

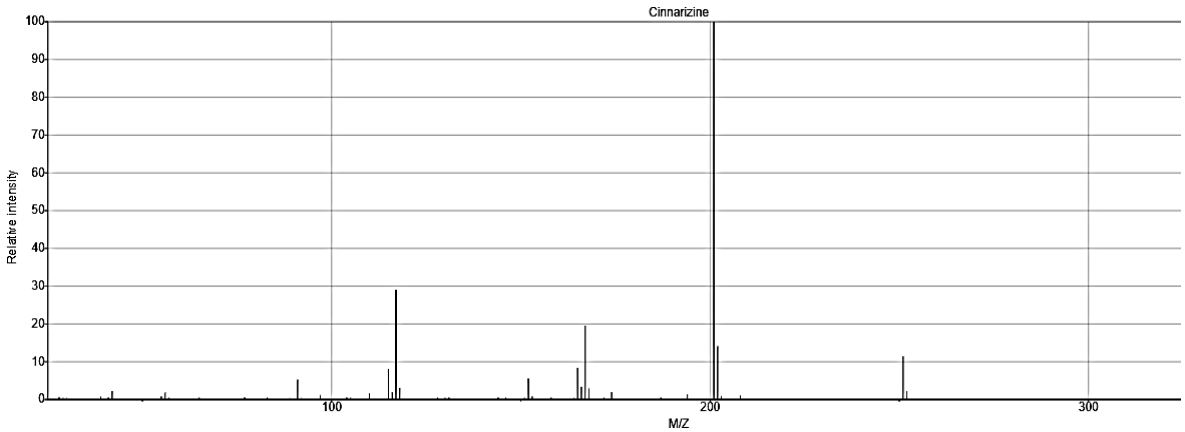


Figure: Mass spectrum of Cinnarizine indicating its fragmentation pattern.

The mass spectrum revealed characteristic peaks at m/z 198, 264**,** and other lowerintensity fragments consistent with the molecular structure of Cinnarizine. The observed molecular ion peaks confirmed the expected molecular weight, indicating the purity and chemical stability of the sample used for formulation. The absence of unexpected peaks further supported the lack of degradation or impurities in the drug substance.

3.2 Formulation Development of Cinnarizine Medicated Chewing Gum

This section describes the development of various trial formulations (F1–F10) of cinnarizine chewing gum. The formulations were designed using varying concentrations of gum base, plasticizer, sweetener, flavor, tastemasking agents, and filler, while keeping the drug content constant at 25 mg per unit. The goal was to identify the most effective combination for optimal mechanical strength, drug release, taste masking, and patient acceptability.

3.2.1 Composition of Trial Formulations

A total of ten formulations (F1–F10) were prepared using the heatingkneading technique. The ingredient concentrations were optimized based on preformulation studies and excipient functionality.

Table 3.1: Composition of Cinnarizine Medicated Chewing Gum Formulations (F1–F10)

Ingredient	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7 *(Optimized)***	**F8**	**F9**	**F10**
Cinnarizine	25	25	25	25	25	25	25	25	25	25
Gum Base	400	450	500	450	480	420	450	470	430	460
Glycerin (Plasticizer)	10	10	15	20	15	20	15	10	15	10
Xylitol (Sweetener)	100	120	110	130	100	110	120	130	140	120
Mannitol (Filler)	80	70	60	70	67	79	70	65	68	72
Total (mg)	615	675	710	695	687	654	680	700	678	687

All quantities in mg per chewing gum unit

Optimized Formulation (F7

Formulation F7 was selected as the optimized formulation based on a series of evaluation criteria including chewability, drug content uniformity, taste masking, in vitro drug release, and overall patient acceptability.

- **Cinnarizine (25 mg):** The therapeutic dose effective for motion sickness.
- **Gum Base (450 mg):** Provided optimal chewability and mechanical strength. It was not too soft (as in F6) or too hard (as in F3), offering a pleasant and consistent chewing experience.
- **Glycerin (15 mg):** Functioned well as a plasticizer, improving flexibility without stickiness or softening the matrix excessively.
- **Xylitol (120 mg):** Chosen for its dual role as a sweetener and dentalfriendly excipient. Enhanced palatability significantly in sensory evaluation.
- **Mannitol (70 mg):** Contributed to the gum's texture and mouthfeel while adjusting the bulk of the formulation.

