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Review Paper

Formulation and Evaluation of Medicated Chewing Gums Containing Alprazolam

Dr. Sunita Devi, Vaibhav Sharma*, Dr Anil Sharma, Dr. Abhishek Soni, Dr. Sunita Devi, Akanksha Sharma, Dr chinu Gautam, Dr Nishant sharma, Kashish Bhanu partap singh

School of Pharmacy, Abhilashi University, Chail Chowk, Mandi (H.P).

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ABSTRACT

Alprazolam, a short-acting benzodiazepine, is widely prescribed for the management of anxiety disorders, panic attacks, and depression-related conditions. Despite its established therapeutic efficacy, conventional oral dosage forms such as tablets and capsules suffer from hepatic first-pass metabolism, delayed onset of action, and reduced bioavailability. Medicated chewing gums (MCGs) have emerged as an innovative drug delivery platform offering buccal and transmucosal absorption, rapid onset, improved patient compliance, and avoidance of hepatic presystemic elimination. This review comprehensively discusses the formulation strategies, gum base selection, physicochemical characterization, in vitro release testing, and evaluation parameters relevant to alprazolam-loaded medicated chewing gums. The potential of MCGs to enhance the bioavailability and therapeutic performance of alprazolam is explored, along with current challenges, regulatory considerations, and future perspectives. The compilation of published research highlights that MCG formulations of alprazolam represent a promising and patient-friendly approach for the management of anxiety spectrum disorders.

INTRODUCTION

Anxiety disorders represent one of the most prevalent categories of psychiatric conditions worldwide, affecting an estimated 264 million individuals globally. Alprazolam, a triazolobenzodiazepine derivative, is widely prescribed for generalized anxiety disorder (GAD), panic disorder, and social phobia owing to its potent anxiolytic, sedative, anticonvulsant, and muscle-relaxant properties. Its mechanism of action involves positive allosteric modulation of

***Corresponding Author:** Vaibhav Sharma
Address: *School of Pharmacy, Abhilashi University, Chail Chowk, Mandi (H.P)*
Email ✉: Vaibhav86289@gmail.com
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gamma-aminobutyric acid type A (GABA-A) receptors, leading to enhanced inhibitory neurotransmission and rapid symptom relief.

Despite its therapeutic advantages, conventional alprazolam formulations (tablets and sublingual tablets) exhibit limitations including hepatic first-pass metabolism, gastrointestinal variability, and swallowing difficulties in pediatric and geriatric populations. These constraints necessitate the development of alternative delivery systems that can overcome such shortcomings.

Medicated chewing gums (MCGs) are solid or semi-solid single-unit dosage forms intended to be chewed for drug release in the buccal cavity. The released drug may be absorbed transmucosally for systemic action or exert local effects. The buccal mucosa offers a highly vascularized, permeable surface with direct systemic access, effectively bypassing first-pass hepatic metabolism. MCGs also demonstrate favorable patient acceptability and compliance, particularly among patients averse to swallowing solid dosage forms.

This review consolidates the pharmacological basis, formulation principles, characterization methods, and current research advancements in alprazolam-containing medicated chewing gums.

2. Classification of Medicated Chewing Gums

2.1 Classification Based on Drug Release Mechanism

A. Conventional Release MCGs

Drug is released entirely in the oral cavity and absorbed through buccal mucosa for systemic effects. Alprazolam-based formulations primarily belong to this class.

B. Gastric-Targeted MCGs

Drug is released in the saliva, swallowed, and absorbed from the gastrointestinal tract, combining buccal and GI absorption.

C. Local-Action MCGs

Drug remains confined to the oral cavity for local therapeutic effects such as fluoride release or antimicrobial action.

2.2 Classification Based on Gum Base Composition

Table 1: Classification Based on Gum Base Composition

Class	Primary Component	Key Features
Natural Resin-Based	Chicle, Jelutong	Biodegradable, soft texture, limited drug loading
Synthetic Polymer-Based	Polyvinyl acetate, polyisobutylene	Customizable release, pharmaceutical grade
Hybrid Gum Base	Natural + synthetic blend	Balanced elasticity and drug compatibility
Functional Gum Base	Modified with bioadhesive polymers	Extended buccal contact, mucoadhesive properties

2.3 Classification Based on Pharmacological Effect

Table 2: Classification Based on Pharmacological Effect

Class	Primary Effect	Secondary Effect
Anxiolytic MCGs	Rapid anxiety relief	Muscle relaxation
Sedative MCGs	Mild CNS depression	Sleep aid

Anticonvulsant MCGs	Seizure threshold elevation	Neuroprotection
Multi-Action MCGs	Anxiolytic + sedation	Improved tolerability

3. Applications of Alprazolam Medicated Chewing Gums

3.1 Therapeutic Applications

3.1.1 Generalized Anxiety Disorder (GAD)

Alprazolam MCGs offer rapid buccal absorption for immediate anxiolytic action, bypassing the delayed onset associated with conventional tablets due to gastric emptying variability. The transmucosal route ensures consistent plasma concentrations, particularly valuable during acute anxiety episodes.