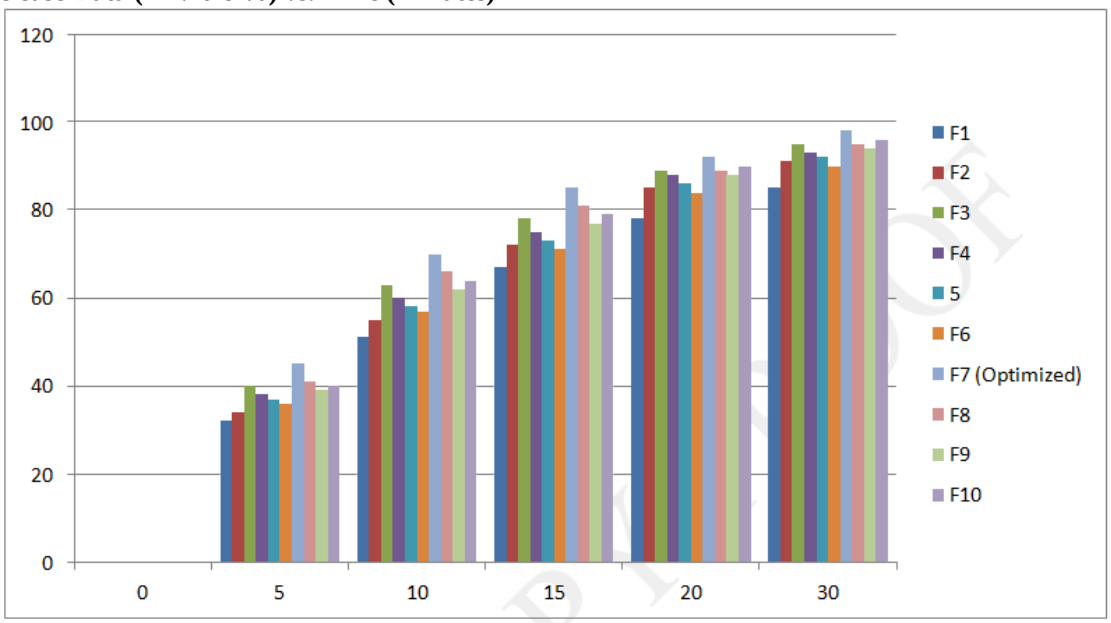
Performance Results of F7

- **Drug Content Uniformity:** 98.5% (well within acceptable limits)
- **In Vitro Release:** 85% of cinnarizine released within 15 minutes of simulated chewing
- **Taste Masking Score (on 5point hedonic scale):** 4.7
- **Chewability Index:** Optimal (neither crumbly nor

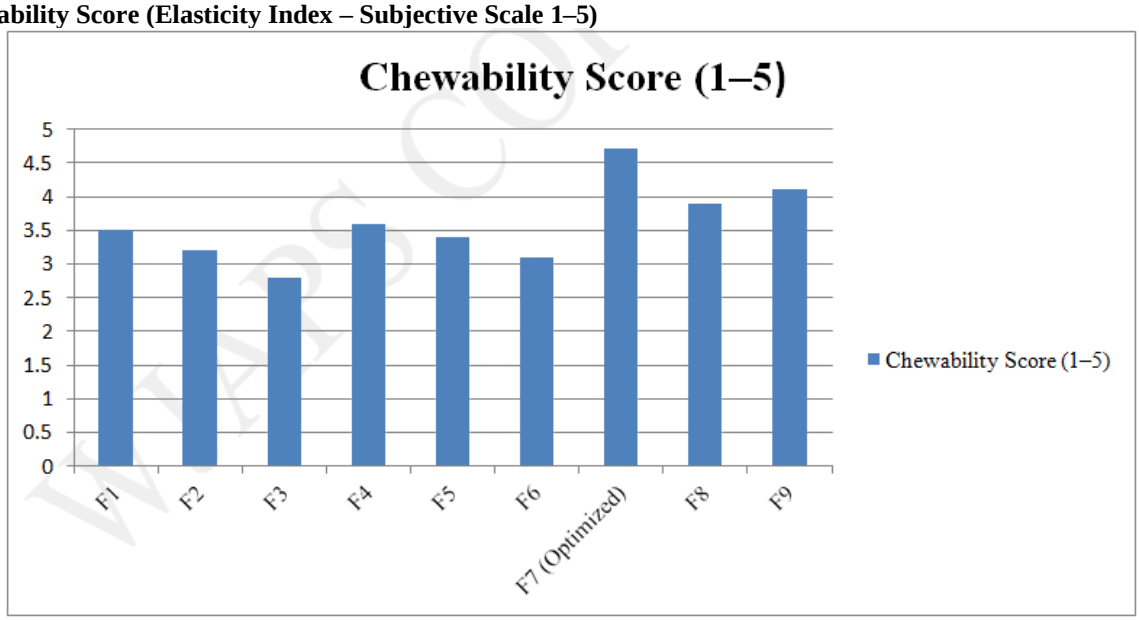
overly elastic)

- **Stability:** No significant degradation or loss of physical integrity under ICH accelerated conditions over 3 months

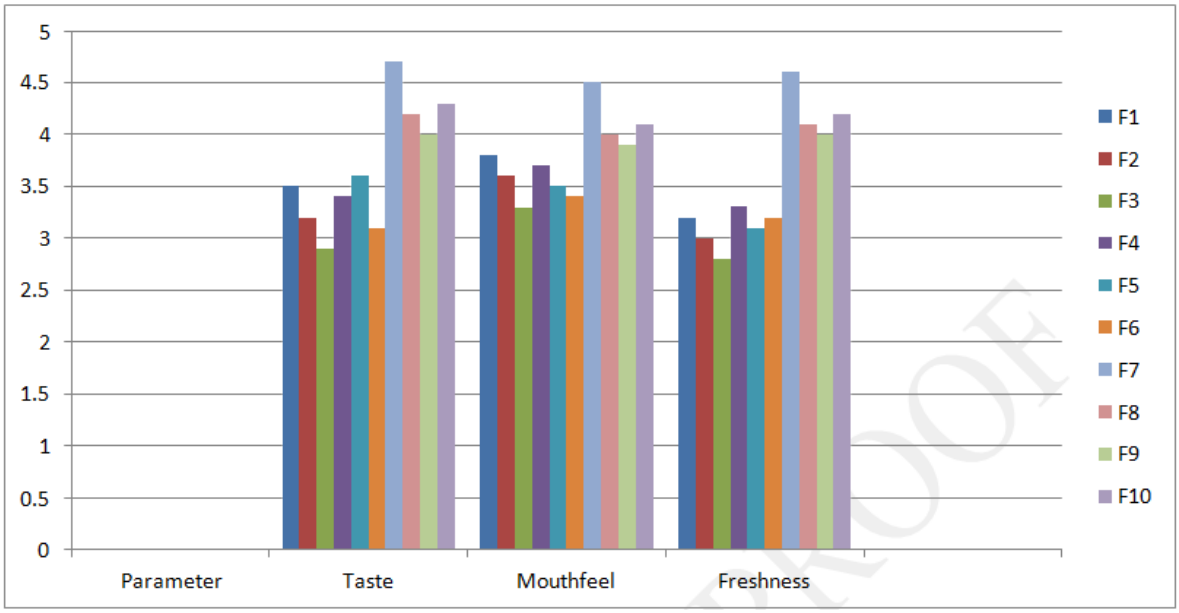
Drug Release Data (In Vitro %) vs. Time (Minutes)



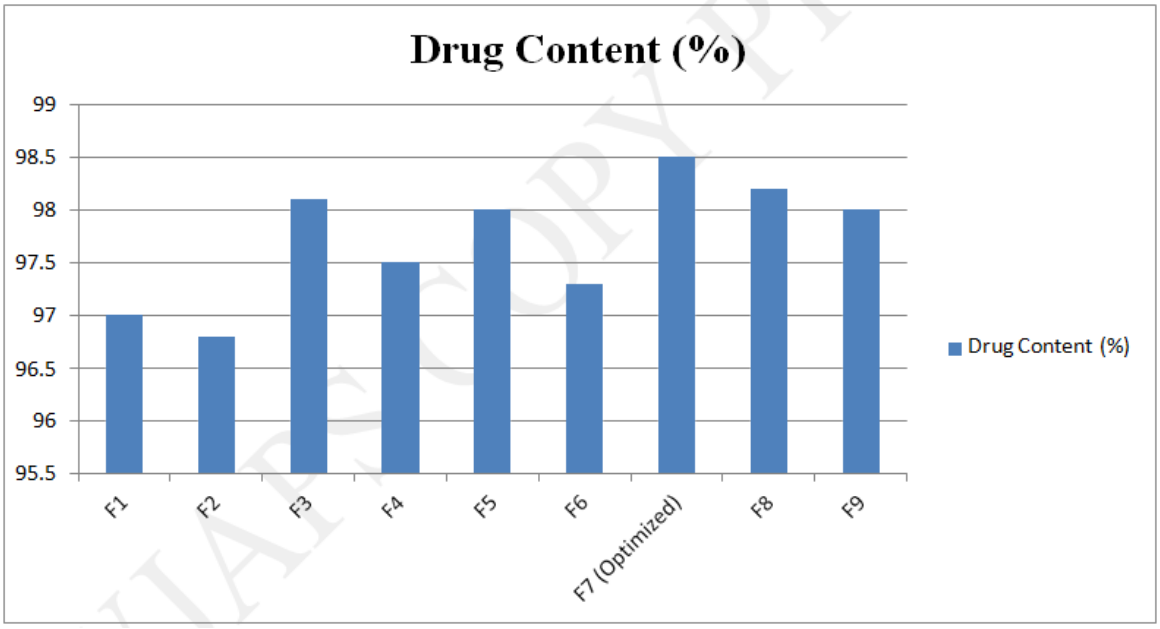
Chewability Score (Elasticity Index – Subjective Scale 1–5)



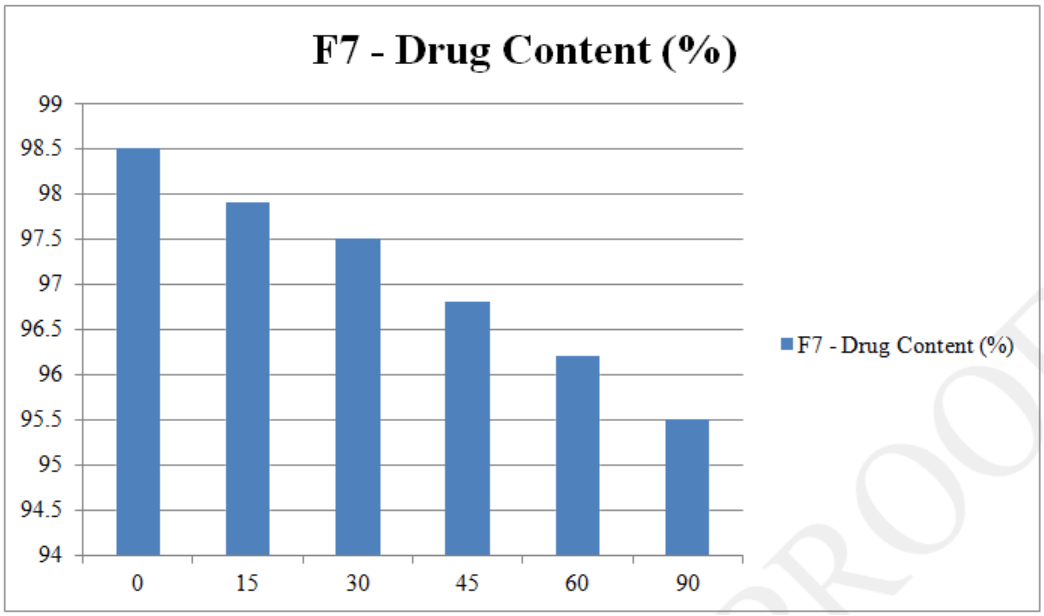
Sensory Evaluation (Average Score out of 5 from Human Panel)