3.1.2 Panic Disorder

Chewing gums allow portable and discreet administration without water, enabling patients to self-administer during panic attacks in public settings. Rapid onset through buccal mucosa provides timely symptomatic control.

3.1.3 Pre-Procedural Anxiolysis

MCGs containing alprazolam serve as convenient pre-operative or pre-dental anxiolytics, offering patient-friendly administration with predictable sedation onset.

3.1.4 Pediatric and Geriatric Use

Populations with dysphagia or swallowing difficulties benefit substantially from chewable formulations, eliminating the risk of tablet aspiration and improving medication adherence.

3.2 Pharmaceutical and Delivery-System Applications

- Buccal and transmucosal drug delivery for rapid systemic absorption
- Avoidance of first-pass metabolism and enhanced bioavailability
- Sustained or controlled release variants for prolonged therapeutic action
- Combination formulations with excipients for taste-masking of alprazolam's bitterness
- Nanoparticle-loaded MCGs for enhanced permeation and reduced dose frequency

3.3 Research and Development Applications

- Platform model for evaluating buccal absorption kinetics of BCS Class II drugs
- Benchmarking chewing simulator data against clinical pharmacokinetic profiles
- Lead formulation optimization using D-optimal and Box-Behnken experimental designs

4. Rationale for Medicated Chewing Gum as a Delivery Platform for Alprazolam

4.1 Pharmacokinetic Advantages

The buccal mucosa has a surface area of approximately 50 cm2 with a relatively high permeability due to its non-keratinized epithelium in regions such as the floor of the mouth and the inner cheeks. Alprazolam's moderate lipophilicity (log P = 2.12) and low molecular weight (308.77 g/mol) render it suitable for transmucosal absorption. Studies have demonstrated that buccal delivery can improve alprazolam's relative bioavailability by 20-40% compared to oral tablets.

4.2 Physicochemical Justification

Table 3: Physicochemical Properties of Alprazolam Relevant to MCG Design

Property	Value / Description	Significance for MCG
Molecular Weight	308.77 g/mol	Suitable for transmucosal permeation

Log P (lipophilicity)	2.12	Balanced partition for buccal absorption
pKa	2.40	Predominantly unionized at salivary pH 6.5-7.4
Water Solubility	40 mg/L (slightly soluble)	Requires solubilization strategies
Protein Binding	~80%	Moderate free fraction available for diffusion
Melting Point	228-229 degrees C	Stable under compression processing

4.3 Patient Compliance Considerations

The discreet, portable, and water-free nature of chewing gums makes them particularly appealing for anxiety management, where patients frequently require on-demand medication. Studies indicate that MCGs score significantly higher on patient preference scales compared to conventional oral dosage forms for acute conditions.

5. Formulation Design Strategies

5.1 Gum Base Selection and Optimization

Table 4: Substituent / Excipient Optimization for Alprazolam MCGs

Modification / Excipient	Expected Effect
Polyvinyl acetate (PVA) gum base	Controlled drug release and textural consistency
Xylitol as sweetener	Taste-masking and anticariogenic benefit
Hydroxypropyl methylcellulose (HPMC)	Mucoadhesion and extended buccal residence
Beta-cyclodextrin complexation	Enhanced aqueous solubility of alprazolam
Peppermint / menthol flavoring	Palatability improvement and permeation enhancement
Carbopol 934	Bioadhesive property enhancement

5.2 Hybrid Formulation Approach

Combining alprazolam with cyclodextrin inclusion complexes within the MCG matrix has been explored to simultaneously address solubility and permeation limitations. Nanoparticle-embedded MCGs using polymeric nanocarriers such as PLGA or chitosan have demonstrated improved drug loading efficiency and sustained transmucosal flux.

6. Manufacturing Methodologies

6.1 Direct Compression Method

This is the most commonly employed technique wherein gum base, drug, sweeteners, softeners, and fillers are blended and directly compressed. It avoids heat-sensitive processing and maintains drug stability.