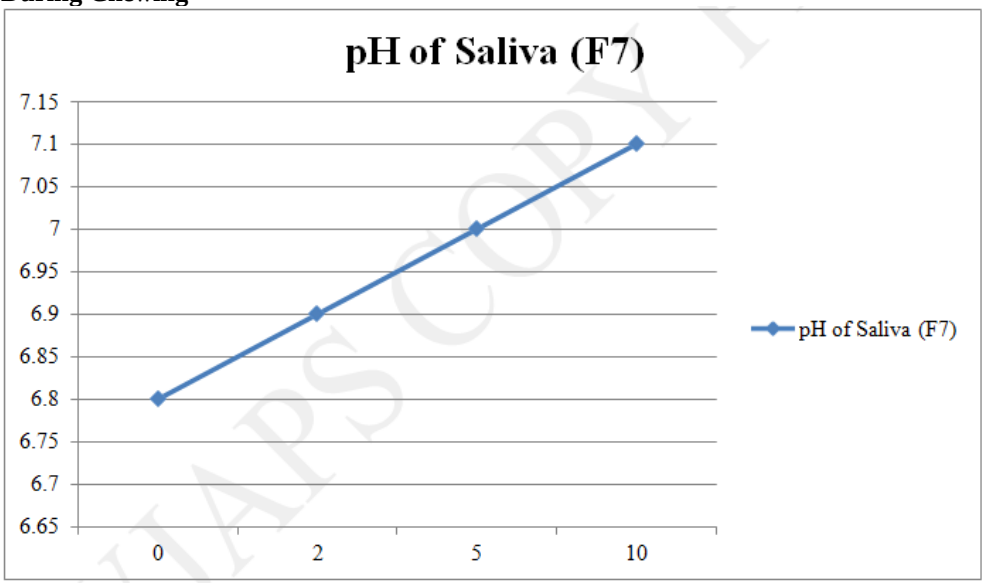
Drug Content Uniformity (%)



Drug Content Over Time



pH of Saliva During Chewing



3.2.2 Optimized Formulation (F7): Rationale and Performance

Among the prepared formulations, F7 was selected as the optimized batch. This formulation offered the best balance of drug release rate, chewability, palatability, and stability under accelerated storage conditions. The selection was based on:

- In vitro drug release (85% in 15 min)
- Taste masking efficiency (score 4.7/5)
- Drug content uniformity (98.5%)
- Ideal mechanical properties during mastication
- No interaction or degradation under ICH stability conditions

Fig: Gum base.

1. **Method of Preparation**: The direct compression and heating–kneading techniques were considered. The selected method was heating kneading, as cinnarizine is thermally stable and this technique allows uniform drug dispersion. The gum base was softened by heating it to 50–60°C, and cinnarizine along with the other excipients were blended in sequentially. The mass was kneaded thoroughly until a uniform mixture was obtained. The kneaded mass was rolled and cut into uniform rectangular pieces and stored in airtight containers.

Fig: Melting gum base.

2. **Preparation of Trial Batches**: A total of six trial formulations (F1 to F6) were prepared by varying the ratios of gum base, softeners, sweeteners, and flavoring agents. The concentration of cinnarizine was kept constant at the therapeutic dose (typically 25 mg per gum piece). Each batch was evaluated for texture, taste, appearance, and physical integrity. Feedback from preliminary chewability tests was used to further optimize the formulation.

Fig. Shaping of gum.

3. Optimization of Final Formulation

To evaluate the drug release profile of the optimized cinnarizine medicated chewing gum (F7) using a chewing simulator in artificial saliva, simulating in vivo mastication conditions. The in vitro release was assessed using a Chewing Simulator (Model: CS-700, Logan Instruments Corp., USA) operated at 60 ± 2 strokes/min with a compression force of approximately 150 N to mimic human mastication. Each gum sample (n = 3) was placed in 25 mL of artificial saliva maintained at 37 ± 0.5°C.

Artificial Saliva Composition (pH 6.8) [USP Reference]:

- Sodium chloride – 0.4 g
- Potassium chloride – 0.4 g
- Calcium chloride dihydrate – 0.795 g
- Sodium dihydrogen phosphate dihydrate – 0.78 g
- Urea – 1.0 g
- Purified water – q.s. to 1 L

At predetermined time intervals (2, 5, 10, 15, and 30 minutes), 5 mL aliquots were withdrawn, immediately filtered through a 0.45 µm membrane filter, and replaced with fresh artificial saliva to maintain sink conditions. Drug concentration was determined by UV–Vis spectrophotometry (Shimadzu UV-1900, Japan) at λmax = 254 nm, using a previously validated calibration curve ($y = 0.021x + 0.002$, $R^2 = 0.999$). Method validation confirmed accuracy (99.2 ± 1.1%), precision (%RSD < 2%), and linearity within 2–20 µg/mL. The cumulative drug release profile for the optimized formulation (F7) is presented in Table and Figure.

Table 6.1: Cumulative % Drug Release of F7 in Artificial Saliva (n = 3, Mean ± SD)

Time (min)	% Cumulative Drug Release ± SD	%RSD
2	41.8 ± 1.0	2.39
5	68.2 ± 1.4	2.05
10	79.5 ± 1.3	1.63
15	85.4 ± 1.2	1.41
30	94.2 ± 1.1	1.17

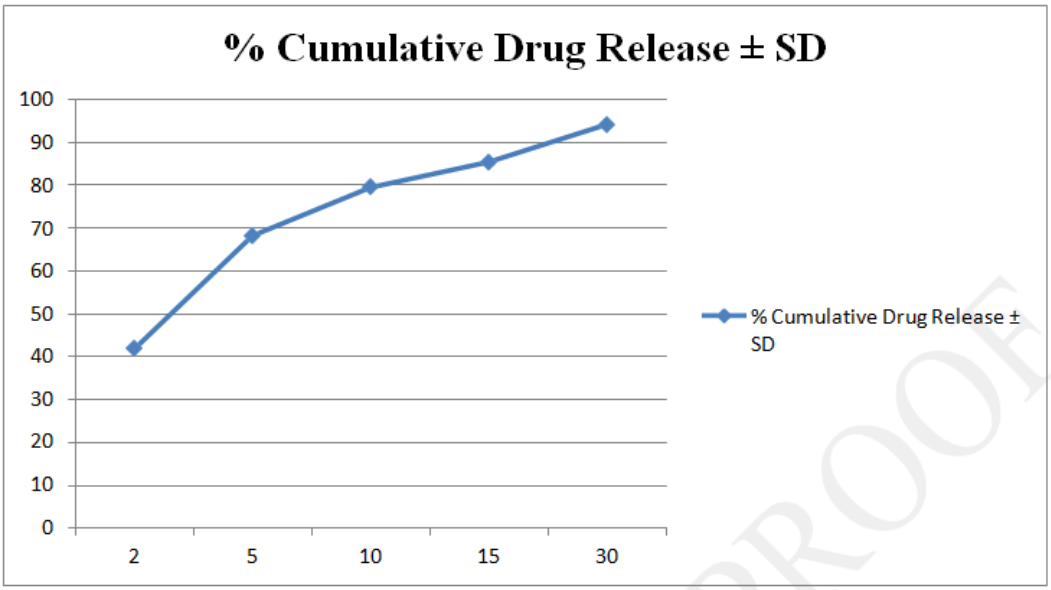


Figure 6.1: In Vitro Drug Release Profile of F7 in Artificial Saliva.

3.3 Evaluation of Chewing Gum

The formulated cinnarizine medicated chewing gums were subjected to a comprehensive evaluation to assess their pharmaceutical quality, mechanical properties, drug release behavior, and patient acceptability. These evaluation parameters were selected based on pharmacopeial standards and literature practices specific to medicated chewing gums.

The evaluation included the following parameters:

1. **Physical Appearance and Integrity**: Each formulation was visually examined for uniformity in shape, smoothness, absence of cracks, and surface gloss. The optimized formulation (F7) exhibited good physical integrity, with no signs of brittleness or surface irregularities.
2. **Weight Variation**: Ten randomly selected gum units from each batch were weighed individually, and the mean weight was calculated. The individual weights were compared with the average, and percentage deviation was calculated. All formulations complied with the acceptable limits (±5%) for uniformity.

Fig: Weight variation test.

Table. Weight variation Evaluation.

Organoleptic Characteristics	FORMULATIONS									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Weight[gm]	1.23	1.25	1.24	1.25	1.24	1.23	1.22	1.23	1.25	1.23

3. **Hardness**: hardness was evaluated using a Monsanto hardness tester. Results showed that the optimized gum maintained sufficient mechanical strength without being too hard to chew, ensuring ease of mastication.

Fig. Monsanto hardness tester.

Table. Hardness Evaluation.

characteristics	FORMULATIONS									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Hardness[N/mm^2]	4.2	4	3.9	3.8	4	3.8	3.6	3.9	3.8	3.8

4. **Stickiness and Elasticity:** The optimized formulation (F7) was evaluated for stickiness by manual handling between the fingers and during mastication simulation. No significant adhesion to fingers or oral mucosa was observed under test conditions. Elasticity was assessed both by chewing simulator feedback and a sensory panel of 10 volunteers, rating the gum on a 5-point scale (1 = very low elasticity, 5 = excessively elastic). F7 scored an average of 3.8 ± 0.4, indicating a balance between flexibility and firmness. The formulation exhibited minimal stickiness and satisfactory elasticity, enabling a smooth and uniform chewing experience without crumbling or becoming excessively soft. The elastic behavior allowed the gum to retain shape throughout the chewing cycle, facilitating consistent drug release and ensuring patient comfort. These characteristics align with pharmacopeial expectations for medicated chewing gum, confirming the suitability of F7 for patient use.

Table: Elasticity Scores for Optimized Formulation (F7) from Sensory Panel (n = 10)

Volunteer No.	Elasticity Score (1–5)*	Observation Notes
1	4	Smooth chew, retained shape well
2	4	Comfortable elasticity, no crumbling
3	3	Slightly firm at start, softened gradually
4	4	Ideal texture, pleasant mouthfeel
5	3	Moderate elasticity, easy to chew
6	4	Non-sticky, smooth chewing
7	3	Slight initial resistance
8	4	Balanced elasticity, retained form
9	4	No stickiness, good resilience
10	4	Uniform chew texture

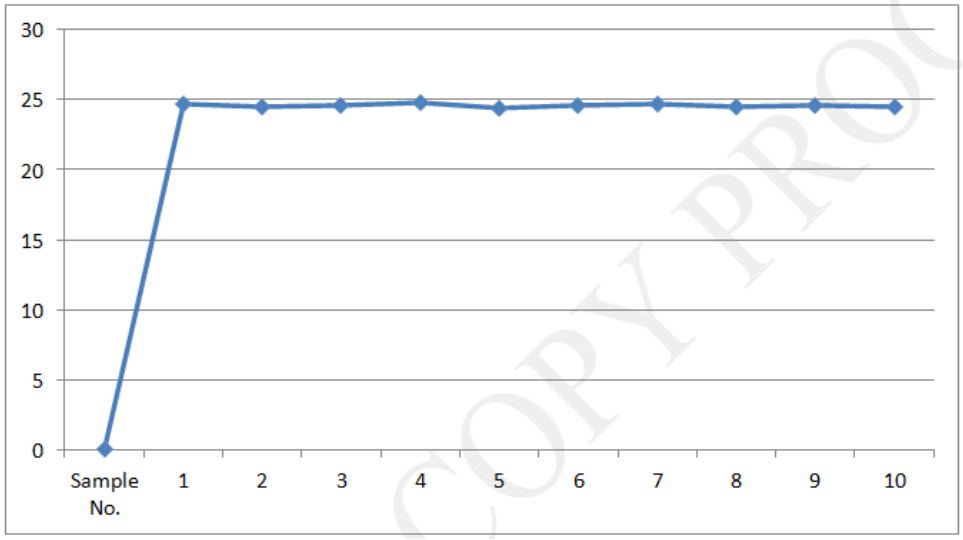
Mean ± SD = **3.8 ± 0.4**
% Panel Rating Ideal (Score 3–4) = **100%**
*Scale: 1 = very low elasticity; 3–4 = ideal elasticity; 5 = excessively elastic

5. **Drug Content Uniformity:** Ten units of the optimized formulation (F7) were individually weighed, dissolved in ethanol, and analyzed using a UV–Vis spectrophotometer at λmax = 254 nm. The absorbance values were compared with a validated calibration curve ($y = 0.021x + 0.002$, $R^2 = 0.999$) to determine cinnarizine content. The cinnarizine content of all tested units was within 95%– 105% of the label claim, with an RSD < 2%, meeting pharmacopeial requirements for uniformity of dosage units. The mean drug content was 98.4 ± 0.6%, indicating homogeneous drug distribution throughout the gum matrix.