6.2 Melting and Mixing Method

Gum base is softened at elevated temperatures (40-50 degrees C), and the drug along with excipients is incorporated homogeneously. The mixture is then molded or compressed into gum pellets.

6.3 Cold Compression Technology

A pharmaceutical-grade method conducted at ambient temperatures, particularly suited for thermolabile drugs. Provides uniform drug distribution and precise dose control.

6.4 Extrusion-Based Processing

Continuous twin-screw extrusion allows homogeneous drug-polymer mixing and can produce novel gum matrices with controlled porosity for modified release patterns.

7. Analytical Characterization Techniques

Table 5: Characterization Techniques for Alprazolam MCGs

Technique	Purpose
FT-IR Spectroscopy	Drug-excipient compatibility and functional group identification
DSC / TGA	Thermal analysis and polymorphic characterization
X-Ray Powder Diffraction (XRPD)	Crystallinity assessment of alprazolam in gum matrix
HPLC / UV Spectrophotometry	Drug content uniformity and purity determination
Texture Profile Analysis (TPA)	Hardness, cohesiveness, and gumminess of MCG
SEM	Surface morphology and drug distribution visualization
Chewing Simulator Studies	In vitro release modeling under physiological conditions

8. Biological Evaluation of Alprazolam MCGs

8.1 In Vitro Drug Release Studies

The European Pharmacopoeia (Ph. Eur.) chewing gum apparatus is the gold standard for in vitro release testing. The apparatus simulates the mechanical action of chewing (frequency and force) in a buffer medium (pH 6.0 simulated saliva). Samples are withdrawn at defined intervals for HPLC quantification of released alprazolam.

8.2 In Vivo Behavioral Models

Table 6: In Vivo Behavioral Models for Anxiolytic Assessment

Model	Anxiety Type Assessed	Endpoint
Elevated Plus Maze (EPM)	Unconditioned anxiety	Open arm time / entries
Light-Dark Box	Exploratory anxiety	Time in light compartment
Vogel Conflict Test	Conditioned anxiety	Punished lick responses
Open Field Test	Locomotion / sedation assessment	Ambulatory counts
Social Interaction Test	Anxiolytic social behavior	Interaction duration

9. Structure-Activity Relationship (SAR) Considerations for Alprazolam

Alprazolam belongs to the 1,4-benzodiazepine class with a triazolo ring fused at the 1,2-position. Key SAR observations relevant to its activity:

- Triazolo ring fusion significantly enhances potency compared to classical 1,4-benzodiazepines
- The 2-chloro substituent on the phenyl ring at C-5 is critical for GABA-A receptor affinity
- Methylation at C-1 of the triazolo ring improves metabolic stability and CNS penetration
- Modifications at the 7-position of the benzodiazepine nucleus alter relative potency
- N-1 substitution with methyl group (triazolo fusion) governs receptor binding kinetics

These structural features collectively render alprazolam highly potent and lipophilic enough for effective transmucosal delivery from MCG formulations.

10. Pharmacokinetic and Safety Considerations

An effective alprazolam MCG must demonstrate:

- Adequate and reproducible buccal bioavailability (target: > 60% relative to oral tablet)
- Tmax less than 30 minutes for acute anxiolytic applications
- Drug plasma levels within therapeutic window (10-40 ng/mL) without dose dumping
- Minimal salivary swallowing of drug (to reduce GI absorption variability)
- No local irritation or sensitization of buccal mucosa
- Compatibility with CYP3A4 metabolic pathway (primary alprazolam metabolism route)

Safety assessments follow ICH guidelines and include acute oral toxicity (OECD 423), buccal irritation models (EpiOral tissue model), and sub-chronic systemic exposure studies.

11. Emerging Trends and Future Perspectives

- Nanotechnology integration: Lipid nanoparticles and polymeric nanocarriers embedded in MCG matrix for enhanced permeation and controlled release
- Mucoadhesive MCGs with bioadhesive coatings for prolonged buccal residence and improved absorption
- 3D-printed chewing gums enabling personalized dose titration for anxiety management
- pH-responsive MCGs designed to release alprazolam specifically at buccal mucosal pH
- Combination MCGs incorporating alprazolam with cognitive enhancers or antiemetics for comprehensive anxiolytic therapy
- Smart packaging and electronic monitoring for dosage compliance in chronic anxiety disorders

12. Challenges in Development

Despite promising outcomes, several obstacles remain in the development of alprazolam MCGs:

- Controlled substance regulatory status of alprazolam (Schedule IV) imposes strict manufacturing and distribution requirements
- Taste masking of alprazolam's inherent bitterness is technically demanding without compromising buccal absorption
- Drug loss through saliva swallowing during chewing reduces predictability of buccal bioavailability
- Variability in chewing behavior (force, frequency, duration) among patients introduces pharmacokinetic variability
- Long-term stability of alprazolam in gum matrix under accelerated conditions requires extensive validation
- Limited clinical trial data supporting MCG bioequivalence to approved tablet formulations

13. Research Till Date

Table 7: Summary of Key Research on Medicated Chewing Gums and Alprazolam Delivery

Sr. No.	Year	Researcher / Group	Compound / Class Studied	Study Type	Key Findings	Significance
1	1988	Hansen et al.	Aspirin MCG	In vitro & In vivo	First pharmacokinetic comparison of drug absorption from MCG vs tablet	Established MCG as viable oral drug delivery platform
2	1995	Rassing MR	Nicotine gum	Clinical Review	Demonstrated effective transmucosal absorption via chewing gum	Validated buccal route for systemic drugs
3	2003	Jacobsen J. et al.	Metronidazole MCG	Formulation study	Optimized chewing patterns for controlled drug release	Chewing frequency critical parameter
4	2008	Aslani A. et al.	Lorazepam MCG	In vitro	Demonstrated benzodiazepine stability in gum matrix	Feasibility of BZD in MCG confirmed
5	2011	Morjaria Y. et al.	Diazepam MCG	PK Study	Compared transmucosal vs GI absorption; 30% bioavailability improvement	Supported BZD buccal delivery strategy
6	2013	Nafee N. et al.	Cyclodextrin inclusion MCGs	Formulation & In vitro	Enhanced solubility and release rate of poorly soluble drugs	Applicable to alprazolam BCS Class II
7	2016	Bhanu P. et al.	Alprazolam MCG	Formulation & Evaluation	Developed compressed MCG; 70% drug release in 30 minutes	First alprazolam-specific MCG report
8	2018	El-Setouhy et al.	Lorazepam buccal gum	In vitro/In vivo	Mucoadhesive gum prolonged plasma levels by 40%	Mucoadhesion enhances BZD delivery

9	2020	Priya K. et al.	Alprazolam MCG (beta-CD complex)	Formulation & In vitro	Complexation improved dissolution by 3-fold	Solubility enhancement validated
10	2021	Bhargava A. et al.	Modified gum base MCG	Comparative Formulation	PVA-based gum gave superior drug incorporation and release	Gum base type critical determinant
11	2022	Rahman M. et al.	Alprazolam nanoparticle MCG	In vitro/Ex vivo	PLGA nanoparticles in MCG improved buccal flux by 50%	Nano-embedding feasibility confirmed
12	2023	Singh R. et al.	Alprazolam MCG Box-Behnken design	Formulation optimization	Optimized gum base: softener: drug ratio for maximum release	QbD approach for MCG development
13	2024	Verma S. et al.	Alprazolam lipid-based MCG	In vitro & Stability	Lipid excipients improved stability and buccal permeation	Lipid MCG as future platform
14	2025*	Sharma P. et al.	3D-printed alprazolam MCG	Proof of Concept	Personalized dose MCG via 3D printing demonstrated feasibility	Next-gen precision dosing approach

CONCLUSION

Medicated chewing gums represent a scientifically compelling and patient-centric platform for the delivery of alprazolam in the management of anxiety disorders. The transmucosal buccal route effectively circumvents first-pass hepatic metabolism, offering rapid onset and enhanced bioavailability compared to conventional oral tablets. The physicochemical properties of alprazolam, including its moderate lipophilicity, low molecular weight, and ionization behavior at physiological pH, make it well-suited for incorporation into medicated gum matrices.

Formulation strategies such as cyclodextrin complexation, mucoadhesive polymer incorporation, nanoparticle embedding, and QbD-guided optimization have demonstrated measurable improvements in drug release, buccal permeation, and stability. Emerging technologies including 3D printing and lipid-based gum matrices offer promising avenues for personalized and advanced alprazolam MCG development.

However, challenges related to the regulatory status of alprazolam, taste masking,

pharmacokinetic variability from chewing behavior, and the limited body of clinical evidence must be systematically addressed. Interdisciplinary collaboration between pharmaceutical technologists, pharmacokineticists, and clinical researchers will be essential to translate promising preclinical findings into approved therapeutic products. Overall, alprazolam MCGs hold significant potential as an innovative, efficacious, and patient-friendly dosage form for acute and chronic anxiety management.

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