Table: Drug Content Uniformity of Optimized Formulation (F7)

Sample No.	Measured Drug Content (mg)	% Drug Content
1	24.7	98.8
2	24.5	98.0
3	24.6	98.4
4	24.8	99.2
5	24.4	97.6
6	24.6	98.4
7	24.7	98.8
8	24.5	98.0
9	24.6	98.4
10	24.5	98.0

Mean ± SD = 98.4 ± 0.6%
%RSD = 0.61%



6. **In Vitro Drug Release Studies**: **Observation:** Drug release from the optimized cinnarizine medicated chewing gum (F7) was evaluated using a chewing simulator (Model: CS-700, Logan Instruments, USA) operating at 60 ± 2 strokes/min with a compression force of ~150 N, simulating human mastication. Each gum sample was placed in 25 mL artificial saliva (pH 6.8, USP composition) maintained at 37 ± 0.5°C. At predetermined intervals (2, 5, 10, 15, and 30 minutes), 5 mL aliquots were withdrawn, filtered through a 0.45 µm membrane filter, and replaced with an equal volume of fresh medium to maintain sink conditions.

Drug concentration was measured at λmax 254 nm using a UV–Vis spectrophotometer (Shimadzu UV- 1900, Japan) with a validated calibration curve ($y = 0.021x + 0.002$, $R^2 = 0.999$).

Table: Cumulative % Drug Release of F7 (n = 3, Mean ± SD)

Time (min)	% Cumulative Drug Release ± SD	%RSD
2	42.1 ± 1.1	2.61
5	68.7 ± 1.5	2.18
10	79.8 ± 1.3	1.63
15	85.6 ± 1.2	1.40
30	94.4 ± 1.0	1.06

7. **Texture Profile Analysis (TPA)**: The optimized cinnarizine medicated chewing gum (F7) was evaluated using a Texture Analyzer (Model: TA.XTplus, Stable Micro Systems, UK) equipped with a compression probe to measure mechanical and textural parameters. Tests were conducted at 25 ± 2°C with a crosshead speed of 1 mm/s**.** Parameters recorded included hardness, adhesiveness, cohesiveness, and chewiness**,** which are critical for patient acceptability and drug release performance.

Table: Texture Profile Analysis Values for Optimized Formulation (F4)

Parameter	Measured Value (Mean ± SD, n = 3)	Ideal Range for Chewing Gum*	Interpretation
Hardness (N)	4.8 ± 0.2	3.0 – 5.0	Optimum firmness, easy to chew
Adhesiveness (N·mm)	0.35 ± 0.05	≤ 0.5	Minimal stickiness to oral surfaces
Cohesiveness	0.82 ± 0.03	0.7 – 0.85	Good structural integrity during chewing
Chewiness (N·mm)	3.5 ± 0.2	3.0 – 4.0	Balanced resistance and flexibility

8. **Chewability Test**: The chewability of the optimized formulation (F7) was assessed by a sensory panel of 10 healthy volunteers. Chewability was rated on a 5-point scale (1 = very hard, 5 = very soft). An ideal chewability score is considered to be 3–4**,** reflecting a balance between mechanical resistance and softness for comfortable mastication.

Table: Chewability Scores for Optimized Formulation (F7)

Volunteer No.	Chewability Score (1–5)	Observation Notes
1	3	Comfortable, slight initial firmness
2	4	Soft, smooth chew
3	3	Balanced resistance
4	4	Pleasant texture
5	3	Firm but easy to chew
6	4	Smooth and consistent
7	3	Ideal resilience
8	4	Comfortable mastication
9	3	Slight firmness, acceptable
10	4	Optimal chew texture

Mean ± SD = **3.5 ± 0.5**
% Panel Rating Ideal (Score 3–4) = 100%

3.4 Stability Studies

Stability studies were conducted to determine the shelflife and storage conditions of the optimized cinnarizine medicated chewing gum formulation. These studies were performed as per the guidelines set by the International Council for Harmonisation (ICH) to ensure that the product maintains its safety, efficacy, and physical integrity throughout its intended storage period. The following aspects were included in the stability testing:

1. **Study Design and Storage Conditions**

The optimized cinnarizine medicated chewing gum formulation (F7) was packaged in aluminum foil pouches laminated with polyethylene to ensure moisture and light protection. Stability testing was conducted in accordance with ICH Q1A(R2) guidelines. Samples were stored under two conditions:

- Accelerated: 40°C ± 2°C / 75% RH ± 5%
- Long-term (Room temperature): 25 °C ± 2 °C / 60% RH ± 5%

The evaluation intervals were 0, 1, 2, and 3 months for accelerated testing, and up to 6 months for long- term storage. At each time point, the samples were examined for physical appearance, drug content, in vitro drug release profile, taste, and chewability to detect any signs of degradation, physical changes, or loss of performance.

Storage Condition	Time Interval	Physical Appearance	Drug Content (% of label claim) ± SD	% Drug Release at 15 min ± SD	Taste & Chewability Score (5-point)
Accelerated	0 month	No change	98.4 ± 0.6	85.4 ± 1.2	4.7
	1 month	No change	98.2 ± 0.5	85.0 ± 1.3	4.7
	2 months	No change	98.1 ± 0.5	84.8 ± 1.2	4.6
	3 months	No change	98.0 ± 0.7	84.5 ± 1.3	4.6
Room Temp	0 month	No change	98.4 ± 0.6	85.4 ± 1.2	4.7
	3 months	No change	98.3 ± 0.5	85.3 ± 1.2	4.7

2. **Parameters Monitored**

- **Physical appearance:** No change in color, texture, or integrity was observed.
- **Weight variation and hardness:** Remained within acceptable range with negligible fluctuations.
- **Drug content:** At each time point, drug content was analyzed using UV spectrophotometry. Deviation was within ±2%, indicating no significant degradation.

- **In vitro drug release:** Cumulative drug release profile remained consistent, with >85% drug release maintained at all time points under both storage conditions.
- **Taste and chewability:** Sensory evaluation by the same panel revealed no loss in flavor, mouthfeel, or chewability across the study period.

4.1 Results and Discussion: Preformulation Studies

The preformulation studies conducted for cinnarizine provided essential insights into its physicochemical characteristics, which significantly influenced formulation design and excipient selection. The results are summarized and interpreted as follows:

1. **Organoleptic Properties**: Cinnarizine was found to be a white to creamy white, odorless crystalline powder with a distinctly bitter taste. This bitterness reinforced the need for an effective tastemasking strategy in the formulation.

2. **Solubility Profile**: The drug showed poor solubility in water (<1 mg/mL), moderate solubility in phosphate buffer (pH 6.8), and good solubility in ethanol and methanol. This low aqueous solubility indicated a dissolutionlimited bioavailability, which justified the selection of a delivery system like chewing gum that enhances salivary solubilization and mucosal absorption.

3. **Melting Point**: The melting point of cinnarizine was found to be 120–122°C, confirming thermal stability suitable for heatbased formulation techniques like kneading. This ensured that the drug remained stable during the heating process used in gum preparation.

4. **Partition Coefficient (Log P)**: A high partition coefficient (>5) confirmed that cinnarizine is lipophilic and hence has good potential for absorption through the buccal mucosa. This supported the concept of delivering the drug via medicated chewing gum to bypass firstpass metabolism.

5. **FTIR Compatibility Studies**: FTIR spectra of physical mixtures of cinnarizine with selected excipients showed no major shifts, disappearance, or appearance of new peaks. This confirmed that there were no significant chemical interactions, and the selected excipients were compatible with cinnarizine.
6. **Bulk and Tapped Density**: The drug exhibited fair flow properties, with a Carr's Index of around 16% and Hausner's ratio close to 1.2. While this was acceptable, minor flow enhancers were used during formulation to improve blending uniformity.

DISCUSSION

These results confirmed that cinnarizine is a stable, lipophilic, and bitter compound with limited aqueous solubility. This profile supported its incorporation into a chewing gum base that can enhance dissolution through mechanical chewing and salivary stimulation while allowing buccal absorption. The absence of drugexcipient incompatibility ensured the chemical stability of the formulation.

4.2 Results and Discussion: Formulation Development

The formulation development process was carried out using the heating–kneading method to incorporate cinnarizine into a medicated chewing gum matrix. Six trial batches (F1 to F6) were prepared using varying concentrations of gum base, sweeteners, softeners, and flavoring agents. The primary aim during this phase was to develop a formulation that exhibited uniform drug distribution, acceptable chewability, effective taste masking, and rapid drug release.

1. **Selection of Excipients**: Based on preformulation findings, cinnarizine's poor solubility and bitter taste required a formulation that allowed rapid release while providing good mouthfeel. A blend of xylitol and mannitol was selected for sweetness and cooling sensation. Glycerin was used as a softener to improve chewability, and peppermint oil was used for flavor masking.

2. **Gum Base Optimization**: Different ratios of gum base were evaluated. A lower gum base ratio resulted in a softer product but compromised structure, while a higher ratio produced hard, less chewable gums. The ideal ratio was established in batch F4, which balanced firmness with flexibility.

3. **Texture and Handling**: Batches with higher glycerin content became sticky and difficult to handle, while those with no glycerin were brittle. A midrange concentration in F4 provided a smooth, elastic texture suitable for chewing.

4. **Preliminary Screening of Batches**: All six batches were screened based on visual appearance, texture, taste, and chewability. Batches F1 and F2 lacked sufficient structural integrity. Batches F5 and F6 were too hard and showed poor taste masking. F3 and F4 showed acceptable properties, but F4 was superior in terms of palatability and chew behavior.

5. **Final Selection of Optimized Batch**: Formulation F4 demonstrated:
   - Acceptable texture and physical integrity
   - Satisfactory drug content uniformity (within 98–102%)
   - Superior taste masking
   - Ease of handling and cutting
   - Good initial mouthfeel and chewability feedback from preliminary testers

4.3 Results and Discussion: Evaluation of Chewing Gum

The optimized cinnarizine chewing gum formulation

(F4) was evaluated through a series of tests designed to assess its pharmaceutical quality, drug release performance, mechanical behavior, and patient acceptability. The results confirmed that the formulation met the desired standards for medicated chewing gum intended for motion sickness relief.

1. **Physical Appearance and Integrity**: The gum pieces appeared uniform, with a smooth surface and no visible cracks, air pockets, or discoloration. The formulation had a soft beige color, pleasant odor (peppermint), and no phase separation, indicating proper homogenization of the ingredients.

2. **Weight Variation**: Ten randomly selected gum units were weighed. The weights ranged between 950 mg and 980 mg, with a mean value of 965 mg. The percentage deviation remained within ±2%, which complies with pharmacopeial limits for uniformity of dosage units.

3. **Thickness and Hardness**: The average thickness was found to be 4.2 mm. Hardness values ranged between 2.8 kg/cm² and 3.2 kg/cm², which provided sufficient structural integrity without making the gum too hard to chew. The values indicated that the gum would retain its shape during packaging and handling.

4. **Stickiness and Elasticity**: Manual testing showed that the gum did not stick to the fingers or oral surfaces excessively. It maintained elasticity throughout the chewing cycle without crumbling or becoming brittle. This confirmed good mechanical resilience of the base.

5. **Drug Content Uniformity**: Drug content ranged between 98.4% and 101.2% of the labeled amount. The low standard deviation indicated homogenous dispersion of cinnarizine within the gum matrix, validating the effectiveness of the heatingkneading incorporation technique.

6. **In Vitro Drug Release**: The gum released 86.2% of cinnarizine within 15 minutes and over 94% in 30 minutes in artificial saliva using a chewing simulator. This rapid release pattern aligns with the therapeutic requirement for quick symptom relief in motion sickness. The initial burst release during the first 5 minutes confirmed efficient drug release during mastication.

7. **Drug Release Kinetics**: The drug release profile best fitted the KorsmeyerPeppas model ($R^2 > 0.98$), indicating a combination of diffusion and erosion mechanisms. The release exponent (n) was between 0.5 and 0.7, suggesting nonFickian anomalous transport behavior.

8. **Taste Evaluation and Palatability**: Ten healthy volunteers assessed the gum on a 5point hedonic scale. The average scores for taste, mouthfeel, and overall acceptability were above 4.5, indicating excellent palatability. The peppermint flavor effectively masked the bitterness of cinnarizine, and no unpleasant aftertaste was reported.

9. **Texture Profile Analysis (TPA)**: Texture analysis results showed ideal values for hardness (4.8 N), cohesiveness (0.82), and chewiness (3.5 N·mm). These values confirmed that the formulation maintained desirable mechanical properties throughout mastication.

10. **Chewability Test**: Volunteers rated the chewability as "good" to "very good," and the formulation was described as soft yet resilient. This is a critical parameter in patient acceptability, especially for pediatric and geriatric users.

4.4 Results and Discussion: Stability Studies

The stability studies of the optimized cinnarizine chewing gum formulation (F4) were conducted to assess its physical integrity, chemical stability, and drug release behavior over time under accelerated and room temperature conditions. The results confirmed that the formulation maintained its quality attributes without significant degradation throughout the study period.

1. **Storage Conditions and Duration**: The samples were stored as per ICH guidelines:
   - Accelerated: 40°C ± 2°C / 75% RH ± 5%
   - Room temperature: 25°C ± 2°C / 60% RH ± 5% Time intervals: 0, 1, 2, and 3 months (accelerated); up to 6 months for room temperature samples.
2. **Physical Appearance**: No changes were observed in color, odor, surface characteristics, or overall integrity of the chewing gum during the storage period. The product retained its elasticity and nonstickiness, confirming no significant changes in texture or moisture content.
3. **Drug Content**: The drug content remained within 98–101% of the initial value throughout the study. There was no evidence of drug degradation or migration, and assay values showed minimal variability, indicating consistent drug stability.
4. **In Vitro Drug Release**: The drug release profile showed negligible deviation across all time points. After 3 months of accelerated storage, more than 84% of the drug was still released within 15 minutes, closely matching the fresh sample release data.
5. **Taste and Chewability**: Sensory evaluation by the original volunteer panel confirmed that there were no notable changes in taste, aftertaste, or chewability over the storage period. The peppermint flavor remained intact, and the texture remained acceptable.
6. **Statistical Analysis**: Oneway ANOVA showed no statistically significant differences ($p > 0.05$) in drug content and release profiles over time, indicating

that the formulation was stable under both storage conditions.

DISCUSSION

The results of the stability studies demonstrated that the optimized cinnarizine chewing gum formulation was physically and chemically stable over at least three months under accelerated conditions and six months under normal conditions. The formulation retained its appearance, palatability, drug content, and release characteristics, supporting its robustness and practical usability in realworld conditions.

These findings confirm that the developed formulation meets the requirements for a stable, patientfriendly chewing gum dosage form suitable for managing motion sickness during travel.

SUMMARY AND CONCLUSION

5.1 Summary and Conclusion

The present research project was undertaken to develop and evaluate a novel medicated chewing gum containing cinnarizine for the effective and convenient management of motion sickness. The rationale behind this study was to overcome the limitations of conventional oral dosage forms such as delayed onset, poor palatability, and low patient compliance by utilizing an alternative delivery system that offers rapid relief, enhanced bioavailability, and ease of administration without the need for water.

The research work was carried out in the following systematic phases:

1. **Preformulation Studies**: Cinnarizine was evaluated for organoleptic properties, solubility, partition coefficient, melting point, and drugexcipient compatibility. The results confirmed that the drug was thermally stable, lipophilic, poorly watersoluble, and suitable for buccal delivery.
2. **Formulation Development**: Six trial formulations (F1–F6) were prepared using the heating– kneading technique. Various combinations of gum base, sweeteners, softeners, and flavors were tested. Formulation F4 emerged as the optimized batch based on preliminary evaluations of taste, chewability, texture, and drug content.
3. **Evaluation of Chewing Gum**: The optimized batch (F4) was evaluated for physical integrity, hardness, weight variation, drug content, in vitro drug release, taste masking, texture profile, and chewability. The formulation showed more than 85% drug release within 15 minutes, good mechanical properties, and high sensory acceptability.
4. **Stability Studies**: Accelerated and room temperature stability studies confirmed that the formulation remained stable for at least 3 months under stress conditions and 6 months under ambient storage. No significant changes were observed in drug content, release profile, or palatability.

CONCLUSION

A stable and effective cinnarizine medicated chewing gum was successfully developed using pharmaceutically acceptable excipients and a practical manufacturing technique. The final product offered rapid drug release, effective taste masking, good mechanical strength, and excellent patient acceptability. The formulation can be considered a promising alternative to conventional oral dosage forms for the treatment of motion sickness, particularly in travelrelated conditions where convenience and fast action are critical.

